STATISTICAL ANALYSIS PLAN (SAP)

Study: RA0043

Product: Certolizumab pegol (CZP)

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)

SAP/Amendment	Date
Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016
SAP Amendment 3	30 Jun 2021
SAP Amendment 4	8 Dec 2022
SAP Amendment 5	21 Jun 2023
SAP Amendment 6	23 May 2024

Confidentiality Statement

Confidential

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LIST OF ABBREVIATIONS

ADAb	Anti-CZP antibody
ADAB-	anti-CZP antibody-negative
ADAB+	anti-CZP antibody-positive
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BSA	body surface area
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
CID	Clinically Inactive Disease
COVID-19	Coronavirus disease 2019
COX-2	cyclooxygenase-2
CRF	case report form
CRM	derived clinical remission (previously referred to as clinical remission on medication)
CRP	C-reactive protein
CSR	clinical study report
CV	coefficient of variation
CZP	certolizumab pegol
DMARD	disease-modifying antirheumatic drug
DMS	duration of morning stiffness
ds-DNA	double-stranded deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram

ECLIA	electrochemiluminescence immunoassay
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
ERA	enthesitis-related arthritis
ES	Enrolled Set
FAS	Full Analysis Set
FASCA	Fatigue Assessment Scale
FPS-R	Faces Pain Scale - Revised
HLT	High -Level Term
ia	intra-articular
im	intramuscular
IMP	investigational medicinal product
iv	intravenous
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
LoQ	limit of quantification
MAR	missing at random
MedDRA®	Medical Dictionary for Regulatory Activities
MRD	Minimum required dilution
MTX	Methotrexate
NRI	Nonresponder Imputation
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
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%

pcJIA	Polyarticular-course juvenile idiopathic arthritis
PK	pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
PK-PP	Pharmacokinetic Per-Protocol
POM	pain on motion
PopPK	population pharmacokinetic
PRN	as needed
PT	Preferred Term
Q2W, Q4W	every 2 weeks, every 4 weeks
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneously
SOC	system organ class
SRC	Safety Review Committee
SS	Safety Set
TE	Treatment-emergent
TEAE	treatment-emergent adverse event
VAS	visual analog scale
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document describes the planned analyses and summary tables, figures, and listings to be included in the final clinical study report (CSR) for RA0043 as well as for the Updated Week 24 Interim Analysis and other analyses supporting marketing applications; specific analyses added just for the Updated Week 24 Interim Analysis have been updated to say that they were only generated for that analysis Note that the Week 16 interim analysis and the 2016 Week 24 interim analyses were completed as specified in SAP Amendment 1 and text about these analyses will be kept as is.

If, after the final database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP, but they will be identified in the CSR. Any deviations from this SAP will be documented in the CSR.

2 PROTOCOL 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 (pcJIA).

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 pcJIA. The primary PK and immunological variables are CZP plasma concentration and anti-CZP antibody (ADAb) levels at Week 16 and Week 48.

Below is the list of protocol amendments, dates and rationales for key updates:

Table 2–1: Protocol, Amendments, Dates and Rationales

RA0043 Protocol/Amendment Number	Date	Rationale for Key Updates
Protocol	10 Jan 2010	NA
Amendment 1	26 Aug 2011	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. Key updates include adding effectiveness as a secondary objective, defining the study population as polyarticular-course JIA, setting minimum number of enrolled participants by body weight and age and adding the study stopping rule.
Amendment 2	02 Jul 2012	The primary purpose of this non-substantial amendment is to 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.

Table 2–1: Protocol, Amendments, Dates and Rationales

Amendment 2.1	21 Aug 2012	Amendment 2 adapted for Russia. The primary purpose of this substantial amendment is to change the age range for enrollment from 2-17 years to 6-17 years of age which is in response to comments received from the Ministry of Health and Social Development of the Russian Federation.
Amendment 3	06 May 2013	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.
Amendment 3.1	06 May 2013	Amendment 3 adapted for Russia as per Amendment 2.1.
Amendment 4	01 Aug 2013	The primary purpose of this substantial amendment is for the dose for study participants already enrolled in RA0043 to be reduced (enrollment into RA0043 was suspended, effective 17 Jul 2013). 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).
Amendment 4.1	01 Aug 2013	Amendment 4 adapted for Russia as per Amendment 2.1.
Amendment 5	20 Jan 2014	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.
Amendment 5.1	20 Jan 2014	Amendment 5 adapted for Russia as per Amendment 2.1.
Amendment 5.2	23 Feb 2015	The primary purpose of this non-substantial amendment is to lift the enrollment cap per site in Russia to allow further enrollment in the weight group of 15 to <20kg for sites that have enrolled the maximum number of 12 study participants.
Amendment 6	17 Sep 2015	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).
Amendment 6.1	17 Sep 2015	Amendment 6 adapted for Russia as per Amendment 2.1.
Amendment 7	22 Sep 2016	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.

Table 2–1: Protocol, Amendments, Dates and Rationales

Amendment 7.1	22 Sep 2016	Amendment 7 adapted for Russia as per Amendment 2.1.
Amendment 8	24 Jun 2019	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.
Amendment 8.1	18 Jul 2019	Amendment 8 adapted for Russia as per Amendment 2.1
Amendment 9	27 Apr 2020	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 pcJIA 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 pcJIA is still to be determined.
Amendment 9.1	28 Jul 2020	Amendment 9 adapted for Russia as per Amendment 2.1
Amendment 9.2	30 Jul 2021	The primary purpose of this non-substantial amendment is to increase the enrollment cap per site in Russia to allow further enrollment on the original dose regimen for sites that have enrolled the maximum number of 16 study participants.

Study participants, prior to Protocol Amendment 4, were enrolled on the Original CZP Dose. Results of a planned interim PopPK analysis conducted suggested that while observed CZP plasma concentrations with the Original Dose administration remained in the adult range, they were at the upper end of the distribution. Based on these findings, the dosing was changed with Protocol Amendments 4 and 5, and the doses to be administered were reduced by 50% for all weight groups, Reduced CZP Dose, see Table 2–3. 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. Based on interactions with FDA, Amendment 9 allowed 30 new participants to be enrolled taking Original CZP Dose; for the study participants who were taking Reduced CZP Dose, it introduced the option to increase to the Original CZP Dose.

Study participants will be summarized by the following 3 dose groups:

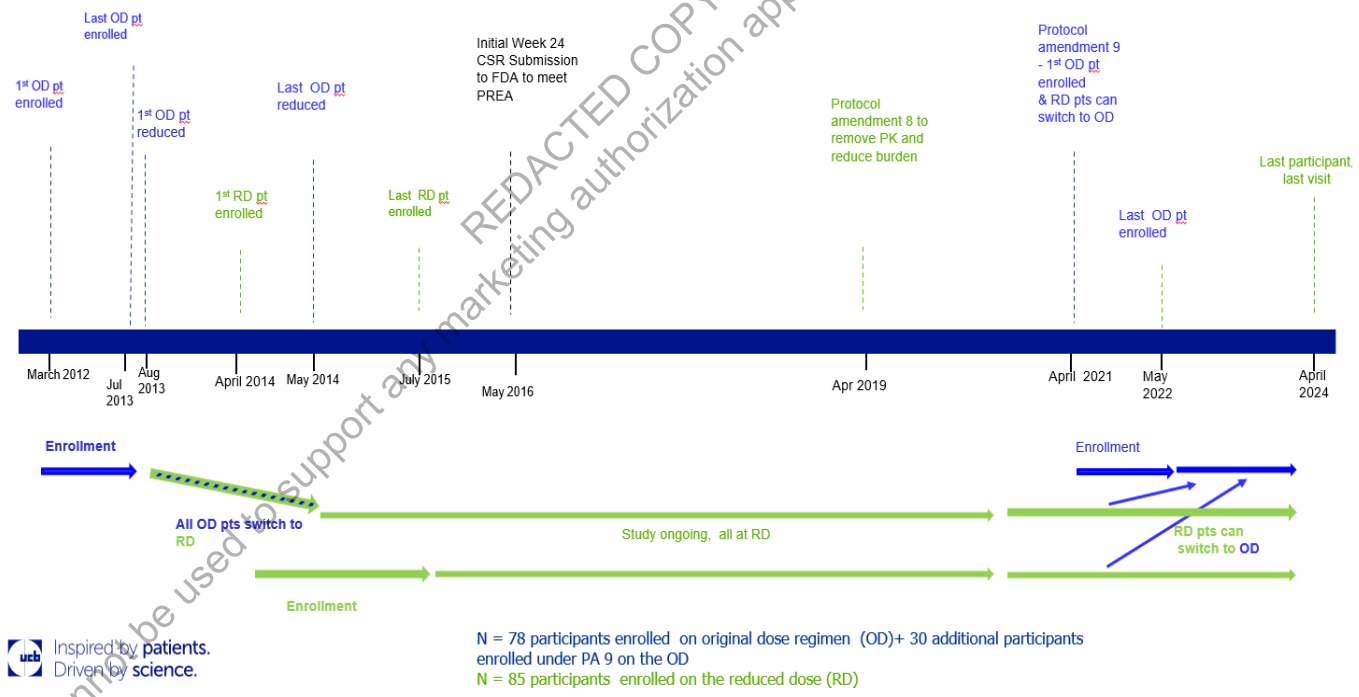
- Any CZP Dose – includes all data from all study participants while being treated in the study

- Original CZP Dose – includes all data for study participants enrolled on Original CZP Dose prior to the first change in dosage
- Reduced CZP Dose – includes all data for study participants enrolled on Reduced CZP Dose prior to the first change in dosage

For the Updated Week 24 Interim Analysis only, study participants were also summarized by the following 2 dose groups:

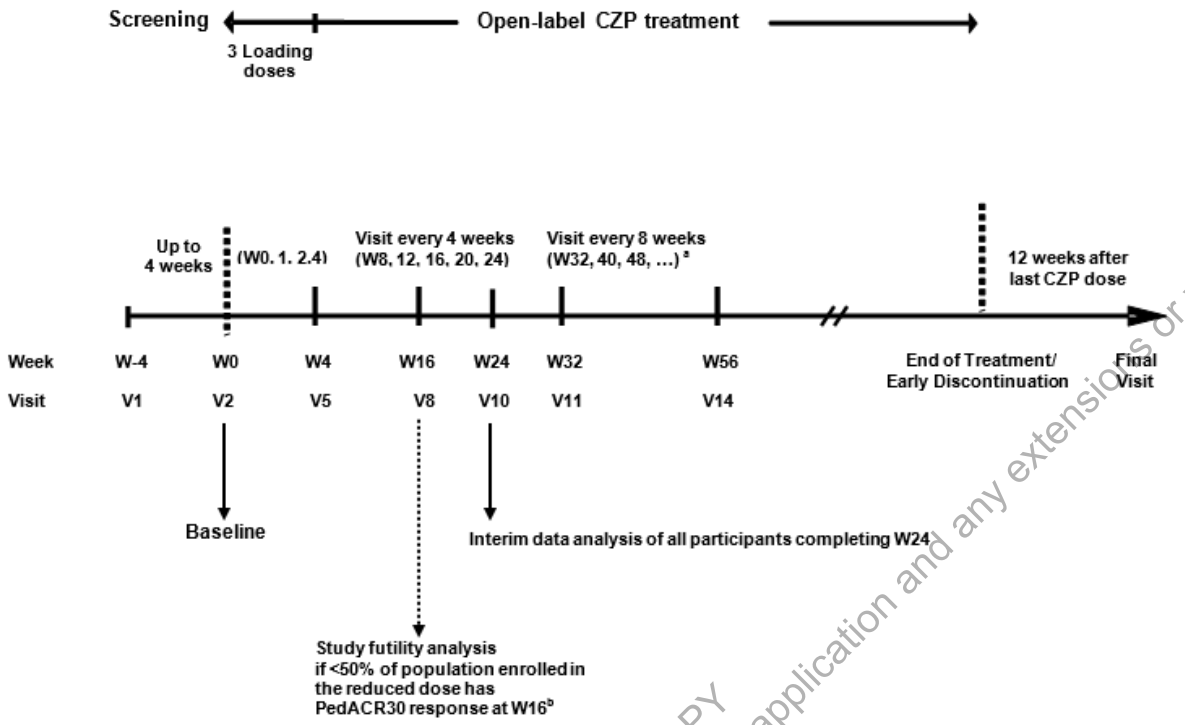
- Complete Original CZP Dose – includes all data for study participants who took Original CZP Dose prior to the first change in dosage as well as the data from when study participants increased their dosage to Original CZP after taking Reduced CZP Dose
- Complete Reduced CZP Dose – includes all data for study participants who took Reduced CZP Dose prior to the first change in dosage as well as the data from when study participants took Reduced CZP Dose after taking Original CZP Dose

The following graphic illustrates the study conduct once study participants taking original dose regimen were allowed to reduce their dose:



OD=Original CZP Dose, RD=Reduced CZP Dose, PA=protocol amendment

The following graphic illustrates the time course of the study as well and analysis timepoints:



An interim analysis of the American College of Rheumatology Pediatric 30% (PedACR30) response rate was performed after all active study participants who enrolled prior to Protocol Amendment 9 completed the Week 16 (Visit 8) assessments. The study would have been discontinued if less than 50% of the study population enrolled on the Reduced CZP Dose (Protocol Amendment 5) achieved a PedACR30 response at Week 16. A further futility analysis will not be performed using the additional study participants that will be enrolled after Protocol Amendment 9.

A full interim analysis was performed in 2016 for all active study participants that had completed the Week 24 (Visit 10) assessments. After Protocol Amendment 9 which enrolls 30 new study participants, interim analyses will be performed after all active study participants have completed the Week 24 (Visit 10) assessments and at other timepoints to support marketing applications.

In order to adequately assess the exposure levels and clinical experience of CZP in pcJIA at both the Reduced and Original CZP Dose and also to further support the safety assessment of the Original CZP Dose, 30 additional study participants will be enrolled on the Original CZP Dose following Protocol Amendment 9.

All study participants enrolled under Protocol Amendment 9 or later will have plasma concentrations of CZP and anti-CZP antibodies analyzed using electrochemiluminescence immunoassay (ECLIA) methods that meets current regulatory standards (versus those previously analyzed using ELISA methods for the prior Week 24 interim analysis). In addition, PK and ADAb samples (for which sufficient volume is available) collected in this study for participants enrolled prior to Protocol Amendment 9 will be re-analyzed with the ECLIA methods. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

2.1 Study objectives

2.1.1 Primary objective

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 pcJIA.

2.1.2 Secondary objective

The secondary objective is to assess the effectiveness of CZP on the clinical response in children and adolescents with moderate to severe pcJIA.

2.1.3 Other objectives

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

2.2 Study variables

2.2.1 Primary variables

2.2.1.1 Pharmacokinetic and immunological variables

- CZP plasma concentrations at Weeks 16 and 48
- Anti-CZP antibody levels at Weeks 16 and 48

2.2.1.2 Safety variables

The primary safety variables are the incidence of serious treatment-emergent adverse events (TEAEs) and TEAEs leading to permanent withdrawal of investigational medicinal product (IMP).

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

2.2.2 Secondary variables

Efficacy will be assessed by the PedACR30, PedACR50, PedACR70 and PedACR90 response rates at Week 16 as compared to Baseline.

2.2.3 Other variables

2.2.3.1 Other PK and immunological variables

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

2.2.3.2 Other safety variables

- Incidence of TEAEs, TEAEs of interest, TEAEs by relatedness, TEAEs by severity, and TEAEs by duration of exposure
- Clinical laboratory values (hematology, biochemistry, urinalysis) at every visit except Visits 3 and 4 (Week 1 and Week 2) and Unscheduled Visits
- Vital sign abnormalities at every visit

- Developmental stages and growth (Tanner stages, height, weight) at Baseline, every protocol-specified visit thereafter, and the Early Discontinuation/End of Treatment Visit (weight at every visit through Final Visit).
- Autoantibody concentrations (antinuclear antibodies (ANA) and anti-double-stranded desoxyribonucleic acid (anti-dsDNA) antibodies) 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

2.2.3.3 Other efficacy and health outcomes variables

Other efficacy and health outcomes variables are:

- PedACR30, PedACR50, PedACR70, and PedACR90 response rates at every post-Baseline visit, except Week 16 and Final Visit, as compared to Baseline.
- Change from Baseline in number of joints with active arthritis at every post-Baseline visit except Final Visit.
- Change from Baseline in number of joints with limitation of range of motion at every post-Baseline visit except Final Visit.
- Change from Baseline in Physician's Global Assessment of Disease Activity (visual analog scale (VAS)) at every post-Baseline visit except Final Visit.
- Change from Baseline in Childhood Health Assessment Questionnaire (CHAQ) at every post-Baseline visit except Final Visit.
- Change from Baseline in Parent's Assessment of Arthritis Pain (VAS) at every post-Baseline visit except Final Visit.
- Change from Baseline in Parent's Global Assessment of Overall Well-Being (VAS) at every post-Baseline visit except Final Visit.
- Percent Change from Baseline in C-reactive protein (CRP) at every post-Baseline visit except Final Visit.
- Change from Baseline in Juvenile Arthritis Disease Activity Score 71-joint (JADAS-71) at every post-Baseline visit except Final Visit.
- Percentage of study participants with Clinically Inactive Disease (CID) at every post-Baseline visit except Final Visit.
- Percentage of study participants with clinical remission on medication (CRM) at every post-Baseline visit from Week 24 onwards except Final Visit.
- Time (in days) to CID calculated from first dose of study medication.
- Time (in days) to CRM calculated from first dose of study medication.
- Change from Baseline in duration of morning stiffness (DMS) at every post-Baseline visit except Final Visit.
- Change from Baseline in Faces Pain Scale-Revised (FPS-R) (child-reported, ages 5 to 11 years), at every post-Baseline visit except Final Visit.

- Change from Baseline in JIA Pain VAS (acute and standard versions); at every post-Baseline visit except Final Visit
- Change from Baseline in Fatigue Assessment Scale (FASCA) at every post-Baseline 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 post-Baseline visit except Final Visit.

2.2.3.4 Additional other variables

Additional variables that were covered under other variables that were specifically analyzed in the Updated Week 24 Interim Analysis only and were used for comparison purposes to support the regulatory submission include:

- CZP plasma concentrations at Weeks 12 and 24
- Anti-CZP antibody levels up to and including Week 24
- CZP plasma concentration from study RA0138 at Weeks 12 and 24
- Anti-CZP antibody levels from study RA0138 up to and including Week 24

2.3 Study design and conduct

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 pcJIA.

The study population will consist of study participants 2 to 17 years of age upon enrollment with a minimum weight of 10kg (22lb) (except in Russia, where the study population will consist of study participants 6 to 17 years of age upon enrollment with a minimum weight of 15kg [33lb]). Study participants must have had onset of signs and symptoms consistent with pcJIA and initiation of pcJIA treatment for at least 6 months prior to Baseline. Active pcJIA 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 pcJIA in the study participant's country or region or closing the study by UCB. A Final Visit will be conducted 12 weeks after last dose of study medication.

The table below shows the data collection schedule prior to Protocol Amendment 8 and after implementing Protocol Amendment 8. For the study participants who switch to the 16-week schedule, the date of the first visit of this schedule will be captured on the "Study Participation" CRF module. Of note, the participants enrolled after Protocol Amendment 9 (the new 30 study participants on Original CZP Dose) will remain on the original visit schedule throughout the study.

Table 2–2: Visit Schedule

Collected/ Assessed/ Administered at	Prior to Protocol Amendment 8[a]	Following Protocol Amendment 8
Most parameters	Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32 and every 8 weeks thereafter, the Early Discontinuation/End of Treatment Visit, and the Final Visit	Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32 and every 16 weeks thereafter, the Early Discontinuation/End of Treatment Visit, and the Final Visit
Height	Screening, Baseline, every 24 weeks thereafter and Early Discontinuation/End of Treatment Visit	Screening, Baseline, every 48 weeks thereafter and Early Discontinuation/End of Treatment Visit; assessed study participants who have not reached Tanner stage V
Tanner	Screening, Baseline, every 24 weeks thereafter and Early Discontinuation/End of Treatment Visit	Screening, Baseline, every 48 weeks thereafter and Early Discontinuation/End of Treatment Visit; assessed study participants who have not reached Tanner stage V
FPS-R and pcJIA Pain VAS	Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, 24 and 32; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment	Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, 24 and 32; and then every 16 weeks thereafter through the Early Discontinuation/End of Treatment
NRS	Baseline, Weeks 1, 2, 4, 8, and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment	Baseline, Weeks 1, 2, 4, 8, 16, 24, 32 and then every 16 weeks thereafter through the Early Discontinuation/End of Treatment

[a] Participants enrolled after Protocol Amendment 9 (the new 30 study participants on Original CZP Dose) will remain on the original visit schedule throughout the study.

Prior to Protocol Amendment 9, 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 (Protocol Amendment 5) in each weight range of 10 < 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.
- 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.
- A minimum of 10 study participants with ERA will be enrolled, irrespective of the dose.

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 are intended to be enrolled on the Original CZP Dose 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.

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 (except the 10 to < 20kg group on the Reduced CZP Dose will be administered 50mg Q4W). The doses are explained in the following table:

Table 2–3: Dosing administration of CZP[a]

Weight range	Loading dose – Weeks 0, 2, and 4 (mg/kg dose range) IMP Description	Maintenance – Week 6[b] and onwards (mg/kg dose range) IMP Description
Original CZP Dose		
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 Dose		
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 Dose 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 Dose describes the dosing administration of CZP after implementation of Protocol Amendments 4 and 5.

[b]Note that for Reduced Dose, 10 to <20kg study participants, maintenance dosing started at Week 8.

Based on 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 with the bioanalytical assays used for RA0043, which rendered the PK data unreliable. Accordingly, PK samples were no longer collected for study participants on the Reduced CZP Dose following implementation

of Protocol Amendment 8, in addition to reducing the burden on participants who had already been in the study for a number of years.

A validated ECLIA method that meets the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics was introduced after Protocol Amendment 9, it has been used for all new analyses, including re-analysis of archived samples collected before Protocol Amendment 9 and for the analysis of bio-samples collected from the additional 30 study participants after Protocol Amendment 9.

Based on 24-week interim results from the first 163 study participants enrolled in RA0043, both the Original CZP Dose and Reduced CZP Dose showed safety profiles similar to the approved CZP dose in the adult RA population. The overall clinical response in this analysis (taking both doses into account) was PedACR30 and PedACR50 responses of 77.3% and 67.5%, respectively at Week 12. The response from the original dose was 75.6% for PedACR30 and 64.1% for PedACR50; the response from the reduced dose was 78.8% for PedACR30 and 70.6% 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 pcJIA at both the Reduced and Original CZP Doses and support the safety for the Original CZP Dose, as more of the safety data collected in the study prior to Amendment 9 were on the reduced dose, 30 additional study participants have been enrolled on the Original CZP Dose 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 ADAb 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 PK analysis, and was the basis for the modeling and simulation work that supported the interim PK analysis in 2023 and the 2024 submission.

Full interim analyses were performed in 2016 after all active study participants completed the Week 24 (Visit 10) assessments. Week 24 full interim analyses were completed as described in SAP Amendment 1. An Updated Week 24 (Visit 10) interim analysis, including the 30 new study participants enrolled after Protocol Amendment 9, was completed as described in SAP Amendments 4, 5, and 6. The final analysis will be completed as described in SAP Amendment 6.

2.4 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, and it was planned to enroll a further 78 study participants on the Reduced CZP Dose, so that a comparable number of study participants on the Reduced CZP Dose 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 was planned to screen 195 study participants in total.

With Protocol Amendment 9, an additional 30 study participants were enrolled 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 pcJIA suggested that the planned sample size of 125 study participants would also be 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.

Available ECLIA-based data from all study participants were included in the final PopPK analysis as described in a separate Data Analysis Plan and reported separately for the Updated Week 24 Interim Analysis only.

2.5 Study RA0138

RA0138 is an open-label study in 33 adult study participants with RA who took 400mg loading dose (Weeks 0, 2, and 4), followed by 200mg CZP Q2W. This study was conducted to generate PK and ADAb data using the same ECLIA assay as used in RA0043 to form the basis of "PK-matching" for CZP approval. For Updated Week 24 Interim Analysis, the PK and ADAb data from RA0138 was analyzed and displayed in the same manner as data from RA0043; comparisons and conclusions were made. Those details are presented in the Appendix, Section 12.1.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

SAS® Version 9.3 (or later) will be used to perform all summaries and analyses, unless specified otherwise.

All study participants received CZP and in most cases, are grouped by their Baseline weight group in the summary tables. Generally, data summaries will be organized by CZP dose, and will include the following CZP dose groups:

- Original CZP Dose: includes all study participants who began treatment in accordance with the Original CZP Dose 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]). Only data obtained prior to their first change in dosage will be included in summaries of the Original CZP Dose.
- Reduced CZP Dose: includes all study participants who began treatment in accordance with the Reduced CZP Dose 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]). Only data obtained prior to their first change in dosage will be included in summaries of the Reduced CZP Dose.

- Any CZP Dose: includes all data from all study participants while being treated with the Original CZP Dose or the Reduced CZP Dose at any time in the study, regardless of dose switching.

The planned data summaries using dose groups of Original CZP Dose and Reduced CZP Dose are designed to allow for the most relevant comparison of PK data and PK extrapolation using only data collected from study participants while receiving one consistent dosing regimen of CZP. This assignment of treatment groups will allow for a pure comparison of PK of the Original CZP Dose and the Reduced CZP Dose between pediatrics and adults without the potential of confounding differences in CZP plasma concentrations due to dose switching. Additionally, these dose groupings allow for the continuity of safety, immunogenicity, and open label efficacy analyses for the Original CZP Dose and Reduced CZP Dose.

Generally, data will be summarized by the Original CZP Dose, Reduced CZP Dose, and Any CZP Dose groups. For PK and ADAb analyses, data will be summarized by Original CZP Dose and Reduced CZP Dose only. For the Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey, data will be summarized by Any CZP Dose group only.

Following recommendations received from [redacted], a few data summaries were organized for the Updated Week 24 Interim Analysis only, by "Complete" CZP dose groups defined below, which allowed assessment of exposure and safety for all time that study participants were receiving the specified dose regardless of dose switching:

- Complete Original CZP Dose: included all study participants who began treatment in accordance with the Original CZP Dose, as well as study participants who began treatment in accordance with the Reduced CZP Dose and then later dose escalated to the Original CZP Dose.

  Only data obtained while the study participant was receiving the Original CZP Dose was included in summaries of the Complete Original CZP Dose. For study participants who began treatment with the Original CZP Dose, this included time on the Original CZP Dose prior to first change in dosage, as well as time after returning to Original CZP Dose after a previous dose reduction. For study participants who began treatment with the Reduced CZP Dose, this included only time after dose escalation to the Original CZP Dose.

- Complete Reduced CZP Dose: included all study participants who began treatment in accordance with the Reduced CZP Dose, as well as study participants who began treatment in accordance with the Original CZP Dose and later dose reduced to the Reduced CZP Dose.

  Only data obtained while the study participant was receiving the Reduced CZP Dose was

included in summaries of the Complete Reduced CZP Dose. For study participants who began treatment with the Reduced CZP Dose, this included time on the Reduced CZP Dose prior to first change in dosage. For study participants who began treatment with the Original CZP Dose, this included only time after dose reduction to the Reduced CZP Dose, and prior to any potential later dose escalation back to the Original CZP Dose.

Selected exposure and TEAE summaries were produced on Complete Original CZP Dose and Complete Reduced CZP Dose in order to answer specific agency questions. Similarly, summaries of the proportion of PK and ADAb samples and participants that have been reanalyzed with the ECLIA assay were also produced with this treatment association.

Further details regarding these displays based upon dose groups can be found in the respective PK, safety and efficacy analysis sections below.

Categorical data will be presented as summary tables. A missing category will be included as applicable.

Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum. For CZP plasma concentrations and CRP, the geometric mean and geometric coefficient of variation (CV) will be presented.

Due to shifts in visit schedules per protocol amendments that were adopted at different times for different sites and study participants, some visits/ time points had very few study participants assessed. For categorical and continuous efficacy variables presented by visit/time point, if the visit/time point for the Any CZP Dose group contains 19 or fewer study participants with non-missing data, those visits/ time points will not be displayed in the efficacy tables or plotted in figures for Reduced CZP Dose, Original CZP Dose and Any CZP Dose groups. All information will appear in the listings.

Mean, standard deviation, and median will be displayed to 1 more decimal place than collected in the case report form (CRF). Minimum and maximum values will be displayed to the same level of precision as collected in the CRF. Percentages will be calculated using the number of study participants in the relevant population or subgroup as the denominator. Presentation of percentages will be to 1 decimal place. Percentages will not be presented if the frequency count is 0.

No formal statistical hypothesis testing will be performed. Ninety-five percent confidence intervals (CIs) for the percentage of responders will be calculated using the exact binomial method.

For certain laboratory parameter results that are collected as either "<XX.X" or ">XX.X", if descriptive statistics are calculated for the parameter, the XX.X will be used in the calculation but the data listing will reflect the actual reported result.

The classification of AEs occurring on the same date as a dose change will belong to the period of the dose change.

In addition, for other subgroup analyses (e.g. Baseline age group, concomitant MTX use, etc.), data will be generally presented by the specified subgroups pooling across all weight groups (with the exception of PK analyses which are specified in the corresponding sections).

3.2 General study level definitions

3.2.1 Analysis time points

The analysis time points of interest are detailed in Table 2–2. Safety assessments will also be done at the Final Visit 12 weeks after the final dose of CZP.

For study participants who withdraw prior to the last time point for the particular analysis being conducted (ie, Week 16, Week 24, other interim analysis, Final), data recorded at the Early Discontinuation/EOT Visit will be assigned to what would have been the next scheduled visit, unless unavailable or otherwise specified, dependent on which visit schedule the study participant is following. This re-assignment should be based upon the study day (relative to the baseline visit date) and also keeping in mind the +/- 3-day window into which visits fall. These data will be included in the summaries of the assigned visit and the "Early Discontinuation/EOT" Visit if applicable. For efficacy data, the Early Discontinuation/EOT Visit will not be summarized and only the re-assigned visit will be included in the summary tables. Note that data from the Early Discontinuation Visit or EOT will be listed as "Visit X (Week Y)/ED" or "Visit X (Week Y)/EOT" where the X was the re-assigned visit number and Y was the re-assigned week number in all safety and efficacy data listings as applicable.

3.2.2 Relative day

Relative day of an event or assessment will be included in data listings and will be calculated as follows:

Relative day 1 is the date of first CZP administration.

Relative day of date X = date X - Date of first CZP administration+1 day if date X is on or after date of first CZP administration.

Relative day of date X = date X - Date of first CZP administration if date X is before date of first CZP administration.

Relative days before first administration of CZP will have the prefix "-".

Relative day after last dose will have the prefix "+",and will be calculated from the date of last CZP administration (date X - date of last CZP administration). Relative day will not be calculated when any part of a corresponding date is missing,and will not be included in corresponding tables and listings.

3.2.3 Medications

The UCB study physician will review a listing of all medications and flag those which are steroids, DMARDs, anti-TNFs, NSAIDs, Cox 2 inhibitors, analgesics, opioids, experimental medications, vaccines, etc. This flagging is then used to generate various medication tables.

3.2.4 Final Visit

Final visit is defined as the visit conducted 12 weeks after the last dose of study medication. Most efficacy variables state that the Final Visit data will not be included in table summaries; the data will be included in study participant data listings.

3.2.5 Week 24

Week 24 is defined as the visit labeled as Week 24 or Visit 10 in the data.

3.2.6 Entire treatment period

The entire treatment period is the same as the entire exposure period which includes all data while the study participant is taking study medication.

3.3 Definition of Baseline values

The Baseline value for all variables will be the last non-missing pre-treatment measurement. The last non-missing pretreatment measurement will generally be the Baseline (Week 0) visit, but could be the Screening Visit if no Baseline value was obtained or an unscheduled Visit that occurs prior to first dose. For study participants enrolled on the Original CZP Dose or Reduced CZP Dose, Baseline is the last non-missing pre-treatment measurement prior to the initial dose on the Original CZP Dose or Reduced CZP Dose.

The change from Baseline will be calculated as the difference between the post-Baseline value and last non-missing pre-treatment measurement. Change from Baseline will only be calculated if a valid Baseline value is available.

3.4 Protocol deviations

Important protocol deviations will be pre-defined and data cleaning meetings will be held on an ongoing basis to review the important protocol deviations. At these data cleaning meetings, protocol deviations from the Clinical Trial Management System (CTMS) as well as those generated programmatically will be reviewed by the study team in order to flag those that are important.

In addition, protocol deviations related to the impact of the global pandemic of coronavirus disease 2019 (COVID-19) will be documented.

Study participants, if taking CZP Q2W, should be dosed 9 to 19 days from the previous dosing; if taking CZP Q4W, study participants should be dosed 23 to 33 days from the previous dosing. Study participants who are taking CZP Q2W, if they have instances where they take their study medication > 42 days from the last dosing, or for those who are taking CZP Q4W, if they have instances where they take their study medication > 84 days from the last dosing, these instances will be flagged as important protocol deviations. For study participants not in derived CRM and taking CZP Q2W, gaps less than 9 days or >19 to 42 days will be considered as protocol deviations. For study participants not in derived CRM and taking CZP Q4W, gaps less than 23 days or >33 to 84 days will be considered as protocol deviations.

3.5 Exclusion of PK data points

Exclusion of specific PK data points will be done for that CZP plasma concentration data presented in the subset of tables and figures where geometric means are calculated and displayed. These exclusions will not occur in the CZP plasma concentration data presented in spaghetti plots or individual profile figures. The reasons why CZP plasma concentration data points may be excluded are the following:

- Study participant taking an incorrect treatment or dose,
- Study participant's discontinuation of CZP,
- Study participant being in derived CRM (and not taking CZP),
- Study participant having deviations where CZP dosings occur outside the scheduled CZP dosing window, and
- Study participant is procedurally non-compliant, in not having plasma concentration samples taken at the appropriate time points.

CZP plasma concentration data that is excluded due to the above reasons will be flagged on the analysis PK dataset. The flagging will allow the data to be excluded from geometric mean calculations which could be more affected by instances of treatment and procedure non-compliance.

3.5.1.1 Rules for exclusions of specific PK samples

The PK sample results taken at a specific visit will be excluded from analysis for the following reasons:

- If the study participant's CZP plasma concentration sample was taken at a visit where the prior 2 consecutive CZP doses were missed, then the study participant's CZP plasma concentration sample is excluded,
  - For study participants returning to CZP dosing, a study participant's CZP plasma concentration result will be included in summaries if the prior 3 consecutive CZP doses are present.
- If in the 168 days prior to the study participant's CZP plasma concentration sample, there were >3 CZP doses missed, then that study participant's CZP plasma concentration sample is excluded,
  - For study participants returning to CZP dosing, a study participant's CZP plasma concentration result will be included in summaries if the prior 3 consecutive CZP doses are present.
- If a study participant is on a Q2W CZP dosing interval, and the study participant's CZP plasma concentration sample is taken <9 days or >19 days from the last CZP dosing, then it is excluded,
- If a study participant is on a Q4W CZP dosing interval, and the study participant's CZP plasma concentration sample is taken <23 days or >33 days from the last CZP dosing, then it is excluded,
- For the Week 1 CZP plasma concentration sample, if a study participant's sample is taken (too soon) <4 days after or (too late) >10 days after the Week 0 CZP dose, it is excluded, or
- For the Week 17 CZP plasma concentration sample, if a study participant's sample is taken (too soon) <4 days after or (too late) >10 days after the Week 16 CZP dose, it is excluded.

In addition, CZP plasma concentrations that have been analyzed outside the stability coverage of the ECLIA assay have also been excluded. In this latter case from all tables and figures and only will appear in the listings with a flag for out of stability.

3.6 Analysis sets

The efficacy variables will be summarized using the Full Analysis Set (FAS). All safety and immunogenicity analyses will be based on the Safety Set (SS). Plasma concentration data will be summarized using the Pharmacokinetic Per-Protocol Set (PK-PP).

3.6.1 Enrolled Set

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

3.6.2 Safety Set

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

3.6.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all study participants in the SS who have no more than one of the 6 core components missing at baseline (count of joints with active arthritis, count of joints with limitation of range of motion, Physician's Global Assessment of Disease Activity score, CHAQ score, Parent's Global Assessment of Overall Well-Being score and CRP result) for calculating PedACR30/50/70/90.

3.6.4 Pharmacokinetic Per-Protocol (PK-PP) Set

The Pharmacokinetic Per-Protocol (PK-PP) Set is a subset of the SS consisting of those study participants who took at least 1 dose of study medication, provided measurable plasma CZP concentration samples (with recorded sampling date/time or for which date/time can be reasonably assumed and it was analyzed using the ECLIA method) on at least 1 occasion. The PK-PP Set will be used for presentations of plasma concentration. The PK-PP Set was used for the PopPK model that was described in a separate data analysis plan (DAP) to support the marketing application in 2024.

3.7 Treatment assignment and treatment groups

All study participants received CZP as a fixed dose based on weight (Table 2–3). Prior to implementation of Protocol Amendments 4 and 5 (where study participants switched to the reduced dose), and after Protocol Amendment 9, the Original CZP Dose was followed; study participants in the 10 to <20kg weight group received CZP loading doses of 100mg and a maintenance dose of 50mg, study participants in the 20 to <40kg weight group received CZP loading doses of 200mg and a maintenance dose of 100mg, and study participants in the >40kg weight group received CZP loading doses of 400mg and a maintenance dose of 200mg, all Q2W. Following implementation of Protocol Amendments 4 and 5, all CZP doses were reduced by 50% (Reduced CZP Dose); study participants in the 10 to <20kg weight group received a CZP loading dose of 50mg Q2W and a maintenance dose of 50mg Q4W, study participants in the 20 to <40kg weight group received a CZP loading dose of 100mg Q2W and a maintenance dose of 50mg Q2W, and study participants in the >40kg

weight group received a loading dose of 200mg Q2W and a maintenance dose of 100mg Q2W.

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.

Prior to the implementation of Protocol Amendment 5, study participants were required to meet additional criteria prior to moving to a higher dosing category. Specifically, the following changes in weight were required prior to dose increases: (1) 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 (2) weight crosses the 20kg/44lb boundary due to a weight change of >2.5kg (5.5lb) (eg, a 19.0kg study participant becomes 21.6kg).

For PK, safety and efficacy analyses, study participants will be grouped by their Baseline weight group. Selected analyses will also group study participants by their Baseline age group, concomitant MTX use, and ADAb titer (as defined in Section 8.2).

Regardless of specific prescribed doses dictated by weight change during study conduct, study participants will be analyzed by the CZP dose group stated in Section 3.1.

3.8 Center pooling strategy

For analyses, all centers will be pooled together.

3.9 Coding dictionaries

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA® version 23.1) according to UCB standard operating procedures (SOP). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD version dated Sep 2020 B3) according to UCB SOPs.

3.10 Changes to protocol-defined analyses

The definition for the FAS has been clarified to the following: The Full Analysis Set (FAS) will consist of all study participants in the SS who have no more than one of the 6 core components (count of joints with active arthritis, count of joints with limitation of range of motion, Physician's Global Assessment of Disease Activity score, CHAQ score, Parent's Global Assessment of Overall Well-Being score and CRP result) for calculating improvement in PedACR30/50/70/90 missing at baseline.

The definition for the PK-PP has been clarified such that study participants in this set must have PK data analyzed using the ECLIA method.

In line with [redacted] response, for the Updated Week 24 Interim Analysis only, additional analyses were added to:

- summarize exposure and treatment-emergent adverse events for when study participants were taking Complete Original CZP Dose and Complete Reduced CZP Dose.
  - Complete Original CZP Dose included all data for study participants who took Original CZP Dose prior to the first change in dosage as well as the data from when study participants increased their dosage to Original CZP after taking Reduced CZP Dose.
  - Complete Reduced CZP Dose included all data for study participants who took Reduced CZP Dose prior to the first change in dosage as well as the data from when study participants took Reduced CZP Dose after taking Original CZP Dose.
- summarize the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples initially analyzed with the ELISA method were summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- summarize the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples analyzed with the ECLIA method (either originally or via re-analysis) will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- summarize the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples initially analyzed with the ELISA method will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- Additionally, to summarize the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples analyzed with the ECLIA method (either originally or vis re-analysis) will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.

In the statistical section of the protocol, it is stated that the AEs will be summarized separately for the periods of exposure to Original CZP Dose and the Reduced CZP Dose, in addition to exposure for study participants that switched from the Reduced CZP Dose to the Original CZP Dose following Protocol Amendment 9. The analysis of AEs after a study participant changes doses will not be separately identified and presented in the Updated Week 24 Interim Analysis or the final analysis although the AEs that occur after dose changes will be summarized in the Any CZP Dose group.

In the statistical section of the protocol, it is stated that the frequency and percentage of AEs reported during the first 16 weeks of study medication exposure will be summarized separately for the 2 CZP doses (the Original CZP Dose, the Reduced CZP Dose), and that this analysis will be repeated, excluding any study participants who switched from the original to the reduced CZP dose prior to Week 16. The protocol-specified safety Week 16 analyses generated for prior interim analyses will not be included in the Updated Week 24 Interim Analysis or any later analyses.

Exposure-adjusted event rates (EAER) are added to selected TEAE tables.

This analysis plan, for the Updated Week 24 Interim Analysis only, includes plots of CZP plasma concentrations, ADAb titers, and maximum PedACR response for individual study participants by visit. Box plots of the PK distribution at Weeks 12 and 24 stratified by Baseline weight group, Baseline age group, concomitant MTX use and participant ADAb classification will be performed as a basis of the comparison with the adult RA PK exposures in RA0138; this comparison of observed PK data will be covered in Appendix Section 12.1. Plots of PK and ADAb data were not pre-specified in the study protocol.

It is not planned to perform a population PKPD modeling analysis of RA0043 data to explore the exposure-response relationship in pcJIA pediatric population for the following reasons: i) the purpose of the RA0043 study is to support the efficacy extrapolation to the pediatric population by PK matching with respect to RA adult PK, and thus the main aim of the analysis that will be performed by nonlinear mixed effect modeling is to characterize the PK in pcJIA pediatrics with precise parameter estimates; and ii) the W24 interim analyses performed and submitted in 2016 (BLA 125160-275) included PedACR and JADAS-71 graphical explorations by dose which concluded that a substantial improvement of the PedACR and JADAS-71 responses across both doses investigated in Study RA0043 was observed, with no differences between these, that would support a pop-PKPD analysis. Hence the PK-PD Set was removed as no analyses are planned for this population.

In the protocol it was stated that continuous efficacy endpoints would be presented using both last observation carried forward (LOCF) and observed case (OC) analyses. Instead, only observed case summaries of continuous efficacy endpoints will be presented since efficacy is not the primary objective of this study and little difference is expected between the two different analyses.

For the Updated Week 24 Interim Analysis, the efficacy data were summarized and plotted up to and including Week 24; all efficacy data were included in listings. For the Final Analysis, all data will be summarized and plotted, by visit (week) when there are 20 or more study participants with non-missing data, as applicable; all efficacy data will be included in listings.

For joints with limitation of motion (LOM), it was stated in the protocol that the assessment of LOM would be made using 69 of the 75 joints from the standard PRINTO/PRCSG standard joint examination. In all SAPs since SAP Amendment 2, the assessment now utilizes 67 joints and this was according to an updated definition of LOM in the PRINTO/PRCSG assessment that was not available prior to the finalization of the protocol.

For CRP, summaries present the percent change from Baseline instead of the ratio to Baseline to aid in interpretation.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

No adjustment for covariates will be performed.

4.2 Handling of dropouts or missing data

For all binary efficacy endpoints assessing response (PedACR30, PedACR50, PedACR70, PedACR90, CID, CRM), a study participant having missing data for the time point assessed will be conservatively counted as a non-remitter or non-responder. This will be done whether the data is missing, the study participant discontinued the study prior to the time point assessed, or the data is considered missing due to use of prohibited or rescue medication.

For all non-missed visits, if any of the PedACR core set measures are missing then those scores will be considered as not having met the criteria for improvement in the PedACR30, PedACR50, PedACR70 and PedACR90 response analyses. PedACR30, PedACR50, PedACR70, and PedACR90 responses will be derived if a single core set measure is missing. However, if 2 or more core set measures are missing, the corresponding PedACR30, PedACR50, PedACR70 and PedACR90 responses will in general be treated as missing.

Derived binary efficacy endpoints at visits affected by the use of rescue medications, or prohibited medications, will be treated as non-response. See Section 6.7 for a list of medications which would result in all efficacy data at only the next scheduled visit (and not all subsequent visits) being treated as missing/non-response. Any joint receiving intra-articular corticosteroids will be treated as missing with respect to assessments of that joint for 3 months (91 days).

For continuous efficacy endpoints, missing assessments will not be imputed.

For the non-responder imputation (NRI) calculations for binary efficacy outcomes,

- the study participants who discontinued up to and including Week 56, NRI will be imputed up to Week 56,
- the study participants who discontinued after Week 56, no imputation will be performed after the last visit,
- for study participants who take rescue and prohibited medications (see Section 6.6),
  - for visits up to and including Week 56, the outcomes are imputed as NRI up to Week 56
  - for visits after Week 56, the outcomes are imputed as NRI if medication initiation is before or on Week 56
- for the initiation of rescue, short-acting or prohibited medications after Week 56, then the NRI imputation is not applied.

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

4.2.1 Incomplete dates for adverse events and concomitant medications

Partial adverse event (AE), medical procedures, and concomitant medication start dates will be imputed as follows:

1. If the year is unknown, the date will be imputed as the date of first intake of study medication if this is possible (ie, the AE end date is not prior to treatment start date).
2. If the month is unknown, then:
   a) If the year matches the first dose date, then impute the month and day of the first dose date.
   b) Otherwise, assign January.
3. If the day is unknown, then:
   a) If the month and year match the first dose date, then impute the day of the first dose date.
   b) Otherwise, assign '01'.

Partial AE and concomitant medication stop dates will be imputed as follows:

1. If the year is unknown, the date will not be imputed and will be assigned a missing value.
2. If the month is unknown, then assign December.
3. If the day is unknown, then assign the last day of the month.

If the date of diagnosis of pcJIA is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing). Duration of pcJIA will not be imputed if the year of diagnosis is missing.

4.2.2 Incomplete date for the last administration of study medication

No imputation should be performed for missing study medication start dates. This field on the CRF should not be partial or missing.

For partial or missing date of last dose of study medication, the following imputation rules will be applied for the purpose of calculating overall exposure:

If the day is missing (but month and year available), impute the last dose date as the minimum of the last day of the month or the date of last contact reported on the Study Termination CRF; if day and month are both missing (only year available), impute the last dose date as the minimum of the last day of the year or the date of last contact on the Study Termination CRF.

If a study participant died and has a partial or missing last administration date, the date is to set to the date of death. If there is a partial date of last dose and the month/year are prior to the month and year of the date of death, follow partial date imputation rules.

If the last dose date is completely missing and no information could be obtained from data cleaning exercises, the last dose date should be imputed as the date of last contact according to the Study Termination CRF. A review of the data for study participants with completely missing last dose dates should be performed to ensure that the imputation does not result in an unrealistic value for duration of exposure.

Imputed date of last dose dates should only be used for calculation of the duration of exposure. The date as recorded on the CRF should be presented in study participant data listings (no imputed dates should be included in study participant data listings).

4.2.3 Handling of questionnaire data

When relevant, the following rules will apply for analysis of (1) out of range and (2) ambiguous answers (i.e. invalid or unable to interpret answers) to questionnaires completed by study participants or parents/caregivers:

1. In case of an out-of-range answer (i.e., an answer that does not correspond to any possible response proposed in the questionnaire, e. g. “?”, “I don’t know” or any value superior or inferior to the ones specified in the response options): the answer will be scored “missing”.

   However, in case the study participant or parent/caregiver selected one of the proposed responses but added a comment (for instance “6 +++” or “5?”), the response (i.e., "6" or "5") will be retained for scoring but not the comment (i.e., "+++" or "?").

   In the same way, if the study participant or parent/caregiver selected one of the proposed responses but added a value superior or inferior to the ones specified in the response options (for instance “4/5” or “-1/2” on a 5-point scale ranging from 0 to 4), the response corresponding to the possible responses options (i.e., "4" or "2") will be retained for scoring but not the values superior or inferior to the responses options (i.e., "5" or "-1").

2. In case of an ambiguous answer (i.e., multiple responses to a question allowing only a single response, a response marked between two allowed responses):
   a) Multiple responses to a question allowing only a single response:
      i) If half or more responses are marked (i.e., 4 responses marked on a seven-point scale, 3 responses marked on a 5-point scale, 2 responses to a Yes/No item…): the answer will be scored “missing”.
      ii) If less than half of the responses are marked:
         (1) if the responses are NOT adjacent to each other: the answer will be scored “missing”,
         (2) if the responses are adjacent to each other (“2/3” or “2/3/4”, for instance), the more severe score will be retained.
   b) If a response is marked between two allowed responses (for instance, the study participant marked his/her response between 2 and 3 on a 4-point scale allowing only responses 1, 2, 3 and 4): the nearest more severe score will be retained.

4.2.4 Missing adverse event intensity

If the intensity of an AE is missing, then it will be counted as severe for analysis purposes.

4.2.5 Missing adverse event relationship to study medication

If the AE relationship to study medication is missing, then it will be counted as related for analysis purposes.

4.3 Interim analyses and data monitoring

A futility analysis of the PedACR30 response rate was performed after all active study participants who enrolled prior to Protocol Amendment 9 had completed the Week 16 (Visit 8) assessments. If less than 50% of the study population enrolled on the Reduced CZP Dose (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 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 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 pcJIA 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 doses 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 RA0043 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, the doses were 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 the previous study in adult study participants with RA (study C87050).

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; this is referred to as the 2016 Week 24 interim analysis. However, it was then determined that there were deficiencies with the bioanalytical assay used within RA0043, which rendered the PK data for the PopPK analysis and simulations not up to current standards and FDA guidelines; therefore those data were not able to support the regulatory filing.

At the time of Protocol Amendment 9, a new assay had been developed and was used to analyze samples from the 30 new study participants enrolled on the original dose as well as any old samples with sufficient volume remaining. An interim analysis, including all enrolled study participants, for all PK, immunogenicity, safety, and efficacy endpoints was performed after all active study participants, including those enrolled following the implementation of Protocol Amendment 9, completed the Week 24 (Visit 10) assessments; this is referred to as the Updated Week 24 Interim analysis that was used in support of the re-submission of BLA 125160-275.

All statistical tables, listings and figures comprising this SAP will be produced for all future interim and final analyses. Interim data from RA0043 may be summarized to support regulatory submissions, regular safety signal detection monitoring, publications and annual reports to regulatory agencies. For any interim data summary, all available data as of the time of the clinical cut-off date will be included. Study participants ongoing at the time of an interim data summary will be assumed to be treated (ie exposed) up to and including the date of the clinical data cut-off; efficacy data will not be imputed for the closest visit to the clinical snapshot date if the visit is not currently in the clinical database; composite variables will not be calculated if one or more components are unavailable for the visit closest to the clinical snapshot date.

A Data and Safety Monitoring Board (DSMB) will periodically review all emerging safety data. The DSMB consists of 3 external pediatric experts and an external pharmacometrician and is independent of the Sponsor and Investigators. The DSMB members will be informed by the Drug Safety representative (or designee) of all serious adverse events (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.

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

4.4 Multicenter studies

All centers will be pooled and no analysis by center will be performed.

4.5 Multiple comparisons/multiplicity

There will be no formal hypothesis testing in this study; therefore, adjustments for multiplicity are not required.

4.6 Use of an efficacy subset of study participants

No efficacy subset will be defined for this study.

4.7 Examination of subgroups

Most PK, safety and efficacy summaries will be presented by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg). For some safety and efficacy endpoints, such as PedACR30, PedACR50, PedACR70, PedACR90 and incidence of treatment-emergent AEs (TEAEs), results will also be presented by the subgroups as listed below (at times, pooling across all baseline weight groups):

- Baseline age group:
  - 2-<6 years
  - 6-<12 years
  - 12-17 years
- ADAb titer classification (defined in Section 8.2 using RA0043 data):):
  - >= 0 to <= Quartile 1
  - > Quartile 1 to <= Quartile 2 (Median)
  - > Quartile 2 (Median) to <= Quartile 3
  - > Quartile 3
  - Missing
- Concomitant MTX use (distinct from Baseline MTX use presented in Section 6.1 and defined as any concomitant MTX use during the Treatment Period):
  - With Concomitant MTX Use
  - Without Concomitant MTX Use
- Gender
  - Female
  - Male
- Race
  - White
  - Non-white

For subgroup analyses of incidence of ADAb formation and CZP plasma concentrations, results will also be presented by Baseline age group. In addition, summaries will be provided by ADAb titer classification, ADAb participant status classification (defined in Section 8.2), and concomitant MTX use group in combination with Baseline weight group.

As specified in Section 3.3, Baseline for all subgroup analyses will always be the original Baseline (ie, prior to the 1st CZP Dose in this study).

In addition, selected outputs will only be summarized for the Any CZP Dose as specified in each relevant section.

5 STUDY POPULATION CHARACTERISTICS

5.1 Study participant disposition

The number of screened study participants, and reasons for screen failure, will be summarized for all screened study participants.

The number and percentage of study participants who were treated, and who discontinued from the study, along with the discontinuation reasons, will be summarized for the Safety Set by CZP Dose (Reduced, Original and Any) and Baseline weight group as well as by CZP Dose and ADAb titer classification; because the study was closed, every ongoing study participant is discontinued from the study. For the Week 16, the number of study participants completing Week 16 was added. For the Updated Week 24 Interim Analysis, the number of study participants completing Week 24 was added. For the Final Analysis, the number of study participants completing Week 24 and Week 48, respectively, will be added. The disposition of study participants in their initial dosing phase, reduction phase and escalation dosing phase of the study will also be presented. The number of study participants in each analysis set will be presented.

Discontinuations due to AEs will be summarized separately for the SS, and will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups.

The number and percentages of study participants impacted by COVID-19 will be presented for overall and by impact visit, for any reason for all study participants in the SS. This data will be presented in study participant data listings.

Study participant disposition details will be listed, along with a listing of visit dates per study participant. A listing of analysis sets per study participant will also be presented.

5.2 Protocol deviations

The number and percentage of study participants with important protocol deviations will be summarized by type for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose. All important protocol deviations will also be listed.

Note that PK sample exclusion will be implemented due to certain protocol deviations; see Section 3.5. Study participants with at least one PK data exclusion from scheduled visits are summarized and listed.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

All summaries of demographics and Baseline characteristics will be provided for the SS; selected summaries as specified below will also be summarized for the PK-PP set.

6.1 Demographics

Demographics will be summarized for the SS and the PK-PP Set for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. The following continuous variables will be summarized by Baseline weight group and ADAb titer classification: age (years), weight (kg), height (cm), body surface area (BSA) and body mass index (BMI) (kg/m^2) at Baseline.

The following categorical variables will be summarized by Baseline weight group and ADAb titer classification: gender (male, female), racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, Not Hispanic or Latino), Country (Argentina, Brazil, Canada, Chile, Mexico, Russia, and USA), Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), Baseline MTX use group (with, without) and Concomitant MTX Use (with, without). Demographics information will be listed.

6.2 Other baseline characteristics

Baseline characteristics described in this section will be summarized for the SS and the PK-PP Set for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. Time since first diagnosis of pcJIA (or onset of signs and symptoms consistent with a diagnosis of pcJIA for those enrolled after Protocol Amendment 3) will be summarized in years. The time will be calculated as the duration from the date of first diagnosis of pcJIA to Baseline (Week 0 [Visit2]); time since diagnosis will not be calculated when date of diagnosis is missing. The number and percentage of study participants with a history of each of the following pcJIA categories will also be summarized:

- Polyarthritis rheumatoid factor-positive
- Polyarthritis rheumatoid factor-negative
- Extended oligoarthritis
- Juvenile psoriatic arthritis
- Enthesitis-related arthritis

Other baseline characteristics information will be listed.

6.3 Medical history and concomitant diseases

Medical history excluding pcJIA will be summarized by MedDRA® System Organ Class (SOC) and Preferred Term (PT) for Reduced CZP Dose, Original CZP Dose, and Any CZP Dose, and will include the number and percentage of study participants with each PT present. Medical history, JIA history and a glossary of medical history conditions will be listed.

6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the start date of study medication, and also include any medications that continue post-Baseline. Past medications are a subset of prior medications and include prior medications with a stop date before the date of first study medication administration. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For Cimzia, the dosing period is from the date of first dose up to (but not including) 14 days Q2W (or 28 days if Q4W) post last dose if a study participant discontinued early or at end of treatment per protocol. For ongoing study participants, the dosing period is from the date of first dose up to the data cutoff date in interim analyses. Thus a concomitant medication is any medication whose start date is prior to the date of last study medication administration + 14 days Q2W

(or +28 days if Q4W) or data cutoff date, and whose stop date is either missing, or on or after the date of first study medication administration.

All prior medications will be summarized by anatomical therapeutic chemical (ATC) classification level 3 (Pharmacological Subgroup) and WHO-DD generic name. The number of DMARDs stopped prior to Baseline and not re-initiated during the study will be assessed and summarized. For those study participants with these stopped DMARDs, the WHO-DD generic name will be summarized. These summaries will be provided for the SS for the Reduced CZP Dose, the Original CZP Dose and the Any CZP Dose.

Concomitant medications will be summarized for all medications, and separately for DMARDs, systemic corticosteroids, and intra-articular corticosteroid injections. DMARDs and corticosteroids will be identified through ATC codes and medical review. Concomitant medications will be summarized by ATC level 3 and WHO-DD generic name. All summaries of concomitant medications will be provided for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups.

Listings of all prior and concomitant medications will be provided as well as a glossary of the concomitant medications.

Medications related to triamcinolone with the following WHO-DD generic names will be grouped and appear in summaries as "Triamcinolone" with the ATC3 level label of "UCB Triamcinolone ATC3": triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, triamcinolone acetate, triamcinolone diacetate, triamcinolone acetonide dipotassium phosphate.

Medications related to prednisone with the following WHO-DD generic names will be grouped and appear in summaries as "Prednisone" with the ATC3 level label of "UCB Prednisone ATC3": prednisone, prednisolone, prednisolone acetate, prednisolone sodium phosphate, methylprednisolone, methylprednisolone acetate.

Medications related methotrexate with the following WHO-DD generic names will be grouped and appear in summaries as "Methotrexate" with the ATC3 level label of "UCB Methotrexate ATC3": methotrexate, methotrexate sodium.

6.5 Prohibited medications

The following medications are prohibited at any time during the study:

- Nonbiologic DMARDs (other than MTX) and biologic DMARDs (eg, anakinra, rilonacept, etanercept, adalimumab, infliximab, golimumab, rituximab, abatacept, tocilizumab, CZP other than study medication).
- 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.

All efficacy data collected at any assessments after the use of prohibited medications that could impact efficacy will be treated as non-response for binary endpoints in all analyses except where specifically stated otherwise. Prohibited medication use and date of first usage will be determined and documented during the data cleaning meetings prior to the database lock. The number and percentage of study participants who used prohibited medication will be summarized. Prohibited medication use will also be listed.

The +1 day rule was applied to the first usage date when considering its impact on efficacy endpoints. Therefore, only efficacy data with dates after the first usage date of the prohibited medication were impacted (using the non-responder imputation (NRI) method).

All summaries of prohibited medications will be provided for the SS for the Reduced CZP Dose, the Original CZP Dose and the Any CZP Dose. Prohibited medication usage will be listed.

6.6 Rescue medications

Rescue medication use is defined as any initiation of treatment or increase in dose of a medication used to treat pcJIA (in addition to the study drug) that is considered to impact the efficacy analyses. In general, a study participant requiring rescue medication after first administration of study drug is considered as a treatment failure from that time point forward for the purpose of efficacy analyses. Use of some short-acting medications (detailed below) may result in efficacy data at the next scheduled visit being treated as non-response (for categorical data).

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 of oral corticosteroids above Baseline.

The following medications are defined as rescue medication when initiated in the first 56 weeks 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 (based upon study participant's most recent body surface area [BSA] prior to an increase in MTX).
- Initiation of oral corticosteroids, or increase to >10mg or 0.2mg/kg prednisone (or equivalent) per day (whichever is the smaller dose). A study participant's most recent weight prior to an increase of oral corticosteroids will be used to determine if the dosage increase meets the criterion.

BSA will be calculated using Mosteller's formula (Mosteller, 1987):

$$\text{BSA}\,(\text{m}^2) = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$$

The following medications are defined as rescue medication when initiated at any time up to Week 56 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 (365 day) period. When such cases occur, the fourth injection within 12 months will be considered the time point at which rescue medication was initiated for the study participant.
- Intravenous (iv) corticosteroids (any dose), if not used for stress dosing for the purposes of surgery.
- Intramuscular (im) corticosteroids.

Any joint injected with ia corticosteroids will be excluded from the efficacy analysis for a period of 3 months (91 days).

In all cases, any medications recorded in the database will be classified as rescue medication only when pcJIA is listed as the indication for that medication. Rescue medication use and date of first usage will be confirmed during the data cleaning meetings prior to the database lock. Generally, the +1 day rule was applied to the first usage date when considering its impact on efficacy endpoints. Therefore, only efficacy data with dates after the first usage date of the rescue medication were impacted (using the non-responder imputation (NRI) method). The number and percentage of study participants who used rescue medication up to the Week 16 visit and after the Week 16 visit will be summarized separately.

All summaries of rescue medications will be provided for the SS for the Reduced CZP Dose, the Original CZP Dose and the Any CZP Dose. All rescue medication will be listed.

6.7 Short-acting medications

Use of the following medications, which are not rescue medications, only results in efficacy data at the next scheduled visit being treated as missing/non-response:

- Higher than Baseline dose of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, including as needed (PRN) use within 72 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).
- Higher than Baseline dose of analgesics or opioids including PRN use within 48 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).
- Any increase in dose of oral corticosteroids within 7 days prior to scheduled study visit (Note: The increase has to be higher than baseline).

All medication data resulting in efficacy data being treated as missing/non-response will be flagged in the concomitant medication listing.

6.8 Medical procedure history and concomitant medical procedures

All medical procedures, in history or concomitant, will be presented in data listings. The historical procedures with no start date will be assigned to Reduced CZP dose (for those study participants who started the study taking Reduced CZP) or Original CZP dose (for those study participants who started the study taking Original CZP).

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Compliance with study drug administration will be based upon comparing the actual number of injections administered $N_{inj.actual}$ with the expected number of injected administered $N_{inj.expected}$. If a study participants is in derived CRM and is not dosed, then no doses are expected for the compliance calculation. Since study participants are dosed on a Q2W or Q4W schedule, the week number of the visit is used to identify weeks where doses are expected starting with Week 0 (Baseline).

$$CR = \frac{N\ inj.actual}{N\ inj.expected}$$

Descriptive statistics will be presented for the compliance ratio for the SS. Total number of CZP administrations expected differs depending on the loading phase or maintenance phase as well as depends on the different dosing scheduling of the 3 different weight groups. For example, in the Original CZP Dose, a study participant is expected to receive 3 loading CZP administrations and then a maintenance dose of CZP Q2W through the Early Discontinuation/EOT Visit, with the exception of following implementation of Protocol Amendment 4; study participants in the 10 to <20kg weight group change from Q2W to a maintenance dose of CZP Q4W.

In addition, a study participant could change dose (or frequency of dosing if in 10-20kg group) if a study participant crossed into a new weight group, which is considered in the above expected calculations of number of CZP administration If a study participant crossed into the 20 to <40kg weight group, the calculations are updated to reflect the weight change. Note that the dose reduction of ongoing study participants following Protocol Amendment 4 is considered in the calculations. Note also the dose escalation of ongoing study participants following Protocol Amendment 9 is considered in the calculations.

For the Original CZP Dose and Reduced CZP Dose groups, treatment compliance is calculated from the first dose of CZP, for the entire time the study participant is taking study medication up to the dose change. For the results presented for Any CZP Dose, treatment compliance is calculated for the entire time the study participant is taking CZP from first dose until the last dose.

The ratios of compliance will be summarized as a continuous variable and categorically (eg. 0 - <0.80, 0.8 - 1.0 and >1.0). Treatment compliance will be summarized and listed for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose for the final analysis; for

the Updated week 24 Interim Analysis, treatment compliance was summarized and listed for the SS for the Reduced CZP Dose and Original CZP Dose.

8 PHARMACOKINETICS AND IMMUNOLOGICAL PROCEDURES

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

Data from the ECLIA methods, that are within the stability coverage of the assay, will constitute the study's main PK and ADAb evaluations; all reported ECLIA assay results will be listed. As such, PK and ADAb data generated with the original ELISA methods will be reported only in study participant listings.

8.1 CZP plasma concentrations

Only CZP plasma results analyzed using the ECLIA method will be summarized using the participants in the PK-PP set. CZP plasma concentrations are measured at Baseline, Weeks 1, 4, 12, 16, 17, 24, 32, 40, 48, every 24 weeks thereafter, the Early Discontinuation/EOT Visit, and the Final Visit; for study participants enrolled prior to Protocol Amendment 8, samples were not collected after implementation of Protocol Amendment 8. CZP plasma concentrations will be summarized by CZP dose (Original CZP Dose, Reduced CZP Dose) using geometric means, 95% CIs for the geometric mean, geometric CV, and the median, minimum and maximum concentrations.

The geometric CV will be calculated using the following formula:

$$geoCV(\%) = \sqrt{\exp(SD^2) - 1} * 100$$

where SD=standard deviation from the log-transformed data.

For the two CZP Dose groups, summaries at all available visits and plots of plasma concentration results will be produced separately by Baseline weight group, Baseline age group, ADAb participant status classification, ADAb titer classification (see Section 8.2) and, concomitant MTX use in combination with Baseline weight group.

Line-plots will be produced to summarize geometric mean (+/- 95% CI) plasma concentration over time. On each plot there will be separate plot lines for each subgroup category as described above. Plasma concentration will be plotted on both linear and semi-logarithmic scales.

In addition, spaghetti plots of CZP plasma concentrations over time will be produced for individual study participants, separately for each CZP dose group. Plots will be provided by Baseline age group, Baseline weight group, concomitant MTX use in combination with Baseline weight group. In each plot, different symbols/colors will be used to identify subgroup categories.

Concentrations below the limit of quantification of 320.0 ng/mL (0.32µg/mL) (BLQ) will be replaced by the LLOQ divided by 2 for the calculation of descriptive statistics. The geometric

mean and CV% will be derived when at least two-thirds of the concentrations at a certain visit are above the LLOQ and not missing. A minimum of 3 values are required to calculate summary statistics. If only 2 values are available then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-") When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ value replaced by half the LLOQ value". If the criteria are not met, only the maximum and minimum values will be shown. Similarly, the 95% CI of the geometric mean will be calculated if at least 5 samples are available at a time point.

All summaries will be provided for the PK-PP Set. All plasma concentration data will be listed. Concentrations should be listed to the same number of significant figures supplied by the bioanalytical laboratory. For listings concentrations below the limit of quantification should be reported as BLQ (below the limit of quantification).

8.1.1 ECLIA vs ELISA samples

In line with [redacted] response, the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples initially analyzed with the ELISA method were summarized for the Updated Week 24 Interim analysis only.

First, the number and percentage of study participants with at least one PK sample re-analyzed using the ECLIA method (after previous analysis using the ELISA method) were presented. For this percentage, the denominator is the number of study participants with at least one non-missing PK result from the ELISA method, and the numerator is the number of study participants with at least one non-missing PK result from the ECLIA method that had also been analyzed with the ELISA method previously. (Below LLOQ is considered a non-missing result.)

Second, the number and percentage of post-baseline PK samples that were re-analyzed using the ECLIA method (after previous analysis using the ELISA method) were presented. For this percentage, the denominator is the number of post-baseline PK samples with non-missing ELISA results. The numerator is the number of post-baseline PK samples with non-missing ECLIA results where the same PK sample had previously been analyzed using the ELISA method. (Below LLOQ is considered a non-missing result.)

Additionally, the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples analyzed with the ECLIA method (either originally or via re-analysis) were summarized.

First, the number and percentage of study participants with at least one PK sample re-analyzed using the ECLIA method (after previous analysis using the ELISA method) were presented. For this percentage, the denominator is the number of study participants with at least one non-missing PK sample that was analyzed using the ECLIA method (either originally or via re-analysis). The numerator is the number of study participants with at least one non-missing PK result from the ECLIA method for a sample that had also been analyzed with the ELISA method previously. Also, the number and percentage of study participants that did not have any PK sample re-analyzed with the ECLIA method were presented. The denominator is the same, but the numerator is the number of study participants for whom all

non-missing PK results obtained using the ECLIA method were on samples that had never been analyzed using the ELISA method. (Below LLOQ is considered a non-missing result.)

Second, the number and percentage of post-baseline PK samples that were re-analyzed using the ECLIA method (after previous analysis using the ELISA method) were presented. For this percentage, the denominator is the number of non-missing post-baseline PK results that were obtained using the ECLIA method (either originally or via re-analysis). The numerator is the number of those non-missing post-baseline PK results that were obtained by re-analysis with the ECLIA method, after having also been analyzed by the ELISA method previously. Also, the number and percentage of those post-baseline samples that were not re-analyzed with the ECLIA method (out of those analyzed with ECLIA method) were presented. The denominator is the same, but the numerator is the number of those non-missing post-baseline PK results for samples that were only ever analyzed using the ECLIA method. (Below LLOQ is considered a non-missing result.)

All summaries were provided for the Safety Set and presented for Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose and Complete Reduced CZP Dose by baseline weight.

8.2 Anti-CZP antibodies

Immunogenicity will be assessed through listing of individual results by study participant and summary tables and graphs for data generated with the ECLIA method only for the SS. Immunogenicity data will be related to PK (using the PK-PP set), efficacy (using the FAS) and safety (using the SS). All data including those results at the Final Visit will be used for analyses for the entire study.

Anti-drug antibodies will be assessed by a three-tiered approach: screening (positive or negative screen), confirmatory (positive or negative immuno-depletion) and titer assays, using ECLIA methods. Cut points will be determined during assay validation and used by the bioanalytical laboratory to determine the status of ADAb in the test samples as described in Table 8–1.

Table 8–1: ADAb status at sample level

ADAb positive (ADAb+)	Sample values that are ‘positive screen’ and ‘positive immuno-depletion.’
ADAb negative (ADAb-)	Sample values that are either ‘negative screen’ or ‘positive screen’ and ‘negative immuno-depletion’ if corresponding drug levels are equal or below the validated drug tolerance limit of the assay allowing detection of 100 ng/ml ADAb positive control or limit dictated by the ADAb assay and project needs (e.g. 250 ng/ml positive control).

Table 8–1: ADAb status at sample level

ADAb inconclusive	Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' but with corresponding drug levels above the validated drug tolerance limit of the assay allowing detection of 100 ng/ml ADAb positive control or limit dictated by the ADAb assay and project needs (e.g. 250 ng/ml positive control).
Missing	Samples that were not collected per schedule or that could not be tested for ADAb status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc.

Confirmed positive samples will be titrated and the titer will be reported including the minimum required dilution (MRD) of the assay.

- If the titer, for an ADAb level that is 'positive screen' and 'positive immunodepletion' status, is missing, then ADAb status will be considered as positive and no imputation rules apply for the missing titer.
- If the ADAb level is 'positive screen' but no confirmatory result could be determined, then a conservative approach will be used and ADAb status will be considered as positive. No imputation rules apply for the missing titer.

8.2.1 Participant ADAb classification

Study participants from the SS will be classified based on their baseline and treatment-emergent ADAb status (Table 8–2). Classification will be done separately for two time periods of interest: (1) using the study participants' data for the entire study treatment period and (2) using the study participants' data up to and including Week 24 (to facilitate comparison with adult RA data from study RA0138 in the Updated Week 24 Interim Analysis). Baseline ADAb values are defined as the latest (not missing, not inconclusive) measurements up to and including the date of administration of first CZP treatment.

Table 8–2: ADAb status classification at participant level

1.	Baseline ADAb negative and treatment-emergent ADAb negative	Study participants who were negative at Baseline and negative at all sampling points post treatment until the time point of interest Note: study participants with Baseline samples missing and negative ADAb status at all sampling points post treatment are included in this category because participants who are pre ADAb positive are expected to have ADAb positive samples post-dosing.

Table 8–2: ADAb status classification at participant level

2.	Baseline ADAb negative and treatment-emergent induced ADAb positive	Study participants who were negative at Baseline and positive at any sampling point post treatment until the timepoint of interest. This group also included study participants who had a missing Baseline sample with 1 or more positive post treatment samples.
3.	Baseline ADAb positive and treatment-emergent reduced ADAb negative	Study participants who were positive at Baseline and negative at all sampling points post treatment until the timepoint of interest.
4.	Baseline ADAb positive and treatment-emergent unaffected ADAb positive	Study participants who were positive at Baseline and were positive at any sampling point post treatment until the timepoint of interest with all titer values of the same magnitude as Baseline (i.e., less than or equal to a predefined fold increase from the Baseline value of 2.10 which is defined with the validation of the assay).
5.	Baseline ADAb positive and treatment-emergent boosted ADAb positive	Study participants who were positive at Baseline and were positive at any sampling point post treatment until the timepoint of interest with any increased titer values compared to Baseline (greater than a predefined fold increase of 2.10 from Baseline value which is defined within the validation of the assay).
6.	ADAb inconclusive	Study participants who were positive at Baseline and some post-treatment samples until the timepoint of interest were missing or inconclusive, while other post-treatment samples until the timepoint of interest were negative. Note: study participants who were positive at Baseline and all post-treatment samples up to the timepoint of interest were missing or inconclusive are also included in this category.
7.	Treatment emergent ADAb positive	Study participants that were classified as 2 or 5.
8.	Baseline treatment ADAb positive	Study participants who are positive ADAb at baseline, so those classified as 3, 4, 5 or 6.
9.	Missing	Study participants who were negative at Baseline or missing their Baseline assessment, were not positive at any post-Baseline visit, and have at least one missing/or inconclusive post-treatment scheduled assessment (until the timepoint of interest).
10	ADAb positive	Study participants who have a positive ADAb sample status at any timepoint (either Baseline or post dose).

Unscheduled visits including early discontinuation visits (ED) or Final visits with missing results are disregarded. Thus, study participants who had missing ADAb measurements at ED but were ADAb negative at all other post-treatment visits will be classified in category 1

above . Study participants who were negative at Baseline or missing their Baseline assessment and whose only post-treatment ADAb assessment was at ED and was missing will be classified in category 9 above. Study participants who were positive at Baseline and whose only post-treatment assessment was at ED and was missing will be classified in category 6 above. Only positive data at unscheduled visits will be used for classification.

Table 8–3: Aid to Programming ADAb participant status category

ADAb Participant Status Category	Post-Treatment ADAb Sample Status[a]		
Baseline ADAb Sample Status	**Any Positive**	**All Scheduled Negative**	**Some/ All Scheduled Missing[b]**
Missing	2	1	9
Negative	2	1	9
Positive	4 or 5[c]	3	6

[a] Unscheduled (including withdrawal visits) with missing data disregarded. Missing data at other (scheduled) visits considered.
[b] And no positive ADAb samples post-treatment (including positive in either scheduled or unscheduled).
[c] Highest ADAb titer used to determine category.

Post-treatment ADAb sample status categories are mutually exclusive and applied left to right. Thus study participants with both positive and missing post-treatment ADAb samples are considered in the "Any Positive" category.

Time point of interest is the entire treatment period including SFU and the treatment period up to Week 24.

8.2.2 ADAb Titer Classification

To further evaluate the impact of ADAb on PK, efficacy and safety, grouped ADAb titer categories will be defined based on ADAb quartiles (see Section 4.7) observed in the study. Quartiles will be calculated separately for the entire treatment period, and then for the period up to and including Week 24, using each study participant's highest post-treatment ADAb titer (ADAb negative participants will be deemed to have zero titer levels for calculation purposes). If all post-baseline scheduled visit results are Negative, then the study participant will be assigned to the lowest titer classification (lowest quartile); unscheduled visits with missing results are disregarded. If a study participant doesn't have any positive results at post-baseline scheduled visits and any of the results at scheduled visits are deemed missing or inconclusive, then the study participant will be assigned to "Missing".

If interpretation of the grouped titer summaries is inconclusive or results from other studies suggest other groupings, additional post-hoc analyses may be conducted to further investigate.

Immunogenicity will be assessed through summary tables and figures and listing of individual results by study participant on the SS. Summaries will be by CZP dose (Reduced

CZP Dose, Original CZP Dose) and each of Baseline weight group, Baseline age group, and concomitant MTX use, unless specified otherwise.

- All individual study participant-level ADAb results will be listed for all study participants. This will include the screening assay, confirmatory assay, and titer (if applicable). A separate listing showing CZP plasma concentrations, ADAb sample status classification, ADAb participant classification, ADAb titer, and ADAb titer classifications will be produced showing concentration and ADAb data in adjacent columns.
- Number and percentage of study participants with positive, negative, inconclusive or missing ADAb sample status (Table 8–1) will be summarized at each visit and overall and by dose (Original CZP dose, Reduced CZP Dose).
- The number and percentage of study participants in each of the ADAb participant status categories (overall and up to Week 24 as defined according to Table 8–2) will be summarized. Percentages for the denominator will include all the participants that have been classified as per Table 8–2, so including missing /inconclusive participants.

Prevalence and incidence:

- Prevalence of Baseline ADAb positivity: number and percentage of study participants that have Baseline positive ADAb sample status, with the denominator for percentages defined as all participants having an evaluable (not missing, not inconclusive) Baseline ADAb sample.
- Incidence of treatment-emergent ADAb positivity: number and percentage of study participants with either treatment boosted ADAb or treatment induced ADAb, with the denominator for percentages all participants except those categorized as inconclusive or missing (overall for the entire treatment period and then up to and including Week 24).

8.2.3 Time to first occurrence of treatment-emergent ADAb positivity

Study participants will be considered to have an event at the first ADAb sampling time point with ADAb positive status in the entire treatment period if the participant is Baseline ADAb negative or first ADAb sampling time point with fold difference increase from Baseline > 2.1 if participant is Baseline ADAb positive. Study participants who are never treatment-emergent ADAb positive will be censored at the date of the last evaluable (not missing, not inconclusive) ADAb sample or on date of first CZP if no evaluable post-treatment ADAb samples. In case of Baseline ADAb positivity present in more than 10% of the study participants, the table will be produced separately for ADAb participant category 2 (induced) and 5 (boosted).

- Summary tables based on Kaplan-Meier (KM) estimates will be produced.
- Kaplan-Meier plots of time to first treatment-emergent ADAb positivity will also be produced separately for the CZP doses (Original CZP dose, Reduced CZP dose). All available data timepoints will be included.

8.2.4 ECLIA vs ELISA samples

In line with [redacted] response, the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples initially analyzed with the ELISA method were summarized for the Updated Week 24 Interim analysis only.

First, the number and percentage of study participants with at least one ADAb sample re-analyzed using the ECLIA method (after previous analysis using the ELISA method) were presented. For this percentage, the denominator is the number of study participants with at least one non-missing ADAb result from the ELISA method and the numerator is the number of study participants with at least one non-missing ADAb result from the ECLIA method that had also been analyzed with the ELISA method previously. (BLQ is considered a non-missing result.)

Second, the number and percentage of baseline and post-baseline ADAb samples that were re-analyzed using the ECLIA method (after previous analysis using the ELISA method) were presented separately. For the percentage of baseline and post-baseline re-analyzed ADAb samples, the denominator is the number of baseline or post-baseline ADAb samples with non-missing ELISA results, respectively. The numerator is the number of baseline or post-baseline ADAb samples, respectively, with non-missing ECLIA results previously where the same ADAb sample had previously been analyzed with the ELISA method. (Below LLOQ is considered a non-missing result.)

Additionally, the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples analyzed with the ECLIA method (either originally or via re-analysis) were summarized.

First, the number and percentage of study participants with at least one ADAb sample re-analyzed using the ECLIA method (after previous analysis using the ELISA method) were presented. For this percentage, the denominator is the number of study participants with at least one non-missing ADAb sample that was analyzed using the ECLIA method (either originally or via re-analyses). The numerator is the number of study participants with at least one non-missing ADAb result from the ECLIA method for a sample that had also been analyzed with the ELISA method previously. Also, the number and percentage of study participants that did not have any ADAb sample re-analyzed with the ECLIA method were presented. The denominator is the same, but the numerator is the number of study participants for whom all non-missing ADAb results obtained using the ECLIA method were on samples that had never been analyzed using the ELISA method. (Below LLOQ is considered a non-missing result.)

Second, the number and percentage of baseline and post-baseline ADAb samples that were analyzed using the ECLIA method (after previous analysis using the ELISA method) were presented. For this percentage, the denominator is the number of non-missing baseline or post-baseline ADAb results, respectively, that were obtained using the ECLIA method (either originally or via re-analysis). The numerator is the number of those non-missing baseline or post-baseline ADAb results, respectively, that were obtained by re-analysis with the ECLIA method, after having been analyzed by the ELISA method previously. Also, the number and

percentage of those baseline or post-baseline samples, respectively, that were not re-analyzed with the ECLIA method (out of those analyzed with the ECLIA method) were presented. The denominator is the same for each, respectively, but the numerator is the number of those non-missing baseline or post-baseline ADAb results, respectively, for samples that were only ever analyzed using the ECLIA method. (Below LLOQ is considered a non-missing result.)

All summaries were provided for the Safety Set and presented for Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose and Complete Reduced CZP Dose by baseline weight.

8.3 CZP plasma concentrations, anti-CZP antibody titers, and PedACR response

The plots described in this section that include an efficacy endpoint will be generated on the FAS, otherwise on the PK-PPS. Individual participants plots displaying CZP plasma concentrations, ADAb titers, and maximum PedACR response (the highest PedACR response at a given visit) will be produced by visit on the same plot. At each time point, the maximum PedACR response at that visit will be plotted on a linear scale. CZP plasma concentration will be plotted on a (natural) log scale and ADAb titer will be plotted on a log 2 scale. CZP dosing and ADAb inconclusive values will be flagged in this plot. A vertical line will be plotted when dose was changed for the study participant. For each study participant, the category of ADAb participant status and demographic information at baseline (body weight and age) will be displayed.

Multi-panel spaghetti plots of individual participant (natural) log CZP plasma concentration by visit will be produced separately for each CZP dose (Original CZP dose, Reduced CZP dose) and ADAb titer classification and ADAb participant classification for the PK-PPS. Concomitant MTX use will be shown in different line colors and CZP concentrations for which ADAb positive samples were positive will be plotted with a red dot. These individual plots will be repeated replacing CZP plasma concentration with maximum PedACR response (linear scale) on the FAS.

Scatter plots of the plasma CZP concentration at each visit with different colors/symbols depending on ADAb participant classification and ADAb titer classification will be produced separately for the doses (Original CZP Dose, Reduced CZP Dose) for the PK-PPS.

8.4 PopPK analyses

Plasma concentrations will be used to build a PopPK model with the nonlinear mixed-effect modeling (NONMEM) software. Details of the PopPK modeling procedures will be described in a separate data analysis plan. This analysis was generated for the Updated Week 24 Interim analysis only.

9 SAFETY ANALYSES

All study participants in the SS will be included in the safety analyses. In addition to the safety summaries described below, all safety results will be listed by study participant.

9.1 Extent of exposure

Over the course of the RA0043 study, study participants follow one of 5 dosing scenarios for CZP exposure:

Table 9–1: Dosing periods

Starting the study taking:	1st dosing period (of variable length)	2nd dosing period (of variable length)	3rd dosing period (of variable length)
Reduced CZP dose	Reduced CZP (A)		
	Reduced CZP (B) ->	Original CZP (E)	
Original CZP dose	Original CZP (F)		
	Original CZP (G) ->	Reduced CZP (C)	
	Original CZP (H) ->	Reduced CZP (D) - >	Original CZP (J)

The extent of exposure to study drug will be evaluated by summarizing the total amount of CZP received in mg and the total duration of exposure in days. Total duration of exposure will be calculated using this general formula as: the Date of Last Dose of study medication – Date of First Dose of study medication + 14 days if administration of CZP is Q2W, +28 days if administration of CZP is Q4W. Dosing gaps (which occur between 2 CZP doses) are not considered in (does not reduce) the duration of exposure calculation.

Duration of exposure will be calculated as appropriate for each of the following dosing periods:

A: use the general formula;

B: Date of Escalation – Date of First Dose;

C: Date of Last Dose – Date of Dose Reduction +14 or 28 days depending on administration of CZP;

D: Date of Escalation – Date of Reduction;

E: Date of Last Dose – Date of Dose Escalation + 14 or 28 days depending on administration of CZP;

F: use the general formula: see A above

G: Date of Dose Reduction – Date of First Dose;

H: Date of Dose Reduction – Date of First Dose;

J: Date of Last Dose – Date of Dose Escalation + 14 or 28 days depending on administration of CZP

Duration of exposure was calculated as appropriate for each of the following CZP Dose groups for the Updated Week 24 Interim Analysis but will only be calculated for Any CZP Dose, Reduced CZP Dose and Original CZP Doze for the final analysis:

- Any CZP Dose: includes the exposure to all CZP doses for all treated study participants; the exposure period is calculated using the general formula.
- Reduced CZP Dose: includes period of exposure to the Reduced CZP Dose for all study participants enrolled on the Reduced CZP dose; use the following formulas:
  - Period A - for study participants without dose escalation; and
  - Period B - for study participants with dose escalation.
- Original CZP Dose: includes period of exposure to the Original CZP Dose for all study participants enrolled on the Original CZP Dose; use the following formulas:
  - Period F - for study participants without dose reduction;
  - Period G - for study participants with dose reduction and without dose escalation; and
  - Period H - for study participants with dose reduction and dose escalation.
- Complete Reduced CZP Dose: includes all periods of exposure to Reduced CZP Dose for all study participants (periods A, B, C and D); use the following formulas:
  - Period A - for study participants enrolled on Reduced CZP Dose without dose escalation;
  - Period B - for study participants enrolled on Reduced CZP Dose with dose escalation;
  - Period C - for study participants enrolled on Original CZP Dose with dose reduction and without dose escalation; and
  - Period D - for study participants enrolled on Original CZP Dose with dose reduction and dose escalation.
- Complete Original CZP Dose: includes all periods of exposure to Original CZP dose for all study participants (periods E, F, G H and J); use the following formulas:
  - Period E - for study participants enrolled on Reduced CZP Dose with dose escalation;
  - Period F - for study participants enrolled on Original CZP Dose without dose reduction;
  - Period G - for study participants enrolled on Original CZP Dose with dose reduction and without dose escalation; and
  - Period H+J - for study participants enrolled on Original CZP Dose with dose reduction and dose escalation.

9.1.1 Subject time at risk

Subject time at risk will also be calculated. Subject time at risk represents the time a study participant is at risk for having an AE while taking CZP. Subject time (in days) at risk will generally be calculated using this general formula: (date of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). However, the calculation of subject time at risk will be modified for study participants who change from Original CZP Dose to Reduced CZP Dose, or who dose escalate from Reduced

CZP Dose to the Original CZP Dose; the subject time at risk will further be modified for study participants who have dosing gaps > 70 days during the study – eg. meaning if a study participant has 100 consecutive day dosing gap, only the first 70 days will be included in the subject time at risk. For the period of exposure prior to a dose change, subject time at risk ends on the date of dose change (ie, do not add 70 days). For the period of exposure on the final CZP dose for a study participant, time at risk should include the additional 70 days. Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Subject time at risk will be calculated as appropriate for each of the following CZP dosing periods:

A: use the general formula;

B: Date of Escalation – Date of First Dose;

C: Date of Last Dose – Date of Dose Reduction +70 days;

D: Date of Escalation – Date of Reduction;

E: Date of Last Dose – Date of Dose Escalation + 70 days;

F: use the general formula;

G: Date of Dose Reduction – Date of First Dose;

H: Date of Dose Reduction – Date of First Dose;

J: Date of Last Dose – Date of Dose Escalation + 70 days;

Subject time at risk was calculated as appropriate for each of the following CZP Dose groups for the Updated Week 24 Interim Analysis but will only be calculated for Any CZP Dose, Reduced CZP Dose and Original CZP Doze for the final analysis:

- Any CZP Dose: includes the time at risk to all CZP doses for all treated study participants; the time at risk is calculated using the general formula.
- Reduced CZP Dose: includes time at risk during the exposure to the Reduced CZP Dose for all study participants enrolled on the Reduced CZP dose up to the first dose change; use the following formulas:
  - Period A - for study participants without dose escalation; and
  - Period B - for study participants with dose escalation.
- Original CZP Dose: includes time at risk during the exposure to the Original CZP Dose for all study participants enrolled on the Original CZP Dose up to the first dose change; use the following formulas:
  - Period F - for study participants without dose reduction;
  - Period G - for study participants with dose reduction and without dose escalation; and
  - Period H - for study participants with dose reduction and dose escalation.

- Complete Reduced CZP Dose: includes time at risk during all periods of exposure to Reduced CZP Dose for all study participants (periods A, B, C and D); use the following formulas:
  - Period A - for study participants enrolled on Reduced CZP Dose without dose escalation;
  - Period B - for study participants enrolled on Reduced CZP Dose with dose escalation;
  - Period C - for study participants enrolled on Original CZP Dose with dose reduction and without dose escalation; and
  - Period D - for study participants enrolled on Original CZP Dose with dose reduction and dose escalation.
- Complete Original CZP Dose: includes all time at risk during all periods of exposure to Original CZP dose for all study participants (periods E, F, G H and J); use the following formulas:
  - Period E - for study participants enrolled on Reduced CZP Dose with dose escalation;
  - Period F - for study participants enrolled on Original CZP Dose without dose reduction;
  - Period G - for study participants enrolled on Original CZP Dose with dose reduction and without dose escalation; and
  - Period H+J - for study participants enrolled on Original CZP Dose with dose reduction and dose escalation.

The extent of study drug exposure will be summarized for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. Exposure over time will be presented as follows: >0 months, ≥6 months, ≥12 months, ≥24 months, ≥36 months, ≥48 months, ≥60 months, ≥72months, ≥84 months, and ≥96 months. In line with [redacted] response, the extent of study drug exposure as well as exposure over time were presented by Complete Original CZP Dose and Complete Reduced CZP Dose.

Study medication administration will be listed.

9.1.2 Updated Week 24 Interim Analysis and other interim analyses

For interim analyses such as for the SSD, DSMB and the Updated Week 24, the following modifications were made to more accurately calculate exposure and time at risk.

For an interim analysis with a database cutoff date,

- if the study participant is ongoing, the exposure calculation was database cutoff date – date of first dose of study medication + 1 day. No data was presented in the analyses that was dated after the database cutoff date
- if the study participant was ongoing, the time at risk calculation was database cutoff date – date of first dose of study medication + 1 day.

- if the study participant had discontinued from the study >28 days before the database cutoff date and had Q4W dosing at the time of study discontinuation, then the exposure was date of last dose of study medication – date of first dose of study medication + 28 days
- if the study participant had discontinued from the study ≤28 days before the database cutoff date and had Q4W dosing at the time of study discontinuation, then the exposure was database cutoff date – date of first dose of study medication + 1 day
- if the study participant had discontinued from the study >14 days before the database cutoff date and had Q2W dosing at the time of study discontinuation, then the exposure was date of last dose of study medication – date of first dose of study medication + 14 days
- if the study participant had discontinued from the study ≤14 days before the database cutoff date and had Q2W dosing at the time of study discontinuation, then the exposure was database cutoff date – date of first dose of study medication + 1 day
- if the study participant had discontinued from the study >70 days before the database cutoff date, then the time at risk was date of last dose of study medication – date of first dose of study medication + 70 days
- if the study participant had discontinued from the study ≤70 days before the database cutoff date, then the time at risk was the database cutoff date – date of first dose of study medication + 1 day.

9.2 Adverse events

Only treatment emergent adverse events (TEAE) will be included in the summary tables. Treatment emergent AEs are defined as AEs starting on or after the first administration of CZP and up to 70 days after the last (most recent) dose of study medication; then only the adverse events occurring up to 70 days after the last (most recent) dose of study medication will be counted as treatment emergent; all other adverse events occurring after first dose will not be flagged as treatment emergent. AEs that are pre-treatment or that start more than 70 days after the last (most recent) dose of study medication will be in the listing but excluded from summaries.

A glossary for the TEAE listing will detail the verbatim terms that are coded to each SOC, HLT, and PT.

Treatment-related TEAEs are those with relationship to study medication of "Related" or "Possibly related" or those with a missing relationship. Severe TEAEs are those with an intensity of "Severe" or those with a missing intensity.

All TEAE summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. TEAEs occurring on the day of dose reduction or dose escalation, respectively, will be summarized in the dose groups that it appears.

The overview of the incidence of TEAEs, overall and by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg), will include the number of events and number of study participants and percentage of study participants with:

- Any TEAE
- Any serious TEAE
- Any treatment-related TEAE
- Any severe TEAE
- Any TEAE leading to permanent withdrawal of IMP
- Any TEAE leading to discontinuation
- All deaths
- Any TEAE leading to death

The overview of the incidence of TEAEs will also be presented by the following subgroups:

- Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years),
- concomitant MTX use,
- gender,
- race,
- ADAb participant status classification, and
- ADAb titer classification pooling across all Baseline weight groups.

The incidence and event rate (per 100 subject-years) of TEAEs will be presented as follows:

- All TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group
- All TEAEs by primary SOC, HLT, and PT by Baseline age group
- All TEAEs by primary SOC, HLT, and PT by concomitant MTX use
- All TEAEs by primary SOC, HLT, and PT by ADAb titer classification
- All TEAEs by primary SOC, HLT, and PT by ADAb participant status classification
- All serious TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group
- All TEAEs leading to study drug discontinuation by primary SOC, HLT, and PT, overall and by Baseline weight group
- All TEAEs leading to death by primary SOC, HLT, and PT, overall and by Baseline weight group
- Injection reaction TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group, further subdivided into injection site reactions and systemic reactions, with systemic reactions further subdivided into acute vs. delayed systemic reactions

The incidence of TEAEs will be presented as follows:

- Injection reaction TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group, further subdivided into injection site reactions and systemic reactions, with systemic reactions further subdivided into acute vs. delayed systemic reactions

- All TEAEs by primary SOC, PT, and intensity, overall and by Baseline weight group
- All TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- All serious TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- All non-serious TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- All fatal TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- TEAEs occurring in at least 5% of study participants by primary SOC, HLT, and PT, overall and by Baseline weight group
- Non-serious TEAEs occurring in more than 5% of study participants by primary SOC and PT, overall and by Baseline weight group

Incidence tables summarizing TEAEs will include the number of TEAEs, number of study participants experiencing the TEAEs and percentage of study participants with the TEAE (all occurrences of the same event will be counted under the number of TEAEs but the study participant will only be counted once).

For disclosure on public registries (eg, ClinicalTrials.gov), information from the incidence tables of TEAEs and treatment-emergent SAEs will be published.

For the Updated Week 24 Interim Analysis only, in line with [redacted] response, incidence tables of TEAEs were presented by primary SOC, HLT, and PT, overall and Baseline weight group by Original CZP, Reduced CZP, Any CZP, Complete Original CZP and Complete Reduced CZP doses. Also, incidence and event rate tables of TEAEs up to Week 24 were presented by primary SOC, HLT, and PT, overall and by Baseline weight group for Reduced CZP and Original CZP dose groups.

For the final analysis, incidence tables of TEAEs will be presented by primary SOC, HLT, and PT, overall and by Baseline weight group by Original CZP, Reduced CZP and Any CZP doses. The incidence and event rate tables of TEAEs up to Week 24 will not be presented for the final analysis.

Incidence and event rate tables will include the descriptive statistics on the incidence table but also include the exposure-adjusted incidence rate (EAIR) with associated 95% confidence interval, and the exposure-adjusted event rate (EAER).

For EAIR, the numerator will be the total number of study participants experiencing a particular TEAE. The denominator will be 100 subject-years, ie, the total summation of individual subject-years at risk up to the first occurrence of the given TEAE for study participants with that TEAE, plus the total subject-years at risk for those study participants not experiencing that TEAE, divided by 100. Details regarding calculation of subject-years at risk are described in Section 9.1. EAIR will be presented with exact 95% confidence intervals based on the link between the chi-square distribution and the Poisson distribution (Ulm, 1990).

For EAER, the numerator will be the number of TEAEs including repeat occurrences in individual study participants. The denominator will be in 100 subject-years (total summation of individual subject-years at risk divided by 100). No confidence interval will be computed.

Listings:

- Individual study participant numbers experiencing a given adverse event, grouped by SOC, PT, intensity, and relation to study drug
- Individual study participant numbers experiencing a serious treatment emergent adverse event, grouped by SOC, PT, intensity, and relation to study drug
- Individual study participant numbers experiencing a TEAE leading to study drug discontinuation, grouped by SOC, PT, intensity and relation to study drug
- Individual study participant numbers experiencing an AE leading to death, grouped by SOC, PT, intensity and relation to study drug

9.2.1 TEAEs of interest

The following are TEAEs of interest for this study and will be summarized in incidence and event rate tables (ie will include the number of events, the number and percentage of study participants with an event, the EAIR with associated 95% CIs and the EAER) as described below:

1) Serious infections, including opportunistic infections. Serious infections will be summarized using the previously described All SAEs table. No separate table is planned. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.

2) Malignancies, including lymphoma. These will be presented in 2 tables using the criteria SMQ = “Malignant or unspecified tumours” and its subset, SMQ=”Malignant tumours”, respectively.

3) Congestive heart failure. These will be manually identified by the study physician from the previously described All TEAEs table. In addition, major adverse cardiac events (MACE) will be presented in a table. using UCB-defined search criteria and will include fatal and serious non-fatal myocardial infarction, cerebrovascular events and congestive heart failure.

4) Demyelinating-like disorders. These will be presented in a table based on the SMQ=”Demyelination” in the TEAEs.

5) Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = “Haematopoietic cytopenias” in the subset of SAEs.

6) Serious bleeding events. These will be presented in a table using the criteria SMQ = “Haemorrhage terms (excl laboratory terms)” in the subset of SAEs.

7) Lupus and lupus-like illness. These will be manually identified by the study physician from the previously described All TEAEs table and not tabulated separately.

8) Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from the previously described All SAEs table and not tabulated separately.

9) Hepatic events. These will be summarized in a table that includes all TEAEs in the following SMQs: Cholestasis and jaundice of hepatic origin; hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions; hepatitis, noninfectious; liver-related investigations, signs and symptoms; liver-related coagulation and bleeding disturbances.

10)Hypersensitivity reactions. These will be determined from all TEAEs that either emerged on the same day as or next day after the administration of study medication injection and summarized in a table. The PTs are: administration site hypersensitivity, documented hypersensitivity to administered product, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis, infusion site hypersensitivity, injection site hypersensitivity, medical device site hypersensitivity, type II hypersensitivity, type IV hypersensitivity reaction.

11) Anaphylactic reactions. These will be determined from all TEAEs that either emerged on the same day as or next day after the administration of study medication injection. Anaphylactic reactions will be summarized in a table using UCB-defined search criteria.

Further information regarding search criteria and algorithms is provided in the guidance document "AEs of Interest – Cimzia Program".

9.2.2 AE of special interest

Potential Hy's Law is an AE of special interest for this study; the definition is below. The occurrence of this AE of special interest is dependent upon laboratory parameters, given that, the associated analysis of these AEs will be described in the Clinical laboratory evaluations section, PDILI paragraph in Section 9.3.

Potential Hy's Law, defined as ≥3xULN alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (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.

9.2.3 Covid vaccine sensitivity analysis

A summary of the incidence and event rate (per 100 subject-years) of TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group will be presented which will exclude TEAEs occurring up to and including 7 days from the date of covid vaccination. The list of the PTs of these TEAEs to be excluded if reported with Mild or Moderate intensity are:

Table 9–2: Covid vaccination related adverse events for sensitivity analysis

ARTHRALGIA	INJECTION SITE INDURATION
AXILLARY SWELLING	INJECTION SITE PAIN

AXILLARY TENDERNESS	INJECTION SITE WARMTH
BACKACHE	MYALGIA
BODY TEMPERATURE INCREASED	NAUSEA
CHILLS	PRURITUS
DIARRHOEA	RASH
FEVER	TENDERNESS
HEAD DISCOMFORT	URTICARIA
HEADACHE	VOMITING
INJECTION SITE ERYTHEMA	

9.3 Clinical laboratory evaluations

All laboratory summaries described in this section will be provided for Reduced CZP Dose, Original CZP Dose, and Any CZP Dose and by Baseline weight group. All laboratory data will be listed.

Descriptive statistics for observed values and change from Baseline will be presented for each visit for the following hematology and biochemistry parameters:

- Hematology: RBC, hemoglobin, hematocrit, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
- Biochemistry: sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphorus, creatinine kinase, glucose, creatinine, uric acid, urea, total protein, albumin, ALP, gamma glutamyl transferase (GGT), AST, ALT, lactate dehydrogenase, bilirubin, and total cholesterol.

The following urinalysis parameters will be tested locally only: pH, protein, glucose, and blood. If abnormalities are found from the dipstick test, microscopic analysis (WBC, RBC, casts, crystals, and bacteria) will be performed, and these results will be listed. A summary of the shift from Baseline to end of treatment will also be provided for hematology and biochemistry parameters. Results will be classified as low, normal, or high based on the normal ranges provided by the central laboratory.

A summary of the incidence of markedly abnormal laboratory results by visit will be presented for hematology and biochemistry parameters. Details of markedly abnormal values will be listed by study participant and parameter for hematology and biochemistry variables for which there is at least 1 markedly abnormal result recorded. Definitions of markedly abnormal values are adopted from the UCB Therapeutic Area: Central Nervous System : Clinical and Laboratory Markedly Abnormal (MA) Values and are given below Table 9–3 for markedly abnormal hematology values and Table 9–4 for markedly abnormal biochemistry values).

Table 9–3: Definitions of Markedly Abnormal Hematology Values

Parameter (Unit)	Age Range	Abnormal Definition	
		Low	High
Hematocrit (%)	<2y	≤27	>45
	2y-<18y	≤29	>47
	≥18y	≤85% of LLN	≥115% of ULN
Hemoglobin (g/L)	<2y	≤90	>150
	2y-<18y	≤95	>160
	≥18y	≤85% of LLN	≥115% of ULN
WBC/Leukocytes (G/L)	<12y	<3.5	>15.0
	≥12y	<3.0	>12.0
Neutrophils Absolute (G/L)	>1m	<1.5	NA
Lymphocytes (%)	<6m	≤30.0	NA
	6m-<6y	≤22.0	NA
	6y-<18y	≤12.0	≥80.0
	≥18y	≤10.0	≥80.0
Basophils (%)	>1m	NA	≥3.0
Eosinophils (%)	>1m	NA	≥10.0
Monocytes (%)	>1m	NA	≥20.0
Platelets (G/L)	>1m	≤100	>600
RBC/Erythrocytes (T/L)	<2y	<3.0	NA
	≥2y	<3.5	NA
y=year; m=month; LLN=lower limit of normal; ULN=upper limit of normal.			

Table 9–4: Definitions of Markedly Abnormal Biochemistry Values

Parameter (Unit)	Age Range	Abnormal Definition	
		Low	High
AST(SGOT) (U/L)	<14y	NA	>180
	≥14y	NA	>144
ALT(SGPT) (U/L)	1y-<18y	NA	>90

Table 9–4: Definitions of Markedly Abnormal Biochemistry Values

Parameter (Unit)	Age Range	Abnormal Definition	
		Low	High
	≥18y	NA	>123
Alkaline Phosphatase (U/L)	<4y	NA	>690
	4y-<10y	NA	>834
	10y-<17y	NA	>1174
	≥18y	NA	>432 (F) >933 (M)
GGT (U/L)	<6m	NA	>522
	6m-<1y	NA	>279
	1y-<13y	NA	>66
	13y-<18y	NA	>126
	≥18y	NA	>255
Total Bilirubin (umol/L)	>1m	NA	≥25.656
Total Protein (g/L)	2m-<1y	<30	>100
	≥1y	<43	>100
Albumin (g/L)	<1y	<16	>60
	≥1y	<24	>70
Urea (mmol/L)	<1y	NA	>7.014
	≥1y	NA	>10.02
Creatinine (umol/L)	1y-<10y	NA	>79.56
	10y-<16y	NA	>123.76
	≥16y	NA	>141.44
Calcium (mmol/L)	<1y	<1.725	>3.05
	1y-<18y	<1.85	>2.925
	≥18y	≤1.975	≥2.775
Lactate dehydrogenase (LDH) (IU/L)	2-17y		>1300
Phosphorus (mmol/L)	<1y	<0.5814	>2.6486
	≥1y	<0.5814	>2.3902
Potassium (mmol/L)	<1y	<3.0	>6.5

Table 9–4: Definitions of Markedly Abnormal Biochemistry Values

Parameter (Unit)	Age Range	Abnormal Definition	
		Low	High
	≥1y	<3.0	>5.8
Sodium (mmol/L)	>1m	≤130	≥150
Glucose (mmol/L)	>1m	<2.775	>9.99
Total Cholesterol (mmol/L)	1y-<18y	NA	>6.475
	≥18y	NA	>7.77
Uric Acid (umol/L)	<1y	NA	>457.996
	1y-<13y	NA	>386.62
	13y-<18y	NA	>511.528
	≥18y	NA	>404.464 (F) >571.008 (M)
Creatine Kinase (CPK) (IU/L)	2-17y		>600
y=year; m=month; F=female; M=male.			

Reference: Based on CTCAE version 5.0

PDILI IMP discontinuation criteria as outlined in the Appendix of Protocol Amendment 9 will be evaluated at all laboratory assessments, for all study participants. The number and percentage of study participants meeting PDILI criteria will be presented. The following criteria will be presented:

- AST or ALT ≥ 3xULN and Total Bilirubin < 2xULN
- AST or ALT ≥ 3xULN and Total Bilirubin ≥ 2xULN
- AST or ALT ≥ 3xULN and Total Bilirubin ≥ 2xULN and Alkaline Phosphatase < 2xULN (Hy's Law if all criteria met at the same visit)
- AST or ALT ≥ 5xULN

Any data that meets the PDILI criteria or is captured regarding PDILI will be listed. Any data that is captured as being a suspected hepatic event will be listed.

A listing of when blood and urine samples were taken as well as serum pregnancy tests were performed will also be produced.

9.4 Vital signs, physical findings, and other observations related to safety

9.4.1 Vital Signs

Vital signs will be measured within approximately 15 minutes prior to dosing, and in addition (following implementation of Protocol Amendment 3), pulse and blood pressure only will be

measured approximately 30 minutes after dosing with study medication. Study participants should be sitting for at least 5 minutes prior to and during the collection of blood pressure and pulse rate measurements. Vital signs to be collected are pulse, systolic/diastolic blood pressure measurement, and temperature.

For pre-dose measurements, if more than one results appears for a specific visit, then the pre-dose results are averaged. The same will occur for post dose measurements. All data will be listed, including the averages. If measurements are labeled as pre-dose in the CRF, but when compared to dosing, it is actually post-dose, the analysis label will reflect a post dose measurement. The same will occur for post-dose measurements.

Descriptive statistics for observed values and change from pre-dose to post-dose pulse and blood pressure when available, will be presented for each visit for each vital sign parameter.

Vital signs summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose) and by Baseline weight group.

A summary of the incidence of markedly abnormal vital signs results by post-baseline scheduled visit will be presented for temperature, blood pressure, and pulse rate parameters. Details of markedly abnormal values will be listed by study participant and parameter for which there is at least 1 markedly abnormal result recorded. Definitions of markedly abnormal values are given below in Table 9–5.

Markedly abnormal high temperature is >40.0 degrees Celsius (>104.0 degrees Fahrenheit) while a markedly abnormal low temperature is 32 – 35 degrees Celsius (89.6 – 95 degrees Fahrenheit). Vital signs data will be listed, including the flagging of markedly abnormal values.

Table 9–5: Definitions of Markedly Abnormal Vital Signs Values

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	3y - <12y	<60 >130
	12y - <17y	≤50 ≥120
	≥17y	<60 >100
Systolic Blood Pressure (mmHg)	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	<90 >140 >160
	3y - <12y	<50 >80

Parameter	Age Range	Abnormality Criteria
Diastolic Blood Pressure (mmHg)	12y - <17y	≤50 ≥105
	≥17y	<50 >90 >100

9.4.2 Other safety variables

9.4.2.1 Height and weight

Descriptive statistics for Baseline and post-Baseline values at selected time points of interest, and change from Baseline for selected time points for percentile height-for-age and percentile weight –for-age (based on growth curves and percentile calculation methods published by CDC for children age 2-20 that was available on 27April 2016 at http://www.cdc.gov/growthcharts/clinical_charts.htm) will be summarized by Baseline age group and gender for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose. All weights and heights will also be listed.

9.4.2.2 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, for those who have not reached Tanner stage V. A summary of shift table of Tanner stages from baseline to relevant post-treatment visit(s) (48 week, 96 week, etc) by age and gender will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose. Overall Tanner stage at each visit is derived as the minimum stage of the 2 components. If one component is missing at a visit, then the overall stage will be set to missing for that visit.

No imputation of missing data will be implemented. Tanner stages will be listed by visit for each study participant.

9.4.2.3 Physical examination

Physical examination findings will be recorded in the CRF only at Screening. Details of subsequent physical examinations should be recorded in the source documentation. Clinically relevant changes in subsequent physical examinations will be recorded as AEs.

Physical examination findings at Screening will be listed.

9.4.2.4 Reproductive potential and birth control

The 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. If the study participant is of reproductive potential and is sexually active, the method of birth

control used will be recorded. Reproductive potential and birth control information will be listed by visit for each study participant.

9.4.2.5 Autoantibodies

Autoantibodies (ANA and anti-dsDNA) will be assessed at Baseline, Weeks 16 and 48, and Early Discontinuation/EOT. For ANA antibodies, normal corresponds to dilutions of <1:160 and antibodies present corresponds to dilutions of 1:160 or higher. A summary of the maximum shift from the Baseline to anytime while on CZP treatment will be summarized for both the ANA and anti-dsDNA antibodies.

All autoantibodies summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose) and by Baseline weight group. All autoantibody assay data will be listed.

9.4.2.6 Tuberculosis assessments

A tuberculin purified protein derivative (PPD) skin test, which is not mandatory for all study participants, will be done ≤3months before Screening, at Week 48, and then yearly thereafter. PPD tests should be read by a trained health care worker between 48 and 72 hours after injection. QuantiFERON TB GOLD testing at Screening 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 BCG vaccination.

Following implementation of Protocol Amendment 3, 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.

The TB questionnaire will be completed twice at each visit, once by the study participant and once by the caregiver.

Tuberculosis testing, chest radiograph results and questionnaire results will be listed for each study participant.

10 EFFICACY ANALYSES

Efficacy will be analyzed using the FAS. All efficacy results will be summarized overall and by Baseline weight group and will be provided for the Original CZP Dose, Reduced CZP Dose, and the Any CZP Dose. For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and ADAb titer classification will be presented pooling across all weight groups unless otherwise specified. In addition, selected summaries will also be presented by gender and race.

In addition to the efficacy summaries described below, all efficacy results will be listed by study participant data listings.

In Section 10, the analyses described for all efficacy variables below will be generated for the final analysis. For the Updated Week 24 Interim analysis, only efficacy data up to and including Week 24 was presented in the analyses described in Section 10 for the following variables:

- PedACR30/50/70/90
- Number of joints with active arthritis
- Number of joints with limitation of range of motion
- Physician's Global Assessment of Disease Activity
- Childhood Health Assessment Questionnaire
- Parent's Global Assessment of Overall Well-Being
- C-Reactive protein
- Juvenile Arthritis Disease Activity Score 71-joint

For the Updated Week 24 Interim analysis, all reported data for other efficacy variables were listed only; any calculations described for the final analysis were not performed. These included the following variables:

- Clinically Inactive Disease
- CRM
- Duration of Morning Stiffness
- Parent's Assessment of Arthritis Pain
- Faces Pain Scale Revised
- JIA Pain
- Fatigue Assessment Scale, and
- Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey.

10.1 Statistical analysis of the primary efficacy variable

The primary objective of this study is to evaluate PK and safety; therefore there is no primary efficacy variable.

10.2 Statistical analysis of the secondary efficacy variables

The PedACR30, PedACR50, PedACR70, and PedACR90 clinical response rates are based on a 30%, 50%, 70%, and 90% or greater improvement from Baseline in at least 3 of the 6 core set measures with no more than 1 of the remaining worsened by >30%. PedACR30, PedACR50, PedACR70, and PedACR90 clinical response will be calculated by statistical programming based upon the core set measures. The 6 core set measures are:

- Number of joints with active arthritis (see Section 10.3.2.1 for definition)
- Number of joints with limitation of range of motion (see Section 10.3.2.2 for definition)

- Physician's Global Assessment of Disease Activity VAS
- CHAQ completed by parent or caregiver
- Parent's Global Assessment of Overall Well-Being VAS
- Acute phase reactant CRP

If 2 or more core set measures are missing, the corresponding PedACR30, PedACR50, PedACR70 and PedACR90 responses will also be treated as missing. For core set measures with values of 0 at Baseline, the percentage change from Baseline cannot be calculated for improvement, however, for worsening, the following rules will be applied:

- If Baseline number of joints for active arthritis or with LoM was 0, an increase to at least 2 joints is required;
- If Baseline Global Assessment scores are 0, worsen to a score at least 20 is required to be considered as a worsening of at least 30%;
- If Baseline CHAQ score is 0, worsen to a score of at least 0.125 is required to be considered as a worsening of at least 30%;

In addition, CRP is used in the determination of worsening or improvement only when either the Baseline value and/or the visit values are higher than the upper limit of the normal reference range (ie, >8mg/L).

The frequency and percentage of study participants achieving a PedACR30, PedACR50, PedACR70, and PedACR90 response and associated 95% exact binomial CIs will be summarized for Week 16 (as well as for the other visits). Results will be presented overall and by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg), as well as by Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), concomitant MTX use, ADAb titer classification, gender and race pooling across all Baseline weight groups.

Plots will be produced to show the percentage of PedACR30/50/70/90 responders by visit and ADAb titer classification.

10.3 Analysis of other efficacy variables

Continuous endpoints will be summarized using observed case, as for the Physician's Global Assessment of Disease Activity.

10.3.1 PedACR30, PedACR50, PedACR70, and PedACR90

The PedACR30, PedACR50, PedACR70, and PedACR90 response rates as compared to Baseline at every visit (including Week 16) except the Final Visit will be summarized. Plots of PedACR30, PedACR50, PedACR70 and PedACR90 response rates (combined on the same plot) by visit will be provided by the same CZP dose groups as in the summary tables above, overall and by Baseline weight group.

PedACR30, PedACR50, PedACR70, and PedACR90 response rates will also be summarized by Baseline age group, concomitant MTX use, ADAb titer classification, gender and race pooling across all Baseline weight groups.

Plots will be produced to show the percentage of PedACR30/50/70/90 responders by visit and ADAb titer classification.

10.3.2 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 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

Joint assessment will be based on a 2-point scale as unaffected (Grade 0) and affected (Grade 1). If a joint is not evaluable at Baseline, then that joint is set to missing throughout the study.

10.3.2.1 Joints with active arthritis

The number of joints with active arthritis is the number of joints with:

- Grade 1 for swelling, or
- Grade 1 for LOM with POM, or
- Grade 1 for LOM with tenderness.

The count of joints with active arthritis is based on 71 of 75 joints from the PRINTO/PRCSG standard joint examination. Although 75 joints are included in the PRINTO/PRCSG standard joint examination, bilateral sacroiliac joints are not assessed for swelling or LOM and as a result are not included in the active arthritis count. Additionally, cervical, thoracic and lumbar joints are treated as a single composite joint in the computation of the number of joints with active arthritis. If 1 or more of these 3 spinal joints satisfy the criteria for joints with active arthritis, then the composite joint will be counted as a joint with active arthritis.

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. Joints treated with an intra-articular corticosteroid are also not assessed.

Eleven joints are not assessed for both LOM and swelling, and consequently active arthritis status will be based on the available partial assessments performed for those joints. Bilateral sternoclavicular and acromioclavicular joints are not assessed for LOM and as a result the

joints with active arthritis status will be based only on swelling. Conversely, bilateral hip and subtalar joints are not assessed for swelling and as a result active arthritis status will be based only on LOM. Cervical, thoracic and lumbar spine joints are also not assessed for swelling and as a result active arthritis status will be based only on LOM.

In addition, joints with completely missing assessments that are otherwise expected to be evaluated will be treated as missing with respect to joints with active arthritis status. For example, MCP joints should be assessed for swelling, POM, tenderness and LOM at all visits. If all assessments for a given MCP joint are missing at a given visit, the joint will be treated as missing and will not be included as an assessed joint in the calculation of the active arthritis count. However, if partial data are available for a given joint, and the available data are sufficient to indicate that a given joint has active arthritis (eg, joint is assessed as swollen, but LOM and/or POM assessment is missing), the joint will be classified as a joint with active arthritis. However, if only partial data are available, and the partial data indicate that the joint is unaffected, the joint will also be treated as missing for the determination of the number of joints with active arthritis at that time point.

The active arthritis count will be weighted by the number of joints assessed:

$$AAC = \frac{71 * \sum_{i=1}^{n} JAA}{\sum_{i=1}^{n} JA}$$

where AAC=active arthritis count, JAA=number of joints with active arthritis, and JA=number of joints assessed. If more than 50% of the joints are not assessed, then the count of joints with active arthritis will be set to missing.

The number of joints with active arthritis and change from Baseline in number of joints with active arthritis will be summarized (observed case) for every visit except the Final Visit.

10.3.2.2 Joints with limitation of range of motion

The assessment for LOM is made on 67 joints from the PRINTO/PRCSG standard joint examination. The sternoclavicular, acromioclavicular, and sacroiliac joints are excluded. Cervical, thoracic and lumbar joints are treated as a single composite joint; LOM in 1 or more of these 3 joints is counted as LOM for the composite joint. The number of joints with limitation of range of motion is the number of joints with Grade 1 for LOM and is weighted by the number of joints assessed:

$$LMC = \frac{67 * \sum_{i=1}^{n} JLM}{\sum_{i=1}^{n} JA}$$

where LMC=limitation of motion count, JLM=number of joints with limitation of range of motion, and JA=number of joints assessed. If more than 50% of the joints are not assessed for LOM, then the limitation of motion count will be set to missing.

The number of joints with limitation of range of motion and change from Baseline in number of joints with limitation of range of motion will be summarized (observed case) for every visit except the Final Visit.

10.3.3 Physician's Global Assessment of Disease Activity VAS

The Investigator will assess the overall status of the study participant with respect to their pcJIA 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 through the Early Discontinuation/EOT Visit.

Descriptive statistics of the observed values and change from Baseline will be presented by visit.

10.3.4 Childhood Health Assessment Questionnaire

The CHAQ is an adaptation of the Health Assessment Questionnaire-Disability Index 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." CHAQ data will be included regardless of the actual age of the study participant at the time the CHAQ was completed (eg. for ages > 19 years old).

The disability section of the CHAQ uses 30 questions (5-point Likert scale) to assess 8 domains of daily living, namely dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. The scoring system used is: 0 = "without any difficulty", 1 = "with some difficulty", 2 = "with much difficulty", and 3 = "unable to do." In addition to the questions on activities of daily living, the CHAQ asks if any aids or devices or help from another person is needed to complete the specified activities. The question with the highest score determines the score for that domain. 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 domain. Table 10–1 indicates which aids/devices correspond to each domain; any aids or devices other than those indicated below will not be considered in the calculation of domain scores. The scores for each of the 8 domains are averaged to calculate the Disability Index which yields a score from 0 representing "no disability" to 3 representing "very severe disability." A study participant must have scores for at least 6 of the 8 domains to calculate the Disability Index. If there is not a score for at least 6 of the 8 domains (ie 3 or more domains scores are missing), the Disability Index is considered missing.

Table 10–1: CHAQ Aids and Devices

CHAQ Domain	Aids/Devices
[redacted]	

Table 10–1: CHAQ Aids and Devices

CHAQ Domain	Aids/Devices
[redacted]	

The CHAQ will be completed by the parents/caregivers at Screening, Baseline, and every visit through the Early Discontinuation/EOT Visit. The same parent/caregiver should complete the questionnaire for each visit. The questionnaire should be checked by site personnel for completeness. The recall period is the past week. To eliminate discrepancies introduced by growth and development, parents/caregivers are asked to note only those difficulties that are caused by arthritis.

Descriptive statistics of the observed scores and change from Baseline will be presented by visit.

No additional analyses are planned to handle instances where the questionnaire is not completed by the same parent/caregiver at each visit. The person completing the CHAQ at each visit will be identified on the listing.

10.3.5 Parent's Assessment of Arthritis Pain VAS

10.3.5.1 Updated Week 24 Interim Analysis

This data was only listed.

10.3.5.2 Final Analysis

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?" and then rates the severity on a 100mm VAS where 0 = "no pain" and 100 = "very severe pain."

The Parent's Assessment of Arthritis Pain VAS will be completed at Screening, Baseline, and every visit through the Early Discontinuation/EOT Visit.

Descriptive statistics of the observed values and change from Baseline will be presented by visit.

No additional analyses are planned to handle instances where the Parent's Assessment of Arthritis Pain VAS is not completed by the same parent/caregiver at each visit. The person completing the Parent's Assessment of Arthritis Pain VAS at each visit will be identified on the listing.

10.3.6 Parent's Global Assessment of Overall Well-Being VAS

For the Parent's Global Assessment of Overall Well-Being, 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 rates their response on a 100mm VAS where 0 = "very well" and 100 = "very poor."

The Parent's Global Assessment of Overall Well-Being VAS will be completed at Screening, Baseline, and every visit through the Early Discontinuation/EOT Visit.

Descriptive statistics of the observed values and change from Baseline will be presented by visit.

No additional analyses are planned to handle instances where the Parent's Global Assessment of Overall Well-Being VAS is not completed by the same parent/caregiver at each visit. The person completing the Parent's Global Assessment of Overall Well-Being VAS at each visit will be identified on the listing.

10.3.7 C-reactive protein

The acute phase reactant CRP will be analyzed by 3 central laboratories.

Given the precision with which CRP values are reported, the following specific algorithms will be followed for each of the central laboratories:

- Cirion laboratory (lab='C_RA0043_1'): the minimum threshold of detection is 0.05mg/L; any CRP value reported as '0mg/L' will be set to 0.05mg/L for the summaries described in this section.
- LFK laboratory (lab='C_RA0043_2'): the minimum threshold of detection is 0.2mg/L. Due to LFK reporting conventions, CRP imputations will be as follows:
    - when reported value is <0.000g/L, impute as 0.2mg/L
    - when reported value is 0g/L, impute as 0.5mg/L
- LBM laboratory (lab='C_RA0043_3'): the threshold of detection is 0.5mg/L; any CRP value reported as '0mg/L' will be set to 0.5mg/L for the summaries described in this section.

CRP will be analyzed at Screening, Baseline, and every visit through the Early Discontinuation/End of Treatment Visit. The observed values and the percent change from Baseline of CRP will be summarized for each post-Baseline visit.

As the normality assumptions are not expected to be met for CRP, the geometric mean and the corresponding CV of the geometric mean will be summarized by visit for CRP and the percent change from Baseline of CRP values. The n, median, first quartile, third quartile, minimum, and maximum will also be presented.

10.3.8 Juvenile Arthritis Disease Activity Score 71-joint

The JADAS-71 is a composite disease activity score based on a 71-joint count and includes the measures:

- Physician's Global Assessment of Disease Activity VAS normalized to a 0 to 10 scale by dividing the score by 10
- The Parent's Global Assessment of Overall Well-Being VAS normalized to a 0 to 10 scale by dividing the score by 10
- The number of joints with active arthritis (0 to 71, weighted by the number of joints assessed)
- CRP normalized to a 0 to10 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 (see Section 10.3.7 for minimum CRP thresholds).

The JADAS-71 is calculated as the linear sum of scores of the 4 components with a total score range of 0 to 101. If any component of the JADAS-71 is missing, the JADAS-71 will be set to missing for the corresponding visit.

Descriptive statistics of the observed composite scores and change from Baseline will be presented by visit (except at Final Visit).

10.3.9 Clinically Inactive Disease

10.3.9.1 Updated Week 24 Interim Analysis

This data was only listed.

10.3.9.2 Final Analysis

A study participant will be considered to be in CID at a given point in time if they meet all of the following criteria:

- No joints with active arthritis: based upon both (1) a "No" response to the question "Has the subject experienced any of the following since the last visit - Joint(s) with active arthritis?", and 0 joints with active arthritis at the current visit
- No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA: based upon a "No" response to the question "Has the subject experienced any of the following since the last visit - Fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA?"
- No active uveitis as defined by the Standardization of Uveitis Nomenclature Working Group: based upon a "No" response to the question "Has the subject experienced any of the following since the last visit - Active uveitis as defined by the Standardization of Uveitis Nomenclature Working Group?"
- CRP within normal limits in the laboratory where tested or, if elevated, not attributable to JIA: based upon a "No" response to the question "Has the subject experienced any of the following since the last visit - Elevated CRP levels attributable to JIA?"
- Physician's Global Assessment of Disease Activity score of best possible on the scale used (ie, 0mm on the 100mm VAS): based upon VAS score at current visit

- Duration of morning stiffness of ≤15 minutes: based upon duration of morning stiffness at current visit

The 6 criteria above will be used to derive CID. If any of the 6 criteria cannot be assessed due to missing data, the study participant will be assumed not to have achieved derived CID at the corresponding visit.

Derived CID will be assessed at every post-Baseline visit except the Final Visit.

The n and percentage of study participants with derived CID will be summarized for each post-Baseline visit. The exact 95% CI for the percentage will also be presented.

Time to initial derived CID in days will be calculated as date of first visit where derived CID is achieved – date of first dose of study medication + 1 day. Time to initial derived CID in days will be presented using Kaplan-Meier product limit estimation. Study participants that discontinue without achieving derived CID will be censored at the time of discontinuation; ongoing study participants that have not achieved derived CID at the time of interim analyses (Week 24 and other interim analyses) and the final analysis will be censored at the time of the last available assessment. The median and 95% CI for the time to initial derived CID will be presented. The 95% CI for the median will be based on the method of Brookmeyer and Crowley. Kaplan-Meier product limit survival estimates of the cumulative proportion of study participants with derived CID (1 minus the product limit estimate of the proportion of study participants without derived CID) will also be presented. Kaplan-Meier plots of time to CID will be presented overall and by Baseline weight group.

Both summaries of derived CID and time to derived CID will be provided as well as listed.

10.3.10 Clinical Remission

10.3.10.1 Updated Week 24 Interim Analysis

This data was only listed.

10.3.10.2 Final Analysis

CRM as indicated by the PI in the eCRF will only be listed.

Derived CRM is defined as achieving the criteria for derived CID for at least 6 continuous months; study participants who reach derived CRM can either stay on CZP or stop taking CZP; so being in derived CRM is not an indicator of whether the study participant is taking CZP while in derived CRM. Derived CRM will be considered achieved at a given visit if the study participant has derived CID at the visit and if the time from the first visit where derived CID is achieved to the given visit is ≥ 6 months (182 days) and the study participant had derived CID at all attended visits in between; if missed visits occur between visits where derived CID is achieved, then derived CID will be assumed for the missed visits. Derived CRM is defined as criteria for derived CID achieved for at least 6 continuous months.

Derived CRM will be assessed at every post-Baseline visit from Week 24 onwards, except the Final Visit.

The n and percentage of study participants with derived CRM will be summarized for each post-Baseline visit starting at Week 24. The exact 95% CI for the percentage will also be presented.

Time to initial derived CRM in days will be calculated as date of first visit where derived CRM is achieved – date of first dose of study medication + 1 day. Time to derived CRM in days will be presented using Kaplan-Meier product limit estimation. Study participants that discontinue without achieving derived CRM will be censored at the time of discontinuation; ongoing study participants that have not achieved derived CRM at the time of interim analyses (Week 24 and other interim analyses) and the final analysis will be censored at the time of the last available assessment. The median and 95% CI for the time to initial derived CRM in days calculated using Kaplan-Meier product limit estimators will be presented. The 95% CI for the median will be based on the method of Brookmeyer and Crowley. Kaplan-Meier product limit survival estimates of the cumulative proportion of study participants in derived CRM (1 minus the product limit estimate of the proportion of study participants without derived CRM) from 6 months onwards will also be presented. Kaplan-Meier plots of time to derived CRM will be presented overall and by Baseline weight group.

Both summaries of derived CRM and time to derived CRM will be provided as well as listings.

10.3.11 Duration of morning stiffness

10.3.11.1 Updated Week 24 Interim Analysis

This data was only listed.

10.3.11.2 Final Analysis

Duration of morning stiffness is defined as 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, JR and Reeback TS, 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.

Descriptive statistics of the observed duration and change from Baseline in duration of morning stiffness in hours will be summarized by visit.

10.3.12 Faces Pain Scale-Revised

10.3.12.1 Updated Week 24 Interim Analysis

This data was only listed.

10.3.12.2 Final Analysis

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 at Baseline.

The 6 faces have scores of 0, 2, 4, 6, 8, and 10 where 0 = "no pain" and 10 = "very much pain."

Descriptive statistics of the observed values and change from Baseline will be presented for each of the specified visits.

Study participants who age out of the 5 to 11 years age group while still on study will continue to be administered the FPS-R for consistency. No combined analyses of the FPS-R and JIA Pain VAS will be done for these study participants. Study participants who are less than 5 years old when they enter the study but then reach 5 years of age while on study will not be administered any pain scale questionnaire.

10.3.13 Patient's Assessment of Arthritis Pain

10.3.13.1 Updated Week 24 Interim Analysis

This data was only listed.

10.3.13.2 Final Analysis

In the JIA Pain VAS, study participants 12 to 17 years old at Baseline 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 VAS to indicate the severity of the pain, where 0 = "no pain" and 100 = "very severe pain".

Descriptive statistics of the observed values and change from Baseline will be presented separately for the acute and standard versions (See Protocol Amendment 9, Section 11.13) for each of the specified visits.

Study participants who are past 17 years old while still on the study will continue to be administered the JIA Pain VAS.

10.3.14 FASCA – Fatigue Assessment Scale

10.3.14.1 Updated Week 24 Interim Analysis

This data was only listed.

10.3.14.2 Final Analysis

The study participant's level of tiredness (fatigue) will be assessed by the FASCA numeric rating scale where the parent/caregiver is asked the 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.

Descriptive statistics of the observed values and change from Baseline will be presented by visit.

No additional analyses are planned to handle instances where the FASCA is not completed by the same parent/caregiver at each visit. The person completing the FASCA at each visit will be identified on the listing.

10.3.15 Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey

10.3.15.1 Updated Week 24 Interim Analysis

This data was only listed.

10.3.15.2 Final Analysis

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 evaluates 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 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, and days with productivity within household reduced by half or more due to child's disease. Questions 1 – 5 address how many and what types of caregivers provide care and support to the child with arthritis. Questions 6 – 12 address how arthritis affects the child's attendance and performance at school. Questions 13 – 20 address how the child's arthritis impacts the caregivers' work productivity.

The Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey will be completed at Baseline, Week 4, and every visit through the Early Discontinuation/EOT Visit.

The following analysis will be presented for the Any CZP dose only. The n and percentages for each of the question responses will be summarized for the following categorical questions: 6, 10-12. Descriptive statistics for the responses to the quantitative questions (8-9, 14-20) will be summarized.

Observed case will be used for all analyses in Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey data.

No additional analyses are planned to handle instances where the Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey is not completed by the same parent/caregiver at each visit. The person completing the Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey at each visit will be identified on the listing.

11 REFERENCES

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Kirwan JR, Reeback TS. Stanford Health Assessment modified to assess disability in British patients with rheumatoid arthritis. Br J Rheumatol. 1986;25:206-9.

Mosteller RD. Simplified calculation of body surface area. N Engl J Med 1987 Oct22; 317(17):1098 (letter).

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Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology 1990;131(2):373-375.

12 APPENDIX

12.1 Comparisons with RA0138 data

The following analysis was only completed for the Updated Week 24 Interim Analysis; it will not be regenerated for the final analysis.

Comparisons between RA0043 and RA0138 data focused on common timepoints (Weeks 12 and 24). The dose groups that were compared are the Original CZP Dose and the Reduced CZP Dose from RA0043 (Section 3.1) and the 200 mg Q2W maintenance dose from RA0138.

Separate boxplots were generated for Week 12 and Week 24 showing plasma CZP concentrations for the two CZP dose groups (Original CZP Dose or Reduced CZP Dose) for RA0043 and the single CZP dose group for RA0138 in the same plot. Box plots of the PK concentrations at Weeks 12 and 24 were presented by CZP dose group for Baseline weight group, Baseline age group, ADAb participant status classification, ADAb titer classification, and concomitant MTX use in combination with Baseline weight group. In the box plots the 5th and 95th percentiles of the concentrations distribution were shown.

Separate plots of individual participant (natural) log CZP plasma concentration versus log2 ADAb titer were produced for Week 12 and Week 24 data for both studies. In these plots, participants study (RA0043 or RA0138) and CZP dose group (Original or Reduced) were shown as a different symbol/color to aid comparison. In addition, for RA0138 only, plots of individual participant area under the plasma concentration curve over the 2-week dosing interval (AUC0-tau) versus log2 ADAb titer at Week 12 were produced.

If there were signs that higher titer levels were associated with lower plasma concentrations, further investigations were performed to attempt to determine at which titer levels differences are observed and to assess the impact on efficacy and safety.

Further analyses were defined in the integrated summary of immunogenicity including comparisons of ADAb titer levels between studies (no pooling of studies across indications are planned) allowing us to put the pcJIA/RA data in context of the AS and PSO indications.

13 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

13.1 AMENDMENT 1

Rationale for the amendment

The primary reason for this SAP amendment was to implement feedback received from FDA on analyses to be done for the different CZP dose regimens and for additional subgroups (gender and race).

Modifications and changes

Global changes

The terms “Baseline concomitant MTX use” have been changed globally to “concomitant MTX use” in SAP amendment1 except for section 6.1 Demographics. In section 6.1 Demographics, “Baseline concomitant MTX” should still be used.

Specific changes

Change #1

SAP Amendment 1 23 Sept 2015

has been added to cover page.

Change #2

Section 2 Protocol Summary

The following protocol amendments

Amendment 5.2 (Russia): 23 Feb 2014

Amendment 6: 17 Sep 2015

Amendment 6.1 (Russia): 17 Sep 2015

has been added.

Change #3

Section 2.3 Study design and conduct

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 methotrexate), 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.

Has been changed to:

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 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.

Change #4

Section 2.4 Determination of sample size

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.

Has been changed to:

Available data from all 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.

Change #5

Section 4.7 Examination of subgroup

- Baseline age group:
  - 2-5 years
  - 6-11 years
  - 12-17 years

Has been changed to:

- Baseline age group:
  - 2-<6 years
  - 6-<12 years
  - 12-17 years

Change #6

Section 4.7 Examination of subgroup

For subgroup analyses of incidence of anti-CZP antibody formation and CZP plasma concentrations, results will be presented by Baseline age group, overall anti-CZP antibody status, ERA status, and Baseline concomitant MTX use group in combination with Baseline weight group.

As specified in Section 3.3, Baseline for all subgroup analyses will always be the original Baseline (ie, prior to the 1st CZP Dose in this study).

In addition, selected outputs will only be summarized for the Any CZP Dose Regimen as specified in each relevant section.

Has been changed to:

For subgroup analyses of incidence of anti-CZP antibody formation and CZP plasma concentrations, results will also be presented by Baseline age group. In addition, summaries will be provided by overall anti-CZP antibody status, ERA status, and Concomitant MTX use group in combination with Baseline weight group. As specified in Section 3.3, Baseline for all subgroup analyses will always be the original Baseline (ie, prior to the 1st CZP Dose in this study).

For efficacy endpoints PedACR30, PedACR50, PedACR70, and PedACR90, results will also be presented by gender and race.

In addition, selected outputs will only be summarized for the Any CZP Dose Regimen as specified in each relevant section.

Change #7

Section 6.4 Prior and concomitant medications

All prior medications will be summarized by anatomical therapeutic chemical (ATC) classification level 3 (Pharmacological Subgroup) and WHO-DD generic name. In addition, past DMARDs will be summarized separately by ATC level 3 and WHO-DD generic name. These summaries will be provided for the SS for the Any CZP Dose Regimen only.

Has been changed to:

All prior medications will be summarized by anatomical therapeutic chemical (ATC) classification level 3 (Pharmacological Subgroup) and WHO-DD generic name. In addition, past DMARDs will be summarized separately by ATC level 3 and WHO-DD generic name.

These summaries will be provided for the SS for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall and the Any CZP Dose Regimen.

Change #8

Section 6.5 Prohibited medications

All summaries of prohibited medications will be provided for the FAS for the Any CZP Dose Regimen only.

Has been changed to:

All summaries of prohibited medications will be provided for the SS for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall and the Any CZP Dose Regimen.

Change #9

Section 6.6 Rescue medications

All summaries of rescue medications will be provided for the FAS for the Any CZP Dose Regimen only. All rescue medication will be listed.

Has been changed to:

All summaries of rescue medications will be provided for the SS for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall and the Any CZP Dose Regimen. All rescue medication will be listed.

Change #10

Section 8.1 CZP plasma concentrations

Summaries of concentration results will be provided by Baseline weight group, as well as Baseline age group, overall anti-CZP antibody status, and concomitant MTX use in combination with Baseline weight group.

Has been changed to:

Summaries of concentration results will be provided by Baseline weight group, as well as Baseline age group. In addition, summaries will be provided by overall anti-CZP antibody status and concomitant MTX use in combination with Baseline weight group.

Change #11

Section 8.2 Anti-CZP antibodies

Summaries of overall anti-CZP antibody status will be provided by Baseline weight group, as well as Baseline age group, and concomitant MTX use in combination with Baseline weight group. Each subgroup summary will be provided for the Reduced,

Original (overall, and prior to and following dose reduction), and Any CZP Dose Regimen groups.
These summaries will be provided for the PK-PP Set. All anti-CZP antibody data will be listed.

Has been changed to:

Summaries of overall anti-CZP antibody status will be provided by Baseline weight group, as well as Baseline age group. In addition, summaries will be provided by concomitant MTX use in combination with Baseline weight group. Each subgroup summary will be provided for the Reduced, Original (overall, and prior to and following dose reduction), and Any CZP Dose Regimen groups.

These summaries will be provided for the PK-PP Set. All anti-CZP antibody data will be listed.

Change #12

Section 8.4 PopPK and PK-PD analyses

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. Details of the PopPK and PK-PD modeling procedures will be described in a separate data analysis plan.

Has been changed to:

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. A graphical analysis of the relationship between PK and the clinical effect will be performed, and if data merits, a more formal modeling exercise will be performed. Details of the PopPK and PK-PD modeling procedures will be described in a separate data analysis plan.

Change #13

Section 9.2 Adverse events

The tables for 1, 2, 3, 5, and 6 above will be summarized by SOC, HLT, and PT and will include the number of events, the number and percentage of study participants with an event, the EAIR with associated 95% CIs and the EAER. AEs of interest tables will be provided for the Any CZP Dose Regimen only.

Has been changed to:

The tables for 1, 2, 3, 5, and 6 above will be summarized by SOC, HLT, and PT and will include the number of events, the number and percentage of study participants with an event,

the EAIR with associated 95% CIs and the EAER. AEs of interest tables will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall, the Original CZP Dose Regimen Prior to Dose Reduction, the Original CZP Dose Regimen Following Dose Reduction, and the Any CZP Dose Regimen.

Change #14

Section 9.3 Clinical laboratory evaluations

Table 9-2 Definitions of markedly Abnormal Biochemistry Values

Parameter (Unit)	**Age Range**	**Abnormal Definition**	
		Low	**High**
Lactate dehydrogenase (U/L)	2-17y	>170	

Has been changed to:

Parameter (Unit)	**Age Range**	**Abnormal Definition**	
		Low	**High**
Lactate dehydrogenase (U/L)	2-17y		>170

Change #15

Section 9.4.2.5 Autoantidobies

Autoantibodies (ANA and anti-dsDNA) will be assessed at Baseline, Weeks 16 and 48, and Early Discontinuation/EOT. For ANA antibodies, normal corresponds to dilutions of <1:160 and antibodies present corresponds to dilutions of 1:160 or higher. For anti-dsDNA antibodies, negative corresponds to dilutions of <1:10 and positive corresponds to dilutions of 1:10 or higher. A summary of the cumulative shift from the Baseline through the Early Discontinuation/EOT Visit will be summarized for both the ANA and anti-dsDNA antibodies.

Has been changed to:

Autoantibodies (ANA and anti-dsDNA) will be assessed at Baseline, Weeks 16 and 48, and Early Discontinuation/EOT. For ANA antibodies, normal corresponds to dilutions of <1:160 and antibodies present corresponds to dilutions of 1:160 or higher. A summary of the cumulative shift from the Baseline through the Early Discontinuation/EOT Visit will be summarized for both the ANA and anti-dsDNA antibodies.

Change #16

Section 10 EFFICACY ANALYSES

Efficacy will be analyzed using the FAS. All efficacy results will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen. Efficacy data collected on the day of dose reduction will be grouped with all other data classified as occurring prior to dose reduction; any efficacy assessments collected after dose reduction will be classified as occurring following dose reduction. For subgroup efficacy analyses, summaries by Baseline age group, Baseline concomitant MTX use, and anti-CZP antibody status will be presented pooling across all weight groups.

Has been changed to:

Efficacy will be analyzed using the FAS. All efficacy results will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen unless otherwise specified. Efficacy data collected on the day of dose reduction will be grouped with all other data classified as occurring prior to dose reduction; any efficacy assessments collected after dose reduction will be classified as occurring following dose reduction. For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and anti-CZP antibody status will be presented pooling across all weight groups unless otherwise specified.

Change #17

Section 10.2 Statistical analysis of the secondary efficacy variables

The frequency and percentage of study participants achieving a PedACR30, PedACR50, PedACR70, and PedACR90 response and associated 95% exact binomial CIs will be summarized for Week 16 as compared to Baseline. Results will be presented overall and by Baseline weight group, as well as by Baseline age group, Baseline concomitant MTX use, and overall anti-CZP antibody status.

Has been changed to:

The frequency and percentage of study participants achieving a PedACR30, PedACR50, PedACR70, and PedACR90 response and associated 95% exact binomial CIs will be summarized for Week 16 as compared to Baseline. Results will be presented overall and by Baseline weight group, as well as by Baseline age group, concomitant MTX use, overall anti-CZP antibody status, gender and race.

Change #18

Section 10.3 Analysis of other efficacy variables

All efficacy variables described in this section will be summarized overall and by Baseline weight group, and will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen.

Has been changed to:

All efficacy variables described in this section will be summarized overall and by Baseline weight group, and will be provided for the Reduced CZP Dose Regimen, the Original CZP

Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen unless specified otherwise**.**

Change #19

Section 10.3.1 PedACR30, PedACR50, PedACR70, and PedACR90

PedACR30, PedACR50, PedACR70, and PedACR90 response rates will also be summarized by Baseline age group, Baseline concomitant MTX use, and overall anti-CZP antibody status pooling across all weight groups.

Has been changed to:

PedACR30, PedACR50, PedACR70, and PedACR90 response rates will also be summarized by Baseline age group, concomitant MTX use, overall anti-CZP antibody status, gender and race pooling across all weight groups.

Change #20

Section 10.3.10 Clinical Remission on Medication

Both summaries of CRM and time to CRM will be provided.

Has been changed to:

Both summaries of CRM and time to CRM will be provided by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall, and the Any CZP Dose Regimen.

13.2 AMENDMENT 2

Rationale for the amendment

The primary reason for this SAP amendment was to add growth analyses and also change efficacy analysis to present Original CZP Dose Regimen Overall which is more appropriate for long term data post week 24.

Modifications and changes

Global changes

All efficacy and health outcome summaries were changed from presented by “Original CZP Dose Regimen prior to dose reduction” to “Original CZP Dose Regimen” regardless of dose reduction.

Specific changes

Change #1

SAP Amendment 2 24 June 2016

has been added to cover page.

Change #2

NRI	Nonresponder Imputation

has been added to List of Abbreviations.

Change #3

Section 1 Introduction

This document describes the planned analyses and summary tables, figures, and listings to be included in the interim and final clinical study reports (CSR) for RA0043.

Has been changed to:

This document describes the planned analyses and summary tables, figures, and listings to be included in the Week 56 interim and final clinical study reports (CSR) for RA0043. Note that Week 16 and Week 24 interim analyses were completed as specified in SAP Amendment 1 and text about these analyses will be kept as is.

Change #4

Section 2.3 Study design and conduct (last two paragraphs)

An interim analysis of the PedACR30 Week 16 response rate will be performed after all active study participants 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. Statistical output for this Week 16 interim analysis will be restricted to a limited subset of the tables and listings described in the current SAP (see Section 3.1).

For purposes of regulatory submissions, full interim analyses will be performed after all active study participants have completed the Week 24 (Visit 10) assessments and after all active study participants have completed the Week 56 (Visit 14) assessments. All statistical tables, figures and listings comprising the current SAP will be produced for both Week 24 and Week 56 full interim analyses, as well as the final analysis of the study.

Has been changed to:

An interim analysis of the PedACR30 Week 16 response rate will be performed after all active study participants 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. Statistical output for this Week 16 interim analysis were completed and were restricted to a limited subset of the tables and listings as described in SAP Amendment 1

Full interim analyses will be performed after all active study participants have completed the Week 24 (Visit 10) assessments and after all active study participants have completed the Week 56 (Visit 14) assessments. Week 24 full interim analyses were completed as described

in SAP Amendment 1. All statistical tables, figures and listings comprising this SAP will be produced for Week 56 full interim analyses, as well as the final analysis of the study.

Change #5

Section 3.1 General presentation of summaries and analyses

However, for efficacy data, summaries will generally be presented by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen.

Has been changed to:

Note that for efficacy data, summaries will be presented by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen (regardless of dose reduction), and the Any CZP Dose Regimen.

Change #6

Section 3.2 General study level definitions

The analysis time points of interest are Screening, Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 17, Week 20, Week 24, Week 32, every 8 weeks after Week 32, and the Early Discontinuation/End of Treatment (EOT) Visit. Safety assessments will also be done at the Final Visit 12 weeks after the final dose of CZP.

For study participants who withdraw prior to the last time point for the particular analysis being conducted (ie, Week 16, Week 24, Week 56, Final), data recorded at the Early Discontinuation/EOT Visit will be assigned to what would have been the next scheduled visit for the particular assessment that is being summarized, unless unavailable or otherwise specified. These data will be included in the summaries of the assigned visit and the "Early Discontinuation/EOT" Visit if applicable.

Has been changed to:

The analysis time points of interest are Screening, Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 17, Week 20, Week 24, Week 32, every 8 weeks after Week 32, and the Early Discontinuation /End of Treatment (EOT) Visit. Safety assessments will also be done at the Final Visit 12 weeks after the final dose of CZP.

For study participants who withdraw prior to the last time point for the particular analysis being conducted (ie, Week 16, Week 24, Week 56, Final), data recorded at the Early Discontinuation/EOT Visit will be assigned to what would have been the next scheduled visit , unless unavailable or otherwise specified. These data will be included in the summaries of the assigned visit and the "Early Discontinuation/EOT" Visit if applicable. For efficacy data, the Early Discontinuation/EOT Visit will not be summarized and only the re-assigned visit will be included in the summary tables. Note that data from the Early Discontinuation Visit or EOT will be listed as "Visit X (Week Y)/ED" or "Visit X (Week Y)/EOT" where the X was

the re-assigned visit number and Y was the re-assigned week number in all safety and efficacy data listings as applicable.

Change #7

Section 3.6 Treatment assignment and treatment groups

For PK, safety and efficacy analyses, study participants will be grouped by their Baseline weight group. Selected analyses will also group study participants by their Baseline age group, concomitant MTX use, and overall anti-CZP antibody status (as defined in Section 8.2). Additionally, PK and selected safety data will be presented by CZP dose regimen (Reduced vs. Original CZP Dose Regimen). For study participants enrolled on the original CZP dose regimen, data will be tabulated overall, and selected data will be further subdivided into events and assessments occurring prior to and following dose reduction. Efficacy summaries will generally be presented by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen.

Has been changed to:

For PK, safety and efficacy analyses, study participants will be grouped by their Baseline weight group. Selected analyses will also group study participants by their Baseline age group, concomitant MTX use, and overall anti-CZP antibody status (as defined in Section 8.2). Additionally, PK and selected safety data will be presented by CZP dose regimen (Reduced vs. Original CZP Dose Regimen). For study participants enrolled on the original CZP dose regimen, data will be tabulated overall, and selected data will be further subdivided into events and assessments occurring prior to and following dose reduction. Efficacy summaries will be presented by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen, and the Any CZP Dose Regimen.

Change #8

Section 3.9 Changes to protocol-defined analyses

For all efficacy analyses, the protocol stated that results would be presented by the Reduced, Original, and Any CZP Dose Regimen groups. However, for more relevant comparisons of interest, summaries of all efficacy endpoints are generally presented by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen.

has been deleted.

Change #9

Section 3.9 Changes to protocol-defined analyses

For joints with limitation of motion (LOM), it was stated in the protocol that the assessment of LOM would be made using 69 of the 75 joints from the standard PRINTO/PRCSG standard joint examination; however, the assessment described in the SAP that utilized

67 joints was conducted. This was according to an updated definition of LOM in the PRINTO/PRCSG assessment at the time of finalization of the original SAP.

has been added.

Change #10

Section 4.2 Handling of dropouts or missing data

For continuous efficacy endpoints, missing assessments will be imputed using an LOCF approach.

Has been changed to:

For continuous efficacy endpoints, missing assessments will be imputed using an LOCF approach. For Week 56 and final analyses, LOCF will only be applied to study participants who have discontinued early prior to reaching the Week 56 visit and data will be carried forward up to the Week 56 visit as appropriate. Data beyond Week 56 will be analyzed as observed cases without any imputation. The same rule will also be applied in nonresponder imputation (NRI) calculations for binary efficacy outcomes.

Change #11

Section 4.2.1 Handling of questionnaire data

The following rules will apply for analysis of (1) out of range and (2) ambiguous answers (i.e. invalid or unable to interpret answers) to questionnaires completed by study participants or parents/caregivers:

Has been changed to:

When relevant, the following rules will apply for analysis of (1) out of range and (2) ambiguous answers (i.e. invalid or unable to interpret answers) to questionnaires completed by study participants or parents/caregivers:

Change #12

Section 4.3 Interim analysis and data monitoring

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 5^{th} and 95^{th} percentile and minimum and maximum observed values.

If the pediatric plasma concentrations demonstrate that the geometric mean and median concentrations are below the adult 5^{th} percentile or above the 95^{th} 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 dosing algorithm will be derived. Any change in dose regimen will require a protocol amendment prior to implementation.

Has been changed to:

Comparisons will be made between the geometric mean 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 pediatric data 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 dosing algorithm will be derived. Any change in dose regimen will require a protocol amendment prior to implementation.

Change #13

Section 4.7 Examination of subgroups

- Concomitant MTX use:
    - with
    - without

Has been changed to:

- Concomitant MTX use (distinct from Baseline MTX use presented in Section 6.1 and defined as any concomitant MTX use during the Treatment Period)::
    - With concomitant MTX use
    - Without concomitant MTX use

Change #14

Section 5.1 Subject disposition

The number and percentage of study participants who were treated, who completed the study, and who discontinued from the study, along with the discontinuation reasons, will be summarized for the Enrolled Set. For the Week 16, Week 24 and Week 56 interim analyses, number of study participants completing Week 16, Week 24 and Week 56 (respectively) will replace number completing the study. The number of study participants in each analysis set will be presented for the Enrolled Set. Both summaries will be provided for the Reduced, Original, and Any CZP Dose Regimen groups.

Has been changed to:

The number and percentage of study participants who were treated, who completed the study, and who discontinued from the study, along with the discontinuation reasons, will be summarized for the Safety Set. For the Week 16, Week 24 and Week 56 interim analyses, number of study participants completing Week 16, Week 24 and Week 56 (respectively) will be added in addition to the number completing the study as appropriate. The number of study

participants in each analysis set will be presented. Summaries will be provided for the Reduced, Original, and Any CZP Dose Regimen groups.

Change #15

Section 5.2 Protocol deviations

The number and percentage of study participants with important protocol deviations will be summarized by type for the ES for the Any CZP Dose Regimen. All important protocol deviations will also be listed.

Has been changed to:

The number and percentage of study participants with important protocol deviations will be summarized by type for the SS for the Any CZP Dose Regimen. All important protocol deviations will also be listed.

Note that partial PK data exclusion is implemented due to certain protocol deviations (eg, incorrect treatment or dose, procedural noncompliance related to PK sampling), minor deviations from the planned treatment schedule (eg, delays or missing doses not considered as important protocol deviations), CZP interruption or CZP discontinuation due to AEs, TB prophylactic treatment, or clinical remission. These exclusions will be reviewed and identified at data cleaning meetings and are only applicable for group PK summary tables and graphs where the geometric mean for plasma concentration are calculated and displayed. However, all PK data will be included in listings, individual graphs, and PopPK analysis. Study participants with at least one PK data exclusion are summarized and listed.

When applicable, exclusion from analysis set will also be summarized and listed.

Change #16

Section 6.1 Demographics

Demographics will be summarized for the SS and the PK-PP Set for the Reduced, Original, and Any CZP Dose Regimen groups. The following continuous variables will be summarized by Baseline weight group: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2) at Baseline.

The following categorical variables will be summarized by Baseline weight group: gender (male, female), racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, Not Hispanic or Latino), Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), and Baseline concomitant MTX use group (with, without).

Has been changed to:

Demographics will be summarized for the SS and the PK-PP Set for the Reduced, Original, and Any CZP Dose Regimen groups. The following continuous variables will be summarized

by Baseline weight group: age (years), weight (kg), height (cm), body surface area (BSA) and body mass index (BMI) (kg/m^2) at Baseline.

The following categorical variables will be summarized by Baseline weight group: gender (male, female), racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, Not Hispanic or Latino), Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), and Baseline MTX use group (with, without).

Change #17

Section 6.2 Other baseline characteristics

Baseline characteristics described in this section will be summarized for the SS and the PK-PP Set for the Reduced, Original, and Any CZP Dose Regimen groups. Time since first diagnosis of JIA (or onset of signs and symptoms consistent with a diagnosis of JIA for those enrolled after Protocol Amendment 3) will be summarized in years. The time will be calculated as the duration from the date of first diagnosis of JIA to the date of informed consent; time since diagnosis will not be calculated when date of diagnosis is missing. The number and percentage of study participants with a history of each of the following JIA categories will also be summarized:

Has been changed to:

Baseline characteristics described in this section will be summarized for the SS and the PK-PP Set for the Reduced, Original, and Any CZP Dose Regimen groups. Time since first diagnosis of JIA (or onset of signs and symptoms consistent with a diagnosis of JIA for those enrolled after Protocol Amendment 3) will be summarized in years. The time will be calculated as the duration from the date of first diagnosis of JIA to Baseline (Week 0 [Visit2]); time since diagnosis will not be calculated when date of diagnosis is missing. The number and percentage of study participants with a history of each of the following JIA categories will also be summarized:

Change #18

Section 6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the start date of study medication, and also include any medications that continue post-Baseline. Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first study medication administration. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For Cimzia, the dosing period is from the date of first dose up to (but not including) 14 days post last dose. Thus a concomitant medication is any medication whose start date is prior to the date of last study medication administration + 14 days, and whose stop date is either missing, or on or after the date of first study medication administration .

Has been changed to:

Prior medications include any medications that started prior to the start date of study medication, and also include any medications that continue post-Baseline. Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first study medication administration. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For Cimzia, the dosing period is from the date of first dose up to (but not including) 14 days Q2W (or 28 days if Q4W) post last dose if a subject discontinued early or at end of treatment per protocol. For ongoing study participants, the dosing period is from the date of first dose up to the data cutoff date in interim analyses. Thus a concomitant medication is any medication whose start date is prior to the date of last study medication administration + 14 days Q2W (or +28 days if Q4W) or data cutoff date, and whose stop date is either missing, or on or after the date of first study medication administration.

Change #19

Section 6.5 Prohibited medications

The +1 day rule was applied to the first usage date when considering its impact on efficacy endpoints. Therefore, only efficacy data with dates after the first usage date of the prohibited medication were impacted (using the nonresponder imputation (NRI) or LOCF imputation method).

has been added.

Change #20

Section 6.6 Rescue medications

- Higher than Baseline dose of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, including as needed (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.

Has been changed to:

- Higher than Baseline dose of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, including as needed (PRN) use within 72 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).
- Higher than Baseline dose of analgesics or opioids including PRN use within 48 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).
- Any increase in dose of oral corticosteroids within 7 days prior to scheduled study visit (Note: The increase has to be higher than baseline).

Change #21

Section 6.6 Rescue medications

Generally, the +1 day rule was applied to the first usage date when considering its impact on efficacy endpoints. Therefore, only efficacy data with dates after the first usage date of the rescue medication were impacted (using the nonresponder imputation (NRI) or LOCF imputation methods). Exceptions are nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, analgesics or opioids, or oral corticosteroids as specified above.

has been added.

Change #22

Section 7 Measurements of treatment compliance

Descriptive statistics will be presented for the total dose received/total dose expected for the SS. Total dose received is the sum of the dose level for each recorded study medication administration. Total dose expected is based on the loading and maintenance doses for the 3 different Baseline weight groups. A subject is expected to receive 3 loading doses and then a maintenance dose Q2W through the Early Discontinuation/EOT Visit, with the exception of study participants enrolled after the implementation of Protocol Amendment 4; study participants in the 10 - <20kg weight group receive a maintenance dose Q4W. In addition, a subject's expected dose could change if a subject crosses into a new weight group which will be considered in the above calculations.

Treatment compliance will be provided for the SS for the Any CZP Dose Regimen only.

Has been changed to:

Descriptive statistics will be presented for the compliance ratio defined as total number of CZP administrations received/total number of CZP administrations expected for the SS. Total number of CZP administrations expected differs depending on the loading phase or maintenance phase as well as depends on the different dosing scheduling of the 3 different weight groups. For example, in the Original CZP Dose Regimen, a subject is expected to receive 3 loading CZP administrations and then a maintenance dose of CZP Q2W through the Early Discontinuation/EOT Visit, with the exception of following implementation of Protocol Amendment 4; study participants in the 10 to <20kg weight group change from Q2W to a maintenance dose of CZP Q4W. In addition, a subject could change dose (or frequency of dosing if in 10-20kg group) if a subject crossed into a new weight group, which is not considered in the above expected calculations of number of CZP administration since all expectations are based on baseline weight group dosing regimen regardless of weight change. This specifically applies to the change of dose frequency from Q4W to Q2W if a subject crossed into the 20 to <40kg weight group, which is not considered in the expected calculations. Note that the dose reduction of ongoing study participants following Protocol Amendment 4 is considered in the calculations.

Treatment compliance is provided for the SS for the Reduced CZP Dose Regimen, Original CZP Dose Regimen Prior to Dose Reduction, Original CZP Dose Regimen Following Dose Reduction and Original CZP Dose Regimen Overall.

Change #23

Section 8.1 CZP plasma concentrations

The geometric mean and CV% was derived when at least two-thirds of the concentrations at a certain visit were above the limit of quantification (LoQ).If that criteria was not met, only the maximum and minimum values were shown. Similarly, the 95% CI of the geometric mean was only calculated if at least 5 samples were available at that time point. Note that a separate partial PK exclusion regarding concentration calculation is detailed in section 5.2.

has been added.

Change #24

Section 8.2 Anti-CZP antibodies

In addition, overall antibody status will be summarized:

- Overall AB+ is defined as having a value > 2.4units/mL at any time in the treatment period (not including the safety follow-up period)
- Overall AB- is defined as having no values > 2.4units/mL during the treatment period.

Has been changed to:

In addition, overall antibody status will be summarized:

- Overall AB+ is defined as having a value > 2.4units/mL at any time in the treatment period (Note: All post-baseline data will be included except for the safety follow-up visit).
- Overall AB- is defined as having no values > 2.4units/mL during the treatment period.

Change #25

Section 8.2 Anti-CZP antibodies

In addition, graphical presentation of cumulative percentage of positive Anti-CZP antibody status will be presented by Reduced CZP Dose Regimen, Original CZP Dose Regimen Prior to Dose Reduction, and Original CZP Dose Regimen Following Dose Reduction respectively.

has been added.

Change #26

Section 9.2 Adverse events

Treatment emergent AEs (TEAEs) are defined as AEs starting on or after the first administration of CZP and up to 70 days after the last dose of study medication. AEs that start more than 70 days after the last dose of study medication will be flagged in the listing but excluded from summaries.

Has been changed to:

Only treatment emergent adverse events (TEAE) will be included in the summary tables. Treatment emergent AEs are defined as AEs starting on or after the first administration of CZP and up to 70 days after the last dose of study medication. AEs that are pre-treatment or that start more than 70 days after the last dose of study medication will be flagged in the listing but excluded from summaries.

Change #27

Section 9.3 Clinical laboratory evaluations

The following urinalysis parameters will be listed: pH, protein, glucose, and blood. If abnormalities are found from the dipstick test, microscopy (WBC, RBC, casts, crystals, and bacteria) will be performed. These results will also be listed.

Has been changed to:

The following urinalysis parameters will be tested locally only: pH, protein, glucose, and blood. If abnormalities are found from the dipstick test, microscopy (WBC, RBC, casts, crystals, and bacteria) will be performed, and these results will be listed. XXXX

Change #28

Section 9.3 Clinical laboratory evaluations (Table 9-2)

Parameter (Unit)	Age Range	Abnormal Definition	
		Low	High
Lactate dehydrogenase (LDH) (IU/L)	2-17y		>1300
Creatine Kinase (CPK) (IU/L)	2-17y		>600

Reference: Based on Rheumatology CTC (Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials II: the Rheumatology Common Toxicity Criteria v.2.0)

THASIAWOODWORTH, DANIEL E. FURST, RIEKE ALTEN, CLIFTON BINGHAM, DAVID YOCUM, VICTOR SLOAN, WAYNE TSUJI, RANDALL STEVENS, JAMES FRIES, JAMES WITTER, KENT JOHNSON, MARISSA LASSERE, and PETER BROOKS

has been added and updated.

Change #29

Section 9.4.2.1 Height and Weight

Descriptive statistics for observed Baseline and post-Baseline values, and change from Baseline for post-Baseline measurements, will be presented separately for height (in cm) and weight (in kg). Pre-study values of height and weight will only be included in the listings.

Summaries of Baseline and post-Baseline height and weight will be provided for the Any CZP Dose Regimen only.

Has been changed to:

Descriptive statistics for Baseline and post-Baseline values at selected time points of interest, and change from Baseline for selected time points for percentile height-for-age and percentile weight –for-age (based on growth curves and percentile calculation methods published by

CDC for children age 2-20 that was available on 27April 2016 at http://www.cdc.gov/growthcharts/clinical_charts.htm) will be summarized by age group and gender for the Any CZP Dose Regimen. All weight and height will also be listed.

Change #30

Section 9.4.2.2 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. Tanner stages will be assessed at Baseline, Weeks 24 and 48, every 24 weeks thereafter, and the Early Discontinuation/EOT Visit. Tanner stages will be listed by visit for each subject.

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. Tanner stages will be assessed at Baseline, Weeks 24 and 48, every 24 weeks thereafter, and the Early Discontinuation/EOT Visit. A summary of shift table of Tanner stages from baseline to relevant post-treatment visit(s) (eg., 48 week) by age and gender will be provided for the Any CZP Dose Regimen. Overall Tanner stage at each visit is derived as the minimum stage of the 2 components. If one component is missing at a visit, then the overall stage will be set to missing for that visit.

No imputation of missing data will be implemented. Tanner stages will be listed by visit for each subject.

Change #31

Section 10 Efficacy Analysis

Efficacy will be analyzed using the FAS. All efficacy results will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen unless otherwise specified. Efficacy data collected on the day of dose reduction will be grouped with all other data classified as occurring prior to dose reduction; any efficacy assessments collected after dose reduction will be classified as occurring following dose reduction. For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and anti-CZP antibody status will be presented pooling across all weight groups unless otherwise specified.

In addition to the efficacy summaries described below, all efficacy results will be listed by subject.

Has been changed to:

Efficacy will be analyzed using the FAS. All efficacy results will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen, and the Any CZP Dose Regimen. For subgroup efficacy analyses, summaries by Baseline age group, concomitant

MTX use, and anti-CZP antibody status will be presented pooling across all weight groups unless otherwise specified. In addition, selected summaries will also be presented by gender and race.

In addition to the efficacy summaries described below, all efficacy results will be listed by subject. However, some listings for study participants in Original CZP Dose Regimen may be grouped by study participants with dose reduction and study participants without dose reduction within each weight group.

Change #32

Section 10.2 Statistical analysis of the secondary efficacy variables

If 2 or more core set measures are missing, the corresponding PedACR30, PedACR50, PedACR70 and PedACR90 responses will also be treated as missing. For core set measures with values of 0 at Baseline, the percentage change from Baseline cannot be calculated and is treated as missing.

Has been changed to:

If 2 or more core set measures are missing, the corresponding PedACR30, PedACR50, PedACR70 and PedACR90 responses will also be treated as missing. For core set measures with values of 0 at Baseline, the percentage change from Baseline cannot be calculated for improvement, however, for worsening, the following rules will be applied:

- If Baseline number of joints for active arthritis or with LoM was 0, an increase to at least 2 joints is required;
- If Baseline Global Assessment scores is 0, worsen to a score at least 20 is required to be considered as a worsening of at least 30%;
- If Baseline CHAQ scores is 0, worsen to a score of at least 0.125 is required to be considered as a worsening of at least 30%;

Change #33

Section 10.3 Analysis of other efficacy variables

All efficacy variables described in this section will be summarized overall and by Baseline weight group, and will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Prior to Dose Reduction, and the Any CZP Dose Regimen unless specified otherwise.

Continuous endpoints will be summarized using LOCF for missing values.

Has been changed to:

All efficacy variables described in this section will be summarized overall and by Baseline weight group, and will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen, and the Any CZP Dose Regimen unless specified otherwise.

Continuous endpoints will be summarized using LOCF for missing values, unless otherwise specified, as for the Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey.

Change #34

Section 10.3.10 Clinical Remission on Medication

Both summaries of CRM and time to CRM will be provided by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall, and the Any CZP Dose Regimen.

Has been changed to:

Both summaries of CRM and time to CRM will be provided.

Change #35

Section 10.3.15 Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey

No LOCF imputation will be implemented and observed case will be used for all analyses in Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey data.

has been added.

13.3 AMENDMENT 3

Rationale for the amendment

The primary reason for this SAP amendment was to update the text based on Protocol Amendment #9.

Modifications and changes

Global changes

The use of "subjects" has been changed to "study participants" throughout the document to match Protocol Amendment #9.

The use of "AE" has been changed to "TEAE" when used in reference to summary analyses and listings.

When referring to summarizing the data for the entire Reduced CZP Dose Regimen, Original CZP Dose Regimen or Any CZP Dose Regimen, the use of "overall" has been added for consistency to "Reduced CZP Dose Regimen Overall" (or "Reduced Overall") and "Original CZP Dose Regimen Overall" (or Original Overall)" throughout sections 6, 7, 8, 9 and 10.

Specific changes

Change #1

SAP/Amendment	Date

Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016

Has changed to:

SAP/Amendment	**Date**
Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016
SAP Amendment 3	30 Jun 2021

Change #2

The list of tables was added.

Change #3

The list of abbreviations has been updated to include the following abbreviations:

AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
COVID-19	Coronavirus disease 2019
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay
IMP	investigational medicinal product
IXRS	interactive voice/web response system
MAR	missing at random
NRS	numeric rating scale
PD	Pharmacodynamic(s)
PDILI	potential drug-induced liver injury
TE	Treatment-emergent

Change #4

Section 1 Introduction

This document describes the planned analyses and summary tables, figures, and listings to be included in the Week 56 interim and final clinical study reports (CSR) for RA0043. Note that Week 16 and Week 24 interim analyses were completed as specified in SAP Amendment 1 and text about these analyses will be kept as is.

Has been changed to:

This document describes the planned analyses and summary tables, figures, and listings to be included in the final clinical study report (CSR) for RA0043 as well as for the Updated Week 24 and Week 56 interim analyses. Note that Week 16 and the 2016 Week 24 interim analyses were completed as specified in SAP Amendment 1 and text about these analyses will be kept as is.

Change #5

Section 2 Protocol Summary

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 concentration and anti-CZP antibody levels at Week 16 and Week 48.

Change #6

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.

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.

Full interim analyses will be performed after all active subjects have completed the Week 24 (Visit 10) assessments and after all active subjects have completed the Week 56 (Visit 14) assessments.

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 concentration and anti-CZP antibody levels at Week 16 and Week 48.

An interim analysis of the American College of Rheumatology Pediatric 30% (PedACR30) response rate was performed after all active study participants 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. A further futility analysis will not be performed using the additional study participants that will be enrolled after Protocol Amendment 9.

A full interim analysis was performed in 2016 for all active study participants that had completed the Week 24 (Visit 10) assessments. After Protocol Amendment 9, full interim analyses will be performed after all active study participants have completed the Week 24 (Visit 10) assessments and after all active study participants have completed the Week 56 (Visit 14) assessments.

Change #7

The following updates have been added to the end of the Section 2 Protocol Summary section:

Amendment 7: 22 Sep 2016

Amendment 7.1 (Russia): 22 Sep 2016

Amendment 8: 24 Jun 2019

Amendment 8.1 (Russia): 18 Jul 2019

Amendment 9: 27 Apr 2020

Amendment 9.1 (Russia): 28 Jul 2020

In order to adequately assess the exposure levels and clinical experience of CZP in JIA at both the reduced and original CZP dose regimen and also to 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 under Protocol Amendment 9 or later will have plasma concentrations of CZP and anti-CZP antibodies analyzed using and electrochemiluminescence immunoassay (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 #8

Section 2.2.1.1 Primary pharmacokinetic and immunological variables

- CZP plasma concentrations

- Anti-CZP antibody concentrations

has been changed to:

- CZP plasma concentrations at Weeks 16 and 48
- Anti-CZP antibody levels at Weeks 16 and 48

Change #9

Section 2.2.2.1 Primary safety variables

The primary safety variable is the incidence of adverse events (AEs).

Has been changed to:

Section 2.2.1.2

The primary safety variables are the incidence of serious treatment-emergent adverse events (TEAEs) and TEAEs leading to permanent withdrawal of investigational medicinal product (IMP).

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

Change #10

Section 2.2.2.1 Other safety variables

- Clinical laboratory values (hematology, biochemistry, urinalysis) at every visit except Visits 3 and 4 (Week 1 and Week 2) and Unscheduled Visits
- Vital signs at every visit
- Developmental stages and growth (Tanner stages, height, weight) at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit (weight at every visit through Final Visit)
- Autoantibody concentrations (antinuclear antibodies (ANA) and anti-double-stranded desoxyribonucleic acid (anti-dsDNA) antibodies) 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

Has been changed to:

Section 2.2.3.1 Other PK and immunological variables

- CZP 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, urinalysis) at every visit except Visits 3 and 4 (Week 1 and Week 2) and Unscheduled Visits
- Vital sign abnormalities at every visit

- Developmental stages and growth (Tanner stages, height, weight) 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 study participants who have not reached Tanner stage V.
- Autoantibody concentrations (antinuclear antibodies (ANA) and anti-double-stranded desoxyribonucleic acid (anti-dsDNA) antibodies) 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

Change #11

Section 2.2.3.3 Other efficacy and health outcomes variables

- Change from Baseline in Faces Pain Scale-Revised (FPS-R), 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).

Has been changed to:

- Change from Baseline in Faces Pain Scale-Revised (FPS-R) (child-reported, ages 5 to 11 years), at every post-Baseline visit except Final Visit
- Change from Baseline in JIA Pain VAS, (acute and standard versions); at every post-Baseline visit except Final Visit.

Change #12

Section 2.3 Study design and conduct

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 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.

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) (study C87050). This CZP 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 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.

Results of an interim population PK (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 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 Amendments 4 and 5) will be performed to confirm that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

An interim analysis of the PedACR30 Week 16 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. Statistical output for this Week 16 interim analysis were completed and were restricted to a limited subset of the tables and listings as described in SAP Amendment 1

Full interim analyses will be performed after all active subjects have completed the Week 24 (Visit 10) assessments and after all active subjects have completed the Week 56 (Visit 14) assessments. Week 24 full interim analyses were completed as described in SAP Amendment 1. All statistical tables, figures and listings comprising this SAP will be produced for Week 56 full interim analyses, as well as the final analysis of the study.

Has been changed to:

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.

The table below shows the data collection schedule prior to Protocol Amendment 8 and after implementing Protocol Amendment 8. For the study participants who switch to the 16 week schedule, the date of the first visit of this schedule will be captured on the "Study Participation" CRF module.

Table 2-2 Visit Schedule

Collected/ Assessed/ Administered at	Prior to Protocol Amendment 8	Following Protocol Amendment 8
Most parameters	Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32 and every 8 weeks thereafter, the Early Discontinuation/End of Treatment Visit, and the Final Visit	Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32 and every 16 weeks thereafter, the Early Discontinuation/End of Treatment Visit, and the Final Visit
Height	Screening, Baseline, every 24 weeks thereafter and Early Discontinuation/End of Treatment Visit	Screening, Baseline, every 48 weeks thereafter and Early Discontinuation/End of Treatment Visit; assessed study participants who have not reached Tanner stage V
Tanner	Screening, Baseline, every 24 weeks thereafter and Early Discontinuation/End of Treatment Visit	Screening, Baseline, every 48 weeks thereafter and Early Discontinuation/End of Treatment Visit; assessed study participants who have not reached Tanner stage V
FPS-R and JIA Pain VAS	Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, 24 and 32; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment	Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, 24 and 32; and then every 16 weeks thereafter through the Early Discontinuation/End of Treatment
NRS	Baseline, Weeks 1, 2, 4, 8, and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment	Baseline, Weeks 1, 2, 4, 8, 16, 24, 32 and then every 16 weeks thereafter through the Early Discontinuation/End of Treatment

Prior to Protocol Amendment 9, 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 < 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.

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 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 GZP 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 Amendments 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.

Based on 24-week interim results from the first 163 study 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 to adequately support the safety assessment of the original CZP dose 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.

Full interim analyses were performed in 2016 after all active study participants completed the Week 24 (Visit 10) assessments. Week 24 full interim analyses were completed as described in SAP Amendment 1. SAP Amendment 3 comprises the analyses to be completed for an Updated Week 24 (Visit 10) interim, Week 56 (Visit 14) interim and the final analysis of the study.

Change #13

Section 2.4 Determination of sample size

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 regimen 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.

Prior to the start of study conduct, simulations using the adult population PK model in pediatric subjects with JIA suggested that the planned sample size of 125 subjects was adequate for PK assessment purposes. Individual apparent clearance (CL/F) and volume of distribution (V/F) were simulated for a total of 125 subjects (using the same approach presented in C87079 report addendum 08 Oct 2008 performed for 190 subjects). 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.

Available data from all subjects will be included in the final PopPK analysis, and therefore should allow CL/F and V/F to be determined with sufficient precision.

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 regimen 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 was 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.

Available ECLIA-based data from all 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.

Change #14

Section 3.1 General presentation of summaries and analyses

- Reduced CZP Dose Regimen: includes all subjects who began treatment in accordance with the reduced CZP 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]).
- Original CZP Dose Regimen: includes all subjects who began treatment in accordance with the original CZP 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 subjects 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.
- Any CZP Dose Regimen: includes all subjects in the reduced and original CZP dosing regimens.

For the Original CZP Dose Regimen group, selected data will be further subdivided into events and assessments occurring prior to and following dose reduction - namely Original CZP Dose Regimen Prior to Dose Reduction vs. Original CZP Dose Regimen Following Dose Reduction. Summaries of data following dose reduction for subjects who began treatment on the original CZP dose regimen will be restricted to subjects whose CZP dose was actually reduced. Original CZP Dose Regimen subjects whose CZP dose was not reduced prior to study discontinuation will be excluded from summaries of data following CZP dose reduction.

Summaries of data that have been subdivided as prior to vs. following dose reduction will generally assign data associated with the dose reduction visit to the "prior to dose reduction" category. The only exception to this rule will be for AEs occurring on the same date as the dose reduction; classification of AEs occurring on the date of dose reduction will be based upon review and classification by the study physician.

Generally, data will be summarized by the Reduced, Original, and Any CZP Dose Regimen groups with selected outputs further summarized by the Original CZP Dose Regimen Prior to Dose Reduction vs. the Original CZP Dose Regimen Following Dose Reduction.

Note that for efficacy data, summaries will be presented by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen (regardless of dose reduction), and the Any CZP Dose Regimen.

Has been changed to:

- Reduced CZP Dose Regimen Overall: includes all study participants who began treatment in accordance with the reduced CZP 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.
    - Under Protocol Amendment 9, study participants are allowed to escalate to the Original CZP Dose
- Original CZP Dose Regimen Overall: includes all study participants who began treatment in accordance with the original CZP 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.
- Any CZP Dose Regimen: includes all study participants in the reduced and original CZP dosing regimens.

For the Original CZP Dose Regimen Overall group, selected data will be further subdivided into events and assessments occurring prior to or without and following dose reduction - namely Original CZP Dose Regimen Prior to or Without Dose Reduction vs. Original CZP Dose Regimen Following Dose Reduction. Original CZP Dose Regimen study participants whose CZP dose was not reduced prior to study discontinuation will be excluded from summaries of data following CZP dose reduction; this will include the 30 study participants enrolled under Protocol Amendment 9 who do not dose reduce. Summaries of data following dose reduction for study participants who began treatment on the original CZP dose regimen will be restricted to study participants whose CZP dose was actually reduced and for the time that the dose was reduced. If study participants escalate their dose after reduction (allowed after Protocol Amendment 9), that data may be summarized or listed separately.

Summaries of data that have been subdivided as prior to or without dose reduction vs. following dose reduction vs following dose escalation will generally assign data associated with the dose reduction visit to the "prior to or without dose reduction" category and data associated with the dose escalation visit to the "dose reduction" category. The only exceptions to this rule will be for AEs occurring on the same date as the dose reduction whereby the classification of AEs occurring on the date of dose reduction will be based upon review and classification by the study physician and for AEs on the same date as the dose escalation, whereby the classification of the AEs occurring on the date of dose escalation will also be based upon review and classification by study physician.

Generally, data will be summarized by the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups with selected outputs further summarized by the Original CZP Dose Regimen Prior to or Without Dose Reduction vs. the Original CZP Dose Regimen Following

Dose Reduction. Selected outputs will further summarize the data occurring during the Escalation CZP Dose Regimen.

Note that for efficacy data, summaries will be presented by the Reduced CZP Dose Regimen Overall (regardless of dose escalation), the Original CZP Dose Regimen Overall (regardless of dose reduction or dose escalation), and the Any CZP Dose Regimen (regardless of dose reduction or dose escalation).

Change #15

Section 3.2.1 Analysis time points

The analysis time points of interest are Screening, Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 17, Week 20, Week 24, Week 32, every 8 weeks after Week 32, and the Early Discontinuation /End of Treatment (EOT) Visit. Safety assessments will also be done at the Final Visit 12 weeks after the final dose of CZP.

For subjects who withdraw prior to the last time point for the particular analysis being conducted (ie, Week 16, Week 24, Week 56, Final), data recorded at the Early Discontinuation/EOT Visit will be assigned to what would have been the next scheduled visit , unless unavailable or otherwise specified. These data will be included in the summaries of the assigned visit and the "Early Discontinuation/EOT" Visit if applicable. For efficacy data, the Early Discontinuation/EOT Visit will not be summarized and only the re-assigned visit will be included in the summary tables. Note that data from the Early Discontinuation Visit or EOT will be listed as "Visit X (Week Y)/ED" or "Visit X (Week Y)/EOT" where the X was the re-assigned visit number and Y was the re-assigned week number in all safety and efficacy data listings as applicable.

Was revised to:

The analysis time points of interest are detailed in Table 2–2: Visit Schedule . Safety assessments will also be done at the Final Visit 12 weeks after the final dose of CZP.

For study participants who withdraw prior to the last time point for the particular analysis being conducted (ie, Week 16, Week 24, Week 56, Final), data recorded at the Early Discontinuation/EOT Visit will be assigned to what would have been the next scheduled visit, unless unavailable or otherwise specified, dependent on which visit schedule the study participant is following. These data will be included in the summaries of the assigned visit and the "Early Discontinuation/EOT" Visit if applicable. For efficacy data, the Early Discontinuation/EOT Visit will not be summarized and only the re-assigned visit will be included in the summary tables. Note that data from the Early Discontinuation Visit or EOT will be listed as "Visit X (Week Y)/ED" or "Visit X (Week Y)/EOT" where the X was the re-assigned visit number and Y was the re-assigned week number in all safety and efficacy data listings as applicable.

Change #16 The following section 3.2.3 was added describing Medications:

The UCB study physician will review a listing of all medications and flag those which are steroids, DMARDs, anti-TNFs, NSAIDs, Cox 2 inhibitors, analgesics, opioids, experimental medications, vaccines, etc. This flagging is then used to generate various medication tables.

Change #17

The following section 3.2.4 was added describing the Final Visit definition:

Final visit is defined as the visit conducted 12 weeks after the last dose of study medication. Most efficacy variables state that the Final Visit data will not be included in table summaries; the data will be included in study participant data listings.

Change #18

Section 3.4 Protocol Deviations was updated with the following sentence:

In addition, protocol deviations related to the impact of the global pandemic of coronavirus disease 2019 (covid-19) will be documented.

Change #19

Section 3.6 Treatment assignment and treatment groups

All subjects received CZP as a fixed dose based on weight. Prior to implementation of Protocol Amendments 4 and 5, the original CZP dose regimen was followed; subjects in the 10 to <20kg weight group received a CZP loading dose of 100mg and a maintenance dose of 50mg, subjects in the 20 to <40kg weight group received a CZP loading dose of 200mg and a maintenance dose of 100mg, and subjects in the >40kg weight group received a loading dose of 400mg and a maintenance dose of 200mg, all Q2W.

Has been changed to:

All study participants received CZP as a fixed dose based on weight. Prior to implementation of Protocol Amendments 4 and 5, and after Protocol Amendment 9, the original CZP dose regimen was followed; study participants in the 10 to <20kg weight group received a CZP loading dose of 100mg and a maintenance dose of 50mg, study participants in the 20 to <40kg weight group received a CZP loading dose of 200mg and a maintenance dose of 100mg, and study participants in the >40kg weight group received a loading dose of 400mg and a maintenance dose of 200mg, all Q2W.

Change #20:

Section 3.6 Treatment assignment and treatment groups, 4th paragraph:

For PK, safety and efficacy analyses, subjects will be grouped by their Baseline weight group. Selected analyses will also group subjects by their Baseline age group, concomitant MTX use, and overall anti-CZP antibody status (as defined in Section 8.2). Additionally, PK and selected safety data will be presented by CZP dose regimen (Reduced vs. Original CZP Dose Regimen). For subjects enrolled on the original CZP dose regimen, data will be tabulated overall, and selected data will be further subdivided into events and assessments occurring prior to and following dose reduction. Efficacy summaries will be presented by the Reduced CZP Dose Regimen, the Original CZP Dose Regimen, and the Any CZP Dose Regimen.

Has been changed to:

For PK, safety and efficacy analyses, study participants will be grouped by their Baseline weight group. Selected analyses will also group study participants by their Baseline age

group, concomitant MTX use, and overall anti-CZP antibody status (as defined in Section 8.2). Additionally, PK and selected safety data will be presented by CZP dose regimen (Reduced Overall vs. Original CZP Dose Regimen Overall). For study participants enrolled on the original CZP dose regimen, data will be tabulated overall, and selected data will be further subdivided into events and assessments occurring prior to or without and following dose reduction. Efficacy summaries will be presented by the Reduced CZP Dose Regimen Overall, the Original CZP Dose Regimen Overall, and the Any CZP Dose Regimen.

Change #21

Section 3.9 Changes to protocol-defined analyses

This analysis plan includes plots of CZP plasma concentrations, anti-CZP antibody concentrations, JADAS-71 and maximum PedACR response for individual subjects by visit; these plots were not pre-specified in the study protocol. In order to simplify the plots of CZP plasma concentrations, only reference lines from adult study C87050 will be included in the plots. The reference lines from adult study C87027, specified in the protocol as an additional adult study for comparison, will not be included.

Has been changed to:

This analysis plan includes plots of CZP plasma concentrations, anti-CZP antibody concentrations, JADAS-71 and maximum PedACR response for individual study participants by visit; these plots were not pre-specified in the study protocol.

Change #22

Section 4.3 Interim analyses and data monitoring

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 (adult study C87050). 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).

Comparisons will be made between the geometric mean 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.

If the pediatric plasma concentrations demonstrate that the geometric mean and pediatric data 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. If necessary, a revised pediatric dosing algorithm will be derived. Any change in dose regimen will require a protocol amendment prior to implementation.

An interim analysis of the PedACR30 Week 16 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 achieves a PedACR30 response at Week 16. Statistical output for this Week 16 interim analysis will be restricted to a limited subset of the tables and listings described in the current SAP, specifically tables and listings related to the following:

- PedACR30 response at Week 16

- Demographic and Baseline characteristics
- Disposition and discontinuation status
- Rescue and prohibited medication use

For purposes of regulatory submissions, full interim analyses will be performed after all active subjects have completed the Week 24 (Visit 10) assessments and after all active subjects 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 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. At the completion of the treatment period and follow-up period of all subjects at the end of the study, a final complete analysis of the study data will be performed.

All statistical tables, listings and figures comprising the current SAP (including the Week 16 interim analysis) will be produced for the Week 24 and Week 56 full interim analyses, as well as for the final analysis at the end of the study.

Given the descriptive nature of the data presentations in all data presentations, there are no statistical implications of these interim analyses.

Has been changed to:

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, 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. 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 Amendments 4 and 5 unusable from a regulatory standpoint.

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; this is referred to as the 2016 Week 24 interim analysis. 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; this will be referred to as the Updated Week 24 Interim analysis. A Week 56 (Visit 14) interim analysis will also be performed after all those enrolled, following the implementation of Protocol Amendment 9, have completed the Week 56 (Visit 14) assessments.

All statistical tables, listings and figures comprising this SAP will be produced for all future interim and final analyses.

Change #23:

Section 4.7 Examination of subgroups

- Overall anti-CZP antibody status:
    - AB+
    - AB-

Has been changed to:

- TE Anti-CZP antibody status and titer classification:
    - TE ADAb status negative
    - TE ADAb status positive <=32

- TE ADAb status positive >32 to <=128
- TE ADAb status positive >128 to <=512
- TE ADAb status positive >512 to <=1024
- TE ADAb status positive >1024 to <=4096

TE ADAb status positive >4096

Change #24

Section 5.1 Subject disposition – the following analysis was updated or added:

The number and percentage of study participants who were treated, who completed the study, and who discontinued from the study, along with the discontinuation reasons, will be summarized for the Safety Set. For the Week 16, Week 24 and Week 56 interim analyses, number of study participants completing Week 16, Week 24 and Week 56 (respectively) will be added in addition to the number completing the study as appropriate. The number of study participants in each analysis set will be presented. Summaries will be provided for the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups.

Discontinuations due to AEs will be summarized separately for the SS, and will be provided for the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups.

The number and percentages of subjects impacted by COVID-19 will be presented for each visit, overall and by impact category, for each relationship to COVID-19 as well as any relationship, overall and by country, for all subjects in the SS. This data will be presented in subject data listings.

Change #25

Section 5.2 Protocol deviations

However, all PK data will be included in listings, individual graphs, and PopPK analysis.

Has been changed to:

However, all PK data will be included in listings and individual graphs.

Change #26

Section 7 Measurements of Treatment Compliance – the following text was added:

Note also the dose escalation of ongoing study participants following Protocol Amendment 9 is considered in the calculations.

Change #27

Section 8 Pharmacokinetics and immunological procedures – the following text was added:

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 only in study participant listings.

Change #28:

Section 8.1 CZP Plasma concentrations

CZP plasma concentrations are measured at Baseline, Weeks 1, 4, 12, 16, 17, 24, 32, 40, 48, every 24 weeks thereafter, the Early Discontinuation/EOT Visit, and the Final Visit.

Has been changed to:

CZP plasma concentrations are measured at Baseline, Weeks 1, 4, 12, 16, 17, 24, 32, 40, 48, every 24 weeks thereafter, the Early Discontinuation/EOT Visit, and the Final Visit; for study participants enrolled prior to Protocol Amendment 8, samples were not collected after implementation of Protocol Amendment 8.

Change #29

Section 8.1 CZP Plasma concentrations

For subjects who began treatment on the original CZP dose regimen, geometric mean plasma concentrations will be summarized separately for the plasma samples obtained during the period of exposure to (1) the original CZP dose (all results before and through the dose reduction visit), and (2) the reduced CZP dose (all results from the initial dose reduction visit onward); plasma concentrations at the dose reduction visit will be included in both summaries for purposes of comparison. For the summarization of geometric mean concentrations on the reduced CZP dose, visits will be identified as number of weeks relative to the dose reduction visit, regardless of the actual visit at which the dose reduction occurred. Subjects that reduce dose are thus expected to have plasma concentration results at the dose reduction visit, 4 weeks after dose reduction (identified as Week 4), 8 weeks after dose reduction (identified as Week 8), and 12 weeks after dose reduction (identified as Week 12). Any subsequent concentration results for the reduced dose period will also be similarly summarized (ie, concentration results 24 weeks after dose reduction will be summarized as Week 24 results).

Summaries of concentration results will be provided by Baseline weight group, as well as Baseline age group. In addition, summaries will be provided by anti-CZP antibody titer and concomitant MTX use in combination with Baseline weight group.

Geometric mean plasma concentration time curves will be provided separately for subjects enrolled on the original CZP dose regimen vs. the reduced CZP dose regimen. For subjects enrolled on the original CZP dose regimen, geometric mean plasma concentrations will be plotted separately for the plasma samples obtained during the period of exposure to (1) the original CZP dose (all results before and through the dose reduction visit), and (2) the reduced CZP dose (all results from the initial dose reduction visit onward). As described above for the tabular summary, plots of geometric mean plasma concentrations at and following dose reduction visits will be identified as number of weeks relative to the dose reduction visit, regardless of the actual visit at which the dose reduction occurred. Plots of

geometric mean plasma concentrations will be provided overall and by Baseline age stratum, Baseline weight group, anti-CZP antibody titer, and concomitant MTX use.

In addition, observed plasma concentrations over time will be plotted for individual subjects, separately for each dose regimen, which will also identify weight group per subject. For subjects who began treatment according to the original CZP dose regimen, plasma concentrations will be plotted separately for the plasma samples obtained during the period of exposure to (1) the original CZP dose (all results before and through the dose reduction visit), and (2) the reduced CZP dose (all results from the initial dose reduction visit onward). As described above, plots of plasma concentrations at and following dose reduction visits will be identified as number of weeks relative to the dose reduction visit, regardless of the actual visit at which the dose reduction occurred. Plots of individual plasma concentrations will be provided by Baseline age stratum, Baseline weight group, anti-CZP antibody titer, and concomitant MTX use.

For purposes of comparison between pediatric and adult subjects, adult CZP plasma concentration data for subjects from the Safety Population on the CZP 200mg arm from adult study C87050 will be used to derive reference boundaries for all of the plots described in this section. The plots of plasma concentrations will have reference lines of the adult 5th and 95th CZP concentration percentiles at Week 12 superimposed on to them, as well as the upper and lower limits of the 95% CI of the geometric mean plasma concentrations from the C87050 study at Week 12. In addition, for the plots of the geometric means, the minimum and maximum range of the pediatric concentrations at each time point will be included. All plots of CZP concentration data described in this section will be presented on a linear scale.

Values below the limit of quantification of 0.41µg/mL will be set to half the limit of quantification for the summaries. The geometric mean and CV% was derived when at least two-thirds of the concentrations at a certain visit were above the limit of quantification (LoQ).If that criteria was not met, only the maximum and minimum values were shown. Similarly, the 95% CI of the geometric mean was only calculated if at least 5 samples were available at that time point. Note that a separate partial PK exclusion regarding concentration calculation is detailed in section 5.2.

Has been changed to:

For study participants enrolled prior to Amendment 9, who began treatment on the original CZP dose regimen, and whose PK samples are analyzed with the ECLIA method, plasma CZP concentrations will be summarized separately for samples obtained during the period of exposure to (1) the original CZP dose (all results before and through the dose reduction visit), and (2) the reduced CZP dose (all results from the initial dose reduction visit onward). Plasma concentrations at the visit where dose reduction was to be initiated will be included in summary (1) only. Concentrations from participants enrolled after Amendment 9 will be included in Summary (1).

For the summarization of geometric mean concentrations on the reduced CZP dose, visits will be identified as number of weeks relative to the dose reduction visit, regardless of the actual visit at which the dose reduction occurred. Study participants that reduce dose are thus expected to have plasma concentration results at the dose reduction visit, 4 weeks after dose

reduction (identified as Week 4), 8 weeks after dose reduction (identified as Week 8), and 12 weeks after dose reduction (identified as Week 12). Any subsequent concentration results for the reduced dose period will also be similarly summarized (ie, concentration results 24 weeks after dose reduction will be summarized as Week 24 results).

Summaries of concentration results will be provided by Baseline weight group, as well as Baseline age group. In addition, summaries will be provided by TE ADAb status with titer classification (see 8.2) and concomitant MTX use in combination with Baseline weight group.

Geometric mean plasma concentration time curves will be provided separately for study participants according to the ECLIA assay and dosing scenarios outlined above for the tabular summaries. Geometric mean plots will be provided overall and by Baseline age stratum, Baseline weight group, TE ADAb status with titer classification (see 8.2), and concomitant MTX use.

In addition, observed plasma concentrations over time will be plotted for individual study participants, separately for each dose regimen whose samples have been analyzed with the ECLIA method. Plots of individual plasma concentrations will be provided by Baseline age stratum, Baseline weight group, TE ADAb status with titer classification (see 8.2), and concomitant MTX use.

Concentrations below the limit of quantification of 32.0 ng/mL (0.032µg/mL) (BLQ) will be replaced by the LLOQ divided by 2 for the calculation of descriptive statistics. The geometric mean and CV% will be derived when at least two-thirds of the concentrations at a certain visit are above the LLOQ. If that criteria are not met, only the maximum and minimum values will be shown. Similarly, the 95% CI of the geometric mean will be calculated if at least 5 samples are available at a time point.

Change #30

Section 8.2 Anti-CZP Antibodies

Anti-CZP antibody concentrations are measured at Baseline, Weeks 1, 4, 12, 16, 17, 24, 32, 40, 48, every 24 weeks thereafter, the Early Discontinuation/EOT Visit, and the Final Visit. Summaries of anti-CZP antibody status will include the frequency and percentage of subjects who are AB- and AB+ for each visit where samples were taken. At each visit:

- Values ≤2.4units/mL are defined as AB-
- Values >2.4units/mL are defined as AB+

In addition, overall antibody status will be summarized:

- Overall AB+ is defined as having a value > 2.4units/mL at any time in the treatment period (Note: All post-baseline data will be included except for the safety follow-up visit).
- Overall AB- is defined as having no values > 2.4units/mL during the treatment period.

Anti-CZP antibody status will be summarized for the Reduced, Original, and Any CZP Dose Regimen groups. For subjects who began treatment on the original CZP dose regimen, anti-CZP antibody status will be summarized combining results prior to and following dose reduction. In addition, summaries of antibody status will be produced separately for the antibody results obtained during the period of exposure to (1) the original CZP dose (all results before and through the dose reduction visit), and (2) the reduced CZP dose (all results after the initial dose reduction visit). As described above for plasma concentration results, for the summarization of antibody status after dose reduction, visits will be identified as number of weeks relative to the dose reduction visit regardless of the actual visit at which the dose reduction occurred.

Summaries of anti-CZP antibody titer will be provided by Baseline weight group, as well as Baseline age group. In addition, summaries will be provided by concomitant MTX use in combination with Baseline weight group. Each subgroup summary will be provided for the Reduced, Original (overall, and prior to and following dose reduction), and Any CZP Dose Regimen groups.

These summaries will be provided for the PK-PP Set. All anti-CZP antibody data will be listed. In addition, graphical presentation of cumulative percentage of positive Anti-CZP antibody status will be presented by Reduced CZP Dose Regimen, Original CZP Dose Regimen Prior to Dose Reduction, and Original CZP Dose Regimen Following Dose Reduction respectively.

Has been changed to:

Immunogenicity will be assessed through listing of individual results by study participant and summary tables for data generated with the ECLIA method only. Immunogenicity data will be related to PK and efficacy readouts.

Anti-drug antibodies will be assessed by a three-tiered approach: screening (positive or negative screen), confirmatory (positive or negative immunodepletion) and titer assays, using ECLIA methods. Cut points will be determined during assay validation and used by the bioanalytical laboratory to determine the status of ADAb in the test samples.

The following definitions will be applied regarding classification of test samples:

· An ADAb status will be confirmed as positive for any sample with an ADAb level that is positive screen and positive immunodepletion.

· An ADAb status of negative will be concluded for any sample with an ADAb level that is either negative screen or positive screen and negative immunodepletion.

Confirmed positive samples will be titrated and the titer will be reported. The ADAb titer is presented in the listings and summaries including the minimum required dilution.

If the titer for an ADAb level that is positive screen and positive immunodepletion is missing, then a conservative approach will be used and ADAb status will be considered as positive. No imputation rules apply for the missing titer.

If the ADAb level is positive screen but no confirmatory result could be determined, then then a conservative approach will be used and ADAb status will be considered as positive.

Anomalous values will not be included in summaries/analysis but they will be reviewed and flagged by the study Clinical Pharmacologist.

Study participants will receive a treatment-emergent (TE) ADAb status and will be classified as follows based on the ADAb assay results:

· TE ADAb status positive is defined as either (i) baseline ADAb negative study participants having at least one ADAb confirmed positive sample post baseline or ii) baseline ADAb positive study participants with at least one post baseline sample with ≥minimum significant ratio (MSR) -fold increase from baseline on CZP treatment. The MSR will be defined during the process of sample analysis and is disease-specific.

· TE ADAb status negative is defined as having no samples either ADAb positive or with values ≥MSR -fold increase from baseline.

Once determined positive, a study participant's highest titer is used to categorize ("titer classification") the study participant as follows:

· Positive ≤32

· Positive >32 - ≤128

· Positive >128 - ≤512.

- Positive >512 - ≤1024
- Positive >1024 - ≤4096
- Positive >4096.

All ADAb summaries will be provided for the SS Set. All ADAb data will be listed.

Summary of shift from Baseline ADAb status with titer classification to TE ADAb Status with titer classification for all study participants will be presented during the entire study, by visit. Summaries of ADAb data will be provided by Baseline weight group, as well as Baseline age group. In addition, summaries will be provided by concomitant MTX use in combination with Baseline weight group.

TE ADAbs will be presented separately (per ADAb status and titer classification) for the Original and Reduced Dose periods (using the study Visit nomenclature previously outlined for PK concentrations), including the Final visit.

The time to achieving TE ADAb for all study participants will be analyzed based on Kaplan-Meier methods. Study participants will be considered to have an event at the time where treatment-emergent ADAb positive is first achieved during treatment period excluding Baseline/pre-treatment. Study participants classified as treatment-emergent ADAb negative will be censored at the time of last available ADAb result. The median and 95% CI based on the Kaplan-Meier estimation will also be presented. A plot of time to first ADAb positivity will be presented.

A scatter plot of CZP plasma concentrations and ADAb titer, separated by concomitant MTX use, will be presented. This plot will be repeated for separation by concomitant MTX use as well as Baseline body Weight group

Change #31

Section 8.3 CZP Plasma concentrations, anti-CZP antibody titers, and PedACR response

Individual subject plots displaying CZP plasma concentrations, anti-CZP antibody concentrations, JADAS-71 score and maximum PedACR response (the highest PedACR response at a given visit) will be produced by visit on the same plot. Plasma concentrations and antibody concentrations will be plotted on a log scale. At each time point, the JADAS-71 score and maximum PedACR response at that visit will be plotted on a linear scale. A vertical line will be drawn at the time point of dose reduction (when applicable). Individual subject plots will be provided separately for overall AB+ and overall AB- subjects.

Has been changed to:

Individual subject plots displaying log CZP plasma concentrations, log2 ADAb titers, JADAS-71 score and maximum PedACR response (the highest PedACR response at a given

visit) will be produced by visit on the same plot. At each time point, the JADAS-71 score and maximum PedACR response at that visit will be plotted on a linear scale. A vertical line will be drawn at the time point of dose reduction (when applicable).

Spaghetti plots of ADAb titer on a log2 scale by week from CZP first dosing separated by concomitant MTX use and ADAb titer classification will be presented for study participants with PedACR0/30/50/70/90 at Week 16 as separate graphs.

Change #32

Section 9.1 Extent of exposure

Subject time at risk will also be calculated. Subject time at risk represents the time a subject is at risk for having an AE. Subject time (in days) at risk will generally be calculated as (date of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). The calculation of subject time at risk will be modified for original CZP dose regimen subjects that reduce dose; for the period of exposure prior to dose reduction, subject time at risk ends on the date of dose reduction (ie, do not add 70 days). Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Duration of exposure and subject time at risk will be calculated as appropriate for each of the following CZP dose regimen groups:

- Reduced CZP Dose Regimen: includes period of exposure to all CZP doses for all subjects enrolled on the reduced CZP dose regimen
- Original CZP Dose Regimen: includes period of exposure to all CZP doses for all subjects enrolled on the original CZP dose regimen regardless of dose or subsequent dose reduction
- Original CZP Dose Regimen Prior to Dose Reduction: includes period of exposure to original CZP dose regimen only (ie, exposure period ends on the date of dose reduction)
- Original CZP Dose Regimen Following Dose Reduction: includes period of exposure to reduced CZP dose regimen only (ie, exposure period begins on the date of dose reduction)
- Any CZP Dose Regimen: includes all CZP doses for all treated subjects

Study drug exposure will be summarized for the Reduced, Original, and Any CZP Dose Regimen groups. For subjects on the original CZP dose regimen, exposure will be summarized combining results prior to and following dose reduction. In addition, for subjects on the original CZP dose regimen, summaries of exposure will be produced separately for the period of exposure to (1) the original CZP dose (all exposure before the dose reduction visit), and (2) the reduced CZP dose (all exposure after the initial dose reduction visit).

Has been changed to:

Subject time at risk will also be calculated. Subject time at risk represents the time a subject is at risk for having an AE. Subject time (in days) at risk will generally be calculated as (date

of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). However, the calculation of subject time at risk will be modified for study participants who change from original CZP dose regimen to reduced CZP dose regimen, or who dose escalate from reduced CZP dose regimen to the original CZP dose regimen. For the period of exposure prior to a dose change, subject time at risk ends on the date of dose change (ie, do not add 70 days). For the period of exposure on the final CZP dose regimen for a study participant, time at risk should include the additional 70 days. Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Duration of exposure and subject time at risk will be calculated as appropriate for each of the following CZP dose regimens:

- Reduced CZP Dose Regimen Overall: includes period of exposure to all CZP doses for all study participants enrolled on the reduced CZP dose regimen regardless to dose escalation
    - Reduced CZP Dose Regimen Prior to or without Dose Escalation: includes period of exposure to reduced CZP dose regimen only (ie, exposure period ends on the date of dose escalation)
- Original CZP Dose Regimen Overall: includes period of exposure to all CZP doses for all study participants enrolled on the original CZP dose regimen regardless of dose or subsequent dose reduction
    - Original CZP Dose Regimen Prior to or without Dose Reduction: includes period of exposure to original CZP dose regimen only (ie, exposure period ends on the date of dose reduction)
    - Original CZP Dose Regimen Following Dose Reduction: includes period of exposure to reduced CZP dose regimen only (ie, exposure period begins on the date of dose reduction)
- Any CZP Dose Regimen: includes all CZP doses for all treated study participants
- Escalation CZP Dose Regimen: includes period of exposure to an escalation CZP dose regimen only (ie, exposure period begins on the date of dose escalation for study participants from Reduced CZP Dose Regimen as well as Original CZP Dose Regimen Following Dose Reduction)

Study drug exposure will be summarized for the Reduced - Overall, Original - Overall, and Any CZP Dose Regimen groups. For study participants on the original CZP dose regimen, exposure will be summarized combining results prior to and following dose reduction. In addition, for study participants on the original CZP dose regimen, summaries of exposure will be produced separately for the period of exposure to (1) the original CZP dose (all exposure before the dose reduction visit or all exposure for study participants with no dose reduction), and (2) the reduced CZP dose (all exposure after the initial dose reduction visit). For study participants who dose escalate, exposure will be summarized.

Change #33

The following was inserted in Section 9.2 Adverse Events:

Any TEAE leading to permanent withdrawal of IMP

Change #34

Section 9.2 Adverse Events

Overall summaries of TEAEs will be provided for the Reduced, Original, and Any CZP Dose Regimen groups. For subjects on the original CZP dose regimen, summaries will be provided combining results prior to and following dose reduction. In addition, overall TEAE summaries for the original CZP dose regimen will be produced separately for TEAEs occurring during the period of exposure to (1) the original CZP dose (all results before the dose reduction visit), and (2) the reduced CZP dose (all results after the initial dose reduction visit). TEAEs occurring on the day of dose reduction will be reviewed by the study physician in order to assign events to the most appropriate time period (before or after dose reduction).

Has been changed to:

Overall summaries of TEAEs will be provided for the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups. For study participants on the reduced CZP dose regimen overall, summaries will be provided for the TEAEs occurring during the period of exposure to reduced CZP dose only. For study participants on the original CZP dose regimen, summaries will be provided combining results prior to and following dose reduction. In addition, overall TEAE summaries for the original CZP dose regimen will be produced separately for TEAEs occurring during the period of exposure to (1) the original CZP dose (all results before the dose reduction visit or all results for study participants with no dose reduction), and (2) the reduced CZP dose (all results after the initial dose reduction visit). For study participants on either Reduced Overall or Original Overall, overall TEAE summaries will be produced for TEAEs occurring during the period of exposure to (3) the escalated CZP dose (all results after the initial dose escalation visit). TEAEs occurring on the day of dose reduction or dose escalation, respectively, will be reviewed by the study physician in order to assign events to the most appropriate time period (before or after dose reduction or dose escalation, respectively).

Change #35

Section 9.2 Adverse Events

For all of the summaries in the above list (except for the ones flagged with an asterisk (*) or double asterisks (**)), TEAEs will be summarized for the Reduced, Original, and Any CZP Dose Regimen groups. For the above summaries flagged with double asterisks (**), only the Any CZP Dose Regimen will be presented. For the above summaries flagged with an asterisk (*), TEAEs for the Original CZP Dose Regimen group will also be summarized separately for events occurring during the period of exposure to (1) the original CZP dose (all results before the dose reduction visit), and (2) the reduced CZP dose (all results after the initial dose reduction visit). As indicated above, TEAEs occurring on the day of dose reduction will be reviewed by the study physician in order to assign events to the most appropriate time period (before or after dose reduction).

Has been changed to:

For all of the summaries in the above list (except for the ones flagged with an asterisk (*) or double asterisks (**)), TEAEs will be summarized for the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups. For the above summaries flagged with double asterisks (**), only the Any CZP Dose Regimen will be presented. For the above summaries flagged with an asterisk (*), TEAEs for the Original CZP Dose Regimen Overall group will also be summarized separately for events occurring during the period of exposure to (1) the original CZP dose (all results before the dose reduction visit or all results for study participants with no dose reduction), and (2) the reduced CZP dose (all results after the initial dose reduction visit); the Reduced Overall will summarize separately events occurring during the period of exposure to Reduced CZP Dose regimen; and study participants from either Reduced Overall and Original Overall will summarize separately events occurring during the period of the escalated CZP dose (all results after the initial dose escalation visit). As indicated above, TEAEs occurring on the day of dose reduction or dose escalation, respectively, will be reviewed by the study physician in order to assign events to the most appropriate time period (before or after dose reduction or dose escalation, respectively).

Change #36

Section 9.2 Adverse Events

Data displayed will include the number of AEs, number of subjects experiencing the AEs and percentage of subjects with the AE (all occurrences of the same event will be counted under the number of AEs but the subject will only be counted once). Summaries of all TEAEs, serious TEAEs, TEAEs leading to death, and TEAEs leading to study discontinuation will also include the exposure-adjusted incidence rate (EAIR) with associated 95% confidence interval, and the exposure-adjusted event rate (EAER).

Has been changed to:

Data displayed will include the number of TEAEs, number of study participants experiencing the TEAEs and percentage of study participants with the TEAE (all occurrences of the same event will be counted under the number of TEAEs but the subject will only be counted once). Summaries of all TEAEs, serious TEAEs, TEAEs leading to death, TEAEs leading to permanent withdrawal of IMP, and TEAEs leading to study discontinuation will also include the exposure-adjusted incidence rate (EAIR) with associated 95% confidence interval, and the exposure-adjusted event rate (EAER).

Change #37:

Section 9.2 Adverse events, the following were updated:

3) Congestive heart failure. These will be manually identified by the study physician from the previously described All TEAEs table. No separate table is planned. In addition, major adverse cardiac events (MACE) will be presented in a table using UCB-defined search criteria and will include fatal and serious non-fatal myocardial infarction, cerebrovascular events and congestive heart failure.

4) Demyelinating-like disorders. These will be manually identified by the study physician from the previously described All TEAEs table. No separate table is planned.

7) Lupus and lupus-like illness. These will be manually identified by the study physician from the previously described All TEAEs table. No separate table is planned.

8) Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from the previously described All SAEs table. No separate table is planned.

Has been changed to:

3) Congestive heart failure. These will be manually identified by the study physician from the previously described All TEAEs table. In addition, major adverse cardiac events (MACE) will be presented in a table using UCB-defined search criteria and will include fatal and serious non-fatal myocardial infarction, cerebrovascular events and congestive heart failure.

4) Demyelinating-like disorders. These will be manually identified by the study physician from the previously described All TEAEs table.

7) Lupus and lupus-like illness. These will be manually identified by the study physician from the previously described All TEAEs table.

8) Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from the previously described All SAEs table.

Change #38

Section 9.2 Adverse Events

The following is an AE of special interest for this study; the associated analysis will be described in the PDILI paragraph in Section 9.3:

Potential Hy's Law, defined as ≥3xULN alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (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.

Further information regarding search criteria and algorithms is provided in the guidance document "AEs of Interest – Cimzia Program".

Change #39

Section 9.2 Adverse events

The tables for 1, 2, 3, 5, and 6 above will be summarized by SOC, HLT, and PT and will include the number of events, the number and percentage of subjects with an event, the EAIR with associated 95% CIs and the EAER. AEs of interest tables will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall, the Original CZP Dose Regimen Prior to Dose Reduction, the Original CZP Dose Regimen Following Dose Reduction, and the Any CZP Dose Regimen.

Has been changed to:

The tables for 1, 2, 3, 5, and 6 above will be summarized by SOC, HLT, and PT and will include the number of events, the number and percentage of study participants with an event, the EAIR with associated 95% CIs and the EAER. TEAEs of interest tables will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall, the Original CZP Dose Regimen Prior to Dose Reduction or without Dose Reduction, the Original CZP Dose Regimen Following Dose Reduction, the Any CZP Dose Regimen, and the Dose Escalation Dose Regimen.

Change #40

Section 9.3 Clinical laboratory evaluations

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.

All laboratory summaries described in this section will be provided overall (ie, Any CZP Dose Regimen) and by Baseline weight group only; no additional summarized by CZP dose regimen will be provided.

Has been changed to:

All laboratory summaries described in this section will be provided overall (ie, Any CZP Dose Regimen) and by Baseline weight group; laboratory summaries will also be provided by the Dose Escalation Dose Regimen and by Baseline weigh group.

Change #41

Section 9.3 Clinical laboratory evaluations – the following paragraph was added:

PDILI IMP discontinuation criteria as outlined in the Appendix of Protocol Amendment 9 will be evaluated at all laboratory assessments, for all study participants. The number and percentage of study participants with elevated liver function tests and meeting PDILI criteria will be presented. Any data that meets the PDILI criteria or is captured regarding PDILI will be listed.

Change #42

Section 9.4.1 Vital Signs

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.

Descriptive statistics for observed values, and change from pre-dose to post-dose pulse and blood pressure when available, will be presented for each visit for each vital sign parameter.

Vital signs summaries will be provided overall (ie, for the Any CZP Dose Regimen) and by Baseline weight group only; no additional summaries by CZP dose regimen will be provided.

Has been changed to:

Descriptive statistics for observed values and change from pre-dose to post-dose pulse and blood pressure when available, will be presented for each visit for each vital sign parameter.

Vital signs summaries will be provided overall (ie, for the Any CZP Dose Regimen) and by Baseline weight group; vital sign summaries will also be provided by the Dose Escalation Dose Regimen and by Baseline weigh group.

Change #43

Section 9.4.2.1 Height and weight

Height will be collected at Screening, Baseline, Weeks 24 and 48, every 24 weeks thereafter, and the Early Discontinuation/EOT Visit. Weight will be collected at Screening, Baseline, and every visit through the Final Visit. Pre-study height and weight measurements will be collected at Screening for a period of up to 12 months prior to study entry, including up to 3 sets of measurements for the 6-month period prior to study entry, and up to 3 sets of measurements for the period of time >6 to 12 months prior to study entry. Where possible, pre-study measurements as close as possible to 6 and 12 months prior to study entry will be collected.

Has been updated to:

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.

Change #44

Section 9.4.2.2 Tanner stages

Assessments of subjects' developmental stages on external genitalia and pubic hair (boys) and on breast and pubic hair (girls) will be performed to determine Tanner stages. Tanner stages will be assessed at Baseline, Weeks 24 and 48, every 24 weeks thereafter, and the Early Discontinuation/EOT Visit. A summary of shift table of Tanner stages from baseline to relevant post-treatment visit(s) (eg., 48 week) by age and gender will be provided for the Any CZP Dose Regimen. Overall Tanner stage at each visit is derived as the minimum stage of the 2 components. If one component is missing at a visit, then the overall stage will be set to missing for that 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, for

those who have not reached Tanner stage V. A summary of shift table of Tanner stages from baseline to relevant post-treatment visit(s) (eg., 48 week) by age and gender will be provided for the Any CZP Dose Regimen. Overall Tanner stage at each visit is derived as the minimum stage of the 2 components. If one component is missing at a visit, then the overall stage will be set to missing for that visit.

Change #45

Section 9.4.2.4 Reproductive potential and birth control

The reproductive potential of all subjects will be assessed by clinical questioning at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32, every 8 weeks thereafter, the Early Discontinuation/EOT Visit, and the Final Visit. If the subject is not of reproductive potential, the reason will be recorded. If the subject is of reproductive potential and is sexually active, the method of birth control used will be recorded. Reproductive potential and birth control information will be listed by visit for each subject.

Has been changed to:

The 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 subject is not of reproductive potential, the reason will be recorded. If the subject is of reproductive potential and is sexually active, the method of birth control used will be recorded. Reproductive potential and birth control information will be listed by visit for each subject.

Change #46

Section 9.4.2.5 Autoantibodies

All autoantibodies summaries will be provided overall (ie, for the Any CZP Dose Regimen) and by Baseline weight group only; no additional summaries by CZP dose regimen will be provided.

Has been changed to:

All autoantibodies summaries will be provided overall (ie, for the Any CZP Dose Regimen) and by Baseline weight group; all autoantibody summaries will also be provided by the Dose Escalation Dose Regimen and by Baseline weigh group.

Change #47

Section 10 Efficacy Analyses

Efficacy will be analyzed using the FAS. All efficacy results will be provided for the Reduced CZP Dose Regimen, the Original CZP Dose Regimen, and the Any CZP Dose Regimen. For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and anti-CZP antibody status will be presented pooling across all weight groups unless otherwise specified. In addition, selected summaries will also be presented by gender and race.

Has been changed to:

Efficacy will be analyzed using the FAS. All efficacy results will be summarized overall and by Baseline weight group and will be provided for the Reduced CZP Dose Regimen Overall, the Original CZP Dose Regimen Overall, and the Any CZP Dose Regimen. For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and anti-CZP antibody status will be presented pooling across all weight groups unless otherwise specified. In addition, selected summaries will also be presented by gender and race.

Change #48

The following sentence was updated in Section 10.3.8 Juvenile Arthritis Disease Activity Score 71-joint:

Descriptive statistics of the observed composite scores and change from Baseline will be presented by visit (except at Final Visit).

13.4 AMENDMENT 4

Rationale for the amendment

The primary reasons for this SAP amendment was to:

- Update the analyses for the CZP plasma concentrations,
- Update the analyses for the anti-CZP antibodies,
- Clarify the definitions for the dose group presentations used in the analyses,
- Slightly modify the definition for FAS at the suggestion of FDA,
- Removal of the LOCF methodology at the suggestion of FDA,
- Clarify the CTCAE criteria for laboratory markedly abnormal criteria,
- Update the subgroup variables used in the analyses,
- Specify the markedly abnormal criteria for vital signs,
- Specify sensitivity analyses of TEAEs in regards to covid vaccination in the Treatment Period, and
- Describe the analyses of PK data that will be done with RA0138 data for comparison to RA0043 analyses.

Modifications and changes

Global changes

The reference to polyarticular-source JIA has been changed to pJIA throughout the SAP.

Three dose groups are now referenced for analysis: Original CZP Dose, Reduced CZP Dose and Any CZP Dose. For Original CZP Dose and Reduced CZP Dose, the data captured from when the study participant takes their first dose until the day before their dose is changed, is what is presented in those analyses. For Any CZP Dose, all data captured from first CZP through the last CZP dose is presented, for completeness.

Specific changes

Change #1

SAP/Amendment	Date
Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016
SAP Amendment 3	30 Jun 2021

Has been changed to:

SAP/Amendment	Date
Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016
SAP Amendment 3	30 Jun 2021
SAP Amendment 4	8 Dec 2022

Change #2

Section 2, Protocol Summary, the following was added:

Below is the list of protocol amendments, dates and rationales for key updates:

Table 13–1: Protocol, Amendments, Dates and Rationales

RA0043 Protocol/Amendment Number	Date	Rationale for Key Updates
Protocol	10 Jan 2010	NA
Amendment 1	26 Aug 2011	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. Key updates include adding effectiveness as a secondary objective, defining the study population as polyarticular-course JIA, setting minimum number of enrolled participants by body weight and age and adding the study stopping rule.
Amendment 2	02 Jul 2012	The primary purpose of this nonsubstantial amendment is to change in the participating countries, including removal of Western Europe. RA0043 will not be included in the European

Table 13–1: Protocol, Amendments, Dates and Rationales

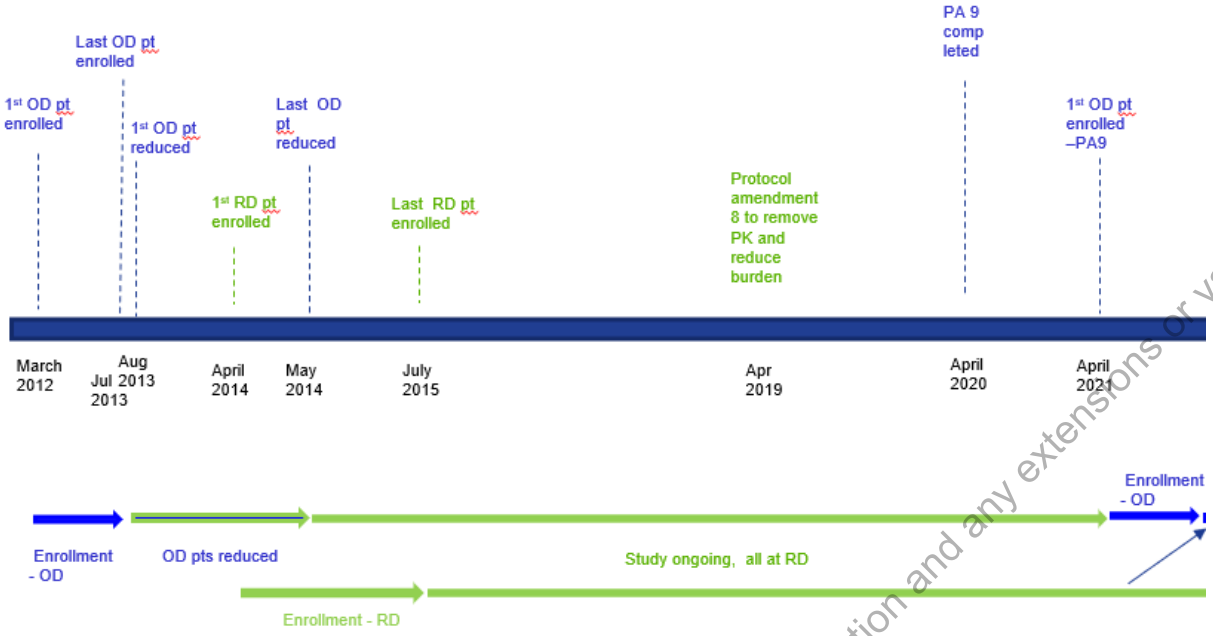
		Paediatric Investigational Plan and will therefore not be conducted in Western Europe.
Amendment 2.1	21 Aug 2012	Amendment 2 adapted for Russia. The primary purpose of this substantial amendment is to change the age range for enrollment from 2-17 years to 6-17 years of age which is in response to comments received from the Ministry of Health and Social Development of the Russian Federation.
Amendment 3	06 May 2013	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.
Amendment 3.1	06 May 2013	Amendment 3 adapted for Russia as per Amendment 2.1.
Amendment 4	01 Aug 2013	The primary purpose of this substantial amendment is for the dose for study participants already enrolled in RA0043 to be reduced (enrollment into RA0043 was suspended, effective 17 Jul 2013). 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).
Amendment 4.1	01 Aug 2013	Amendment 4 adapted for Russia as per Amendment 2.1.
Amendment 5	20 Jan 2014	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.
Amendment 5.1	20 Jan 2014	Amendment 5 adapted for Russia as per Amendment 2.1.
Amendment 5.2	23 Feb 2015	The primary purpose of this nonsubstantial amendment is to lift the enrollment cap per site in Russia to allow further enrollment in the weight group of 15 to <20kg for sites that have enrolled the maximum number of 12 study participants.
Amendment 6	17 Sep 2015	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).
Amendment 6.1	17 Sep 2015	Amendment 6 adapted for Russia as per Amendment 2.1.
Amendment 7	22 Sep 2016	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

Table 13–1: Protocol, Amendments, Dates and Rationales

		Week 56 will be analyzed "as observed" and will no longer be imputed as nonresponse or missing.
Amendment 7.1	22 Sep 2016	Amendment 7 adapted for Russia as per Amendment 2.1.
Amendment 8	24 Jun 2019	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.
Amendment 8.1	18 Jul 2019	Amendment 8 adapted for Russia as per Amendment 2.1
Amendment 9	27 Apr 2020	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.
Amendment 9.1	28 Jul 2020	Amendment 9 adapted for Russia as per Amendment 2.1
Amendment 9.2	30 Jul 2021	The primary purpose of this nonsubstantial amendment is to increase the enrollment cap per site in Russia to allow further enrollment on the original dose regimen for sites that have enrolled the maximum number of 16 study participants.

Results of a planned interim PopPK analysis conducted suggested that while observed CZP plasma concentrations with the original dose regimen administration remained in the adult range, they were at the upper end of the distribution. 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. Based on interactions with FDA, Amendment 9 re-introduced the original dose regimen for 30 new participants and the option to increase to this dose for ongoing participants that had been receiving the reduced dose.

The following graphic illustrates the study conduct once study participants taking original dose regimen were allowed to reduce their dose:



OD=Original CZP Dose, RD=Reduced CZP Dose

Change #3

Section 2, Protocol Summary

In order to adequately assess the exposure levels and clinical experience of CZP in JIA at both the reduced and original CZP dose regimen and also to 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 under Protocol Amendment 9 or later will have plasma concentrations of CZP and anti-CZP antibodies analyzed using electrochemiluminescence immunoassay (ECLIA) methods 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 methods. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation

Was changed to:

In order to adequately assess the exposure levels and clinical experience of CZP in pJIA at both the Reduced and Original CZP Dose and also to further support the safety assessment of the Original CZP Dose, 30 additional study participants will be enrolled on the Original CZP Dose following Protocol Amendment 9.

All study participants enrolled under Protocol Amendment 9 or later will have plasma concentrations of CZP and anti-CZP antibodies analyzed using electrochemiluminescence immunoassay (ECLIA) methods that meets current regulatory standards (versus those previously analyzed using ELISA methods for the prior Week 24 interim analysis). In addition, PK and ADAb samples (for which sufficient volume is available) collected in this

study for participants enrolled prior to Protocol Amendment 9 will be re-analyzed with the ECLIA methods. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

Change #4

Section 2.2.3.4, Additional other variables was added

Additional variables that were covered under other variables that will be specifically analyzed and intended to be used for comparison purposes to support the regulatory submission include:

- CZP plasma concentrations at Weeks 12 and 24
- Anti-CZP antibody levels up to and including Week 24
- CZP plasma concentration from study RA0138 at Weeks 12 and 24
- Anti-CZP antibody levels from study RA0138 up to and including Week 24

Change #5

Section 2.3, Study design and conduct

The table below shows the data collection schedule prior to Protocol Amendment 8 and after implementing Protocol Amendment 8. For the study participants who switch to the 16 week schedule, the date of the first visit of this schedule will be captured on the "Study Participation" CRF module.

Was changed to:

The table below shows the data collection schedule prior to Protocol Amendment 8 and after implementing Protocol Amendment 8. For the study participants who switch to the 16-week schedule, the date of the first visit of this schedule will be captured on the "Study Participation" CRF module. Of note, the participants enrolled after Protocol Amendment 9 (the new 30 study participants on Original CZP Dose) will remain on the original visit schedule throughout the study.

Change #6

Section 2.3, Study design and conduct

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 are CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the original minimum and maximum maintenance doses are CZP 50mg Q2W and CZP 200mg Q2W, respectively.

Based on 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 Amendments 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.

Based on 24-week interim results from the first 163 study 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 to adequately support the safety assessment of the original CZP dose 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.

Full interim analyses were performed in 2016 after all active study participants completed the Week 24 (Visit 10) assessments. Week 24 full interim analyses were completed as described in SAP Amendment 1. SAP Amendment 3 comprises the analyses to be completed for an Updated Week 24 (Visit 10) interim, Week 56 (Visit 14) interim and the final analysis of the study.

Was 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 (except the 10 to < 20kg group on the reduced dose will be administered 50mg Q4W). The doses are explained in the following table:

Table 13–2: 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.

Based on 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 with the bioanalytical assays used for RA0043, which rendered the PK data unreliable. Accordingly, PK samples were no longer collected for study participants on the Reduced CZP Dose following implementation of Protocol Amendment 8, in addition to reducing the burden on participants who had already been in the study for a number of years.

A validated ECLIA method that meets the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics will be used for any new analyses, including re-analysis of archived samples collected before Protocol Amendment 9 and for the analysis of bio-samples collected from the additional 30 study participants after Protocol Amendment 9.

Based on 24-week interim results from the first 163 study participants enrolled in RA0043, both the original and reduced doses showed safety profiles similar to the approved CZP dose regimen in the adult RA population. The overall clinical response in this analysis (taking both doses into account) was PedACR30 and PedACR50 responses of 77.3% and 67.5%, respectively at Week 12. The response from the original dose was 75.6% for PedACR30 and 64.1% for PedACR50; the response from the reduced dose was 78.8% for PedACR30 and 70.6% 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 Doses and support the safety for the Original CZP Dose, 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 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 ADAb 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.

Full interim analyses were performed in 2016 after all active study participants completed the Week 24 (Visit 10) assessments. Week 24 full interim analyses were completed as described in SAP Amendment 1. SAP Amendment 4 comprises the analyses to be completed for an Updated Week 24 (Visit 10) interim analysis including the 30 new study participants enrolled after Protocol Amendment 9, any interim analyses to support marketing applications and the final analysis of the study.

Change #7

Section 2.5, Study RA0138 was added

RA0138 is an open-label study in 30 adult study participants with RA. This study was conducted to generate PK and ADAb data using the same ECLIA assay as used in RA0043 to form the basis of "PK-matching" for CZP approval. The PK and ADAb data from RA0138 will be analyzed and displayed in the same manner as data from RA0043 so that comparisons and conclusions can be made. Those details will be presented in the Appendix, Section 12.1.

Change #8

Section 3.1, General presentation of summaries and analyses

SAS® Version 9.3 (or later) will be used to perform all summaries and analyses, unless specified otherwise.

All study participants received CZP and are grouped by their Baseline weight group in the summary tables. Generally, data summaries will be organized by CZP dosing regimen, and will include the following CZP dose regimen groups with results presented in this order:

- Reduced CZP Dose Regimen Overall: includes all study participants who began treatment in accordance with the reduced CZP 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.
    - Under Protocol Amendment 9, study participants are allowed to escalate to the Original CZP Dose
- Original CZP Dose Regimen Overall: includes all study participants who began treatment in accordance with the original CZP 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.
- Any CZP Dose Regimen: includes all study participants in the reduced and original CZP dosing regimens.

For the Original CZP Dose Regimen Overall group, selected data will be further subdivided into events and assessments occurring prior to or without and following dose reduction - namely Original CZP Dose Regimen Prior to or Without Dose Reduction vs. Original CZP Dose Regimen Following Dose Reduction. Original CZP Dose Regimen study participants whose CZP dose was not reduced prior to study discontinuation will be excluded from summaries of data following CZP dose reduction; this will include the 30 study participants enrolled under Protocol Amendment 9 who do not dose reduce. Summaries of data following dose reduction for study participants who began treatment on the original CZP dose regimen will be restricted to study participants whose CZP dose was actually reduced and for the time that the dose was reduced. If study participants escalate their dose after reduction (allowed after Protocol Amendment 9), that data may be summarized or listed separately.

Summaries of data that have been subdivided as prior to or without dose reduction vs. following dose reduction vs following dose escalation will generally assign data associated with the dose reduction visit to the "prior to or without dose reduction" category and data associated with the dose escalation visit to the "dose reduction" category. The only exceptions to this rule will be for AEs occurring on the same date as the dose reduction whereby the classification of AEs occurring on the date of dose reduction will be based upon review and classification by the study physician and for AEs on the same date as the dose escalation, whereby the classification of the AEs occurring on the date of dose escalation will also be based upon review and classification by study physician.

Generally, data will be summarized by the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups with selected outputs further summarized by the Original CZP Dose Regimen Prior to or Without Dose Reduction vs. the Original CZP Dose Regimen Following Dose Reduction. Selected outputs will further summarize the data occurring during the Escalation CZP Dose Regimen.

Note that for efficacy data, summaries will be presented by the Reduced CZP Dose Regimen Overall (regardless of dose escalation), the Original CZP Dose Regimen Overall (regardless of dose reduction or dose escalation), and the Any CZP Dose Regimen (regardless of dose reduction or dose escalation).

Further details regarding these displays based upon dose regimen can be found in the respective PK, safety and efficacy analysis sections below.

Categorical data will be presented as summary tables. A missing category will be included as applicable.

Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum. For CZP plasma concentrations and CRP, the geometric mean and geometric coefficient of variation (CV) will be presented.

Mean, standard deviation, and median will be displayed to 1 more decimal place than collected in the case report form (CRF). Minimum and maximum values will be displayed to the same level of precision as collected in the CRF. Percentages will be calculated using the number of study participants in the relevant population or subgroup as the denominator. Presentation of percentages will be to 1 decimal place. Percentages will not be presented if the frequency count is 0.

No formal statistical hypothesis testing will be performed. Ninety-five percent confidence intervals (CIs) for the percentage of responders will be calculated using the exact binomial method.

In addition, for other subgroup analyses (Baseline age group, concomitant MTX use, ERA status and overall anti-CZP antibody status), data will be generally presented by the specified subgroups pooling across all weight groups (with the exception of PK analyses which are specified in the corresponding sections).

In some listings, study participants who started on the original CZP dose regimen will be divided into two subgroups as listed below:

Original CZP Dose with Dose Reduction: includes all study participants who started with the original CZP dose regimen and then subsequently switched to the reduced dose.

Original CZP Dose without Dose Reduction: includes all study participants who started with the original CZP dose regimen without switching to reduced dose (for example, discontinued study drug prior to dose reduction visit).

Was changed to:

SAS® Version 9.3 (or later) will be used to perform all summaries and analyses, unless specified otherwise.

All study participants received CZP and in most cases, are grouped by their Baseline weight group in the summary tables. Generally, data summaries will be organized by CZP dose, and will include the following CZP dose groups:

- Original CZP Dose: includes all study participants who began treatment in accordance with the Original CZP Dose 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]). Only data obtained prior to their first change in dosage will be included in summaries of the Original CZP Dose.
- Reduced CZP Dose: : includes all study participants who began treatment in accordance with the Reduced CZP Dose 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]). Only data obtained prior to a dose change will be included in summaries of the Reduced CZP Dose.
- Any CZP Dose: includes all data from all study participants while being treated with the Original CZP Dose or the Reduced CZP Dose at any time in the study, regardless of dose switching.

Generally, data will be summarized by the Original CZP Dose, Reduced CZP Dose, and Any CZP Dose groups. For PK and ADA analyses, data will be summarized by Original CZP Dose and Reduced Dose only.

Further details regarding these displays based upon dose groups can be found in the respective PK, safety and efficacy analysis sections below.

Categorical data will be presented as summary tables. A missing category will be included as applicable.

Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum. For CZP plasma concentrations and CRP, the geometric mean and geometric coefficient of variation (CV) will be presented.

Mean, standard deviation, and median will be displayed to 1 more decimal place than collected in the case report form (CRF). Minimum and maximum values will be displayed to the same level of precision as collected in the CRF. Percentages will be calculated using the number of study participants in the relevant population or subgroup as the denominator. Presentation of percentages will be to 1 decimal place. Percentages will not be presented if the frequency count is 0.

No formal statistical hypothesis testing will be performed. Ninety-five percent confidence intervals (CIs) for the percentage of responders will be calculated using the exact binomial method.

For certain laboratory parameter results that are collected as either "<XX.X" or ">XX.X", if descriptive statistics are calculated for the parameter, the XX.X will be used in the calculation but the data listing will reflect the actual reported result.

The classification of AEs occurring on the same date as a dose change will belong to the period of the dose change.

In addition, for other subgroup analyses (e.g. Baseline age group, concomitant MTX use, etc.), data will be generally presented by the specified subgroups pooling across all weight groups (with the exception of PK analyses which are specified in the corresponding sections).

Change #9

Section 3.2.1, Analysis time points

For study participants who withdraw prior to the last time point for the particular analysis being conducted (ie, Week 16, Week 24, Week 56, Final), data recorded at the Early Discontinuation/EOT Visit will be assigned to what would have been the next scheduled visit, unless unavailable or otherwise specified, dependent on which visit schedule the study participant is following. These data will be included in the summaries of the assigned visit and the "Early Discontinuation/EOT" Visit if applicable. For efficacy data, the Early Discontinuation/EOT Visit will not be summarized and only the re-assigned visit will be included in the summary tables. Note that data from the Early Discontinuation Visit or EOT will be listed as "Visit X (Week Y)/ED" or "Visit X (Week Y)/EOT" where the X was the re-assigned visit number and Y was the re-assigned week number in all safety and efficacy data listings as applicable.

Was changed to:

For study participants who withdraw prior to the last time point for the particular analysis being conducted (ie, Week 16, Week 24, other interim analysis, Final), data recorded at the Early Discontinuation/EOT Visit will be assigned to what would have been the next scheduled visit, unless unavailable or otherwise specified, dependent on which visit schedule the study participant is following. This re-assignment should be based upon the study day (relative to the baseline visit date) and also keeping in mind the +/- 3-day window into which visits fall. These data will be included in the summaries of the assigned visit and the "Early Discontinuation/EOT" Visit if applicable. For efficacy data, the Early Discontinuation/EOT Visit will not be summarized and only the re-assigned visit will be included in the summary tables. Note that data from the Early Discontinuation Visit or EOT will be listed as "Visit X (Week Y)/ED" or "Visit X (Week Y)/EOT" where the X was the re-assigned visit number and Y was the re-assigned week number in all safety and efficacy data listings as applicable.

Change #10

Section 3.4, Protocol deviations

Important protocol deviations will be predefined and data cleaning meetings will be held on an ongoing basis to review the important protocol deviations.

In addition, protocol deviations related to the impact of the global pandemic of coronavirus disease 2019 (COVID-19) will be documented.

Was changed to:

Important protocol deviations will be pre-defined and data cleaning meetings will be held on an ongoing basis to review the important protocol deviations. At these data cleaning

meetings, protocol deviations from the Clinical Trial Management System (CTMS) as well as those generated programmatically will be reviewed by the study team in order to flag those that are important.

In addition, protocol deviations related to the impact of the global pandemic of coronavirus disease 2019 (COVID-19) will be documented.

Change #11

Section 3.4.1, PK protocol deviations was added

Exclusion of specific PK data points will be done for that PK data presented in the subset of tables and figures where geometric means are calculated and displayed. These exclusions will not occur in the PK data presented in spaghetti plots or individual profile figures. The reasons why PK data points may be excluded are the following:

- Study participant taking an incorrect treatment or dose,
- Study participant's discontinuation of CZP,
- Study participant being in Clinical remission (and not taking CZP),
- Study participant having deviations where CZP dosings occur outside the scheduled CZP dosing window, and
- Study participant is procedurally non-compliant in having PK samples taken at the appropriate time points.

PK data that is excluded due to the above reasons will be flagged on the analysis PK dataset. The flagging will allow the data to be excluded from geometric mean calculations which could be more affected by instances of treatment and procedure non-compliance.

Change #12

Section 3.4.1.1, Rules for exclusions of specific PK samples was added

The PK sample results taken at a specific visit will be excluded from analysis for the following reasons:

- For study participants in documented clinical remission (and not taking CZP), any study participant's PK sample results during clinical remission (after CZP dose is stopped) are excluded,
  - For study participants returning to CZP dosing after having stopped taking CZP (eg. when in clinical remission), a study participant's PK sample result will be included in summaries if the prior 3 consecutive CZP doses are present,
- If the study participant's PK sample was taken at a visit where the prior 2 consecutive CZP doses were missed, then the study participant's PK sample is excluded,
- If in the 168 days prior to the study participant's PK sample, there were >3 CZP doses missed, then that study participant's PK sample is excluded,

- If the PK sample is taken following the study participant's noncompliance in CZP dosing as indicated by an important protocol deviation, then the study participant's affected PK sample (the one following that noncompliant dose) will be excluded,
- If a study participant is on a Q2W CZP dosing interval, and the study participant's PK sample is taken <9 days or >19 days from the last CZP dosing, then it is excluded,
- If a study participant is on a Q4W CZP dosing interval, and the study participant's PK sample is taken <23 days or >33 days from the last CZP dosing, then it is excluded,
- For the Week 1 PK sample, if a study participant's PK sample is taken (too soon) <4 days after or (too late) >10 days after the Week 0 CZP dose, it is excluded, or

For the Week 17 PK sample, if a study participant's PK sample is taken (too soon) <4 days after or (too late) >10 days after the Wk 16 CZP dose, it is excluded.

Change #12

Section 3.5.3, Full Analysis Set

The Full Analysis Set (FAS) will consist of all study participants in the SS who have at least 1 valid Baseline and 1 valid post-Baseline assessment for the same efficacy variable.

Was changed to:

The Full Analysis Set (FAS) will consist of all study participants in the SS who have no more than one of the 6 core components missing at baseline (count of joints with active arthritis, count of joints with limitation of range of motion, Physician's Global Assessment of Disease Activity score, CHAQ score, Parent's Global Assessment of Overall Well-Being score and CRP result) for calculating PedACR30/50/70/90.

Change #13

Section 3.5.5, Pharmacokinetic-Pharmacodynamic (PK-PD) Set was removed

Change #14

Section 3.6, Treatment assignment and treatment groups

For PK, safety and efficacy analyses, study participants will be grouped by their Baseline weight group. Selected analyses will also group study participants by their Baseline age group, concomitant MTX use, and overall anti-CZP antibody status (as defined in Section 8.2). Additionally, PK and selected safety data will be presented by CZP dose regimen (Reduced Overall vs. Original CZP Dose Regimen Overall). For study participants enrolled on the original CZP dose regimen, data will be tabulated overall, and selected data will be further subdivided into events and assessments occurring prior to or without and following dose reduction. Efficacy summaries will be presented by the Reduced CZP Dose Regimen Overall, the Original CZP Dose Regimen Overall, and the Any CZP Dose Regimen.

Regardless of changes in dosing due to weight change, study participants will generally be analyzed by the CZP dosing regimen they received at Baseline (with the exception of study participants that began treatment on the original CZP dose regimen and underwent dose reduction, as described in Section 3.1).

Was changed to:

For PK, safety and efficacy analyses, study participants will be grouped by their Baseline weight group. Selected analyses will also group study participants by their Baseline age group, concomitant MTX use, and ADAb titer (as defined in Section 8.2).

Regardless of specific prescribed doses dictated by weight change during study conduct, study participants will be analyzed by the CZP dose group stated in Section 3.1.

Change #15

Section 3.8, Coding dictionaries

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) according to UCB standard operating procedures (SOP). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) according to UCB SOPs.

Was changed to:

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA® version 18.1) according to UCB standard operating procedures (SOP). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD version dated Sep 2013) according to UCB SOPs.

Change #16

Section 3.9, Changes to protocol-defined analyses

The protocol stated that vital sign abnormalities will be evaluated at every visit. Vital signs are collected at every visit, not vital sign abnormalities, and observed values and changes from Baseline in observed values will be summarized.

In the statistical section of the protocol, it is stated that 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 (the Original CZP Dose Regimen, the Reduced CZP Dose Regimen), and that this analysis will be repeated, excluding any study participants who switched from the original to the reduced CZP dose prior to Week 16. Given that only 1 study participant switched from the original to the reduced CZP dose prior to Week 16 (at Week 12), the analysis will not be repeated with this subject excluded. Exposure-adjusted event rates (EAER) are added to selected TEAE tables.

This analysis plan includes plots of CZP plasma concentrations, anti-CZP antibody concentrations, JADAS-71 and maximum PedACR response for individual study participants by visit; these plots were not pre-specified in the study protocol.

Subgroup analyses by ERA status were not pre-specified in the protocol, but are included for selected outcomes.

In the protocol it was stated that continuous efficacy endpoints would be presented using both last observation carried forward (LOCF) and observed case (OC) analyses. Instead, only LOCF summaries of continuous efficacy endpoints will be presented since efficacy is not the

primary objective of this study and little difference is expected between the two different analyses.

For joints with limitation of motion (LOM), it was stated in the protocol that the assessment of LOM would be made using 69 of the 75 joints from the standard PRINTO/PRCSG standard joint examination; however, the assessment described in the SAP that utilized 67 joints was conducted. This was according to an updated definition of LOM in the PRINTO/PRCSG assessment at the time of finalization of the original SAP.

For CRP, summaries present the percent change from Baseline instead of the ratio to Baseline to aid in interpretation.

Was changed to:

The definition for the FAS has been clarified to the following: The Full Analysis Set (FAS) will consist of all study participants in the SS who have no more than one of the 6 core components (count of joints with active arthritis, count of joints with limitation of range of motion, Physician's Global Assessment of Disease Activity score, CHAQ score, Parent's Global Assessment of Overall Well-Being score and CRP result) for calculating improvement in PedACR30/50/70/90 missing at baseline.

The definition for the PK-PP has been clarified that study participants in this set must have PK data analyzed using the ECLIA method.

In the statistical section of the protocol, it is stated that the AEs will be summarized separately for the periods of exposure to Original CZP Dose and the Reduced CZP Dose, in addition to exposure for study participants that switched from the Reduced CZP Dose to the Original CZP Dose following Protocol Amendment 9. The analysis of AEs after a study participant changes doses will not be separately identified and presented in the Updated Week 24 Interim Analysis although the AEs that occur after dose changes will be summarized in the Any CZP Dose group.

In the statistical section of the protocol, it is stated that the frequency and percentage of AEs reported during the first 16 weeks of study medication exposure will be summarized separately for the 2 CZP doses (the Original CZP Dose, the Reduced CZP Dose), and that this analysis will be repeated, excluding any study participants who switched from the original to the reduced CZP dose prior to Week 16. The protocol-specified safety Week 16 analyses generated for prior interim analyses will not be included in the Updated Week 24 Interim Analysis or any later analyses.

Exposure-adjusted event rates (EAER) are added to selected TEAE tables.

This analysis plan includes plots of CZP plasma concentrations, ADAb titers, JADAS-71 and maximum PedACR response for individual study participants by visit. Box plots of the PK distribution as Weeks 12 and 24 stratified by Baseline weight group, Baseline age group, concomitant MTX use and participant ADAb classification will be performed as a basis of the comparison with the adult RA PK exposures in RA0138; this comparison of observed PK data will be covered in Appendix Section 12.1. Plots of PK and ADAb data were not pre-specified in the study protocol.

It is not planned to perform a population PKPD modeling analysis of RA0043 data to explore the exposure-response relationship in JIA pediatric population for the following reasons: i) the purpose of the RA0043 study is to support the efficacy extrapolation to the pediatric population by PK matching with respect to RA adult PK, and thus the main aim of the analysis that will be performed by nonlinear mixed effect modeling is to characterize the PK in JIA pediatrics with precise parameter estimates; and ii) the W24 interim analyses performed and submitted in 2016 (BLA 125160-275) included PedACR and JADAS-71 graphical explorations by dose regimen which concluded that a substantial improvement of the PedACR and JADAS-71 responses across both dosing regimens investigated in Study RA0043 was observed, with no differences between these, that would support a pop-PKPD analysis. Hence the PK-PD Set was removed as no analysis are planned for this population.

In the protocol it was stated that continuous efficacy endpoints would be presented using both last observation carried forward (LOCF) and observed case (OC) analyses. Instead, only observed case summaries of continuous efficacy endpoints will be presented since efficacy is not the primary objective of this study and little difference is expected between the two different analyses.

For the Updated Week 24 Interim Analysis, the efficacy data will be summarized and plotted up to and including Week 24; all efficacy data will be included in listings. Efficacy analyses will not be submitted for the 120 Day Safety Update.

For joints with limitation of motion (LOM), it was stated in the protocol that the assessment of LOM would be made using 69 of the 75 joints from the standard PRINTO/PRCSG standard joint examination. In all SAPs since SAP Amendment 2, the assessment now utilizes 67 joints and this was according to an updated definition of LOM in the PRINTO/PRCSG assessment that was not available prior to the finalization of the protocol.

For CRP, summaries present the percent change from Baseline instead of the ratio to Baseline to aid in interpretation.

Change #17

Section 4.2, Handling of dropouts or missing data

For continuous efficacy endpoints, missing assessments will be imputed using an LOCF approach. For Week 56 and final analyses, LOCF will only be applied to study participants who have discontinued early prior to reaching the Week 56 visit and data will be carried forward up to the Week 56 visit as appropriate. Data beyond Week 56 will be analyzed as observed cases without any imputation. The same rule will also be applied in nonresponder imputation (NRI) calculations for binary efficacy outcomes.

Unless otherwise stated, the following guidelines apply for the LOCF analyses:

- If a Baseline value is missing, carry forward the Screening value as far as Baseline but no further.
- For post-Baseline assessments, only carry forward earlier post-Baseline values. Baseline and pre-Baseline values do not get carried forward to the post-Baseline visits.

Was changed to:

For continuous efficacy endpoints, missing assessments will not be imputed. For all analyses, the data will be analyzed as observed cases without any imputation. For the non-responder imputation (NRI) calculations for binary efficacy outcomes, the data beyond Week 56 will be analyzed as observed cases without any imputation while the data up to and including Week 56, NRI will only be applied to study participants who have discontinued early prior to reaching Week 56.

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

Change #18

Section 4.2.2, Incomplete date for the last administration of study medication was added

No imputation should be performed for missing study medication start dates. This field on the CRF should not be partial or missing.

For partial or missing date of last dose of study medication, the following imputation rules will be applied for the purpose of calculating overall exposure:

If the day is missing (but month and year available), impute the last dose date as the minimum of the last day of the month or the date of last contact reported on the Study Termination CRF; if day and month are both missing (only year available), impute the last dose date as the minimum of the last day of the year or the date of last contact on the Study Termination CRF.

If a subject died and has a partial or missing last administration date, the date is to set to the date of death. If there is a partial date of last dose and the month/year are prior to the month and year of the date of death, follow partial date imputation rules.

If the last dose date is completely missing and no information could be obtained from data cleaning exercises, the last dose date should be imputed as the date of last contact according to the Study Termination CRF. A review of the data for subjects with completely missing last dose dates should be performed to ensure that the imputation does not result in an unrealistic value for duration of exposure.

Imputed date of last dose dates should only be used for calculation of the duration of exposure. The date as recorded on the CRF should be presented in subject data listings (no imputed dates should be included in subject data listings).

Change #19

Section 4.2.4, Missing adverse event intensity was added

If the intensity of an AE is missing, then it will be counted as severe for analysis purposes.

Change #20

Section 4.2.5, Missing adverse event relationship to study medication was added

If the AE relationship to study medication is missing, then it will be counted as related for analysis purposes.

Change #21

Section 4.3, Interim analyses and data monitoring

Based on results of this interim PopPK analysis, 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. 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 Amendments 4 and 5 unusable from a regulatory standpoint.

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; this is referred to as the 2016 Week 24 interim analysis. 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; this will be referred to as the Updated Week 24 Interim analysis. A Week 56 (Visit 14) interim analysis will also be performed after all those enrolled, following the implementation of Protocol Amendment 9, have completed the Week 56 (Visit 14) assessments.

All statistical tables, listings and figures comprising this SAP will be produced for all future interim and final analyses.

Was changed to:

Based on results of this interim PopPK analysis, the doses 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 the previous study in adult study participants with RA (study C87050). However, it was later determined that there were deficiencies detected with in the bioanalytical assay used within RA0043, which rendered the PK data for the PopPK analysis and simulations that informed the dose reduction in Protocol Amendments 4 and 5 were not up to current standards and FDA guidelines; therefore, those data were not able to support the regulatory filing.

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; this is referred to as the 2016 Week 24 interim analysis. 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; this will be referred to as the Updated Week 24 Interim analysis to be used in support of the re-submission of BLA 125160-275.

All statistical tables, listings and figures comprising this SAP will be produced for all future interim and final analyses. Interim data from RA0043 may be summarized to support regulatory submissions, regular safety signal detection monitoring, publications and annual reports to regulatory agencies. For any interim data summary, all available data as of the time of the clinical cut-off date will be included. Subjects ongoing at the time of an interim data summary will be assumed to be treated (ie exposed) up to and including the date of the clinical data cut-off; efficacy data will not be imputed for the closest visit to the clinical snapshot date if the visit is not currently in the clinical database; composite variables will not be calculated if one or more components are unavailable for the visit closest to the clinical snapshot date.

Change #22

Section 4.7, Examination of subgroups

All PK, safety and efficacy summaries will be presented by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg). For some safety and efficacy endpoints, such as PedACR30, PedACR50, PedACR70, PedACR90 and incidence of treatment-emergent AEs (TEAEs), results will also be presented by Baseline age group, overall anti-CZP antibody status, ERA status, and concomitant MTX use group as listed below pooling across all weight groups:

- Baseline age group:
  - 2-<6 years
  - 6-<12 years
  - 12-17 years
- TE Anti-CZP antibody status and titer classification:
  - TE ADAb status negative
  - TE ADAb status positive <=32
  - TE ADAb status positive >32 to <=128
  - TE ADAb status positive >128 to <=512
  - TE ADAb status positive >512 to <=1024
  - TE ADAb status positive >1024 to <=4096
  - TE ADAb status positive >4096
- ERA status:
  - presence
  - absence
- Concomitant MTX use (distinct from Baseline MTX use presented in Section 6.1 and defined as any concomitant MTX use during the Treatment Period):
  - With concomitant MTX use

- Without concomitant MTX use

For subgroup analyses of incidence of anti-CZP antibody formation and CZP plasma concentrations, results will also be presented by Baseline age group. In addition, summaries will be provided by overall anti-CZP antibody status, ERA status, and concomitant MTX use group in combination with Baseline weight group.

As specified in Section 3.3, Baseline for all subgroup analyses will always be the original Baseline (ie, prior to the 1st CZP Dose in this study).

For efficacy endpoints PedACR30, PedACR50, PedACR70, and PedACR90, results will also be presented by gender and race.

In addition, selected outputs will only be summarized for the Any CZP Dose Regimen as specified in each relevant section.

Was changed to:

Most PK, safety and efficacy summaries will be presented by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg). For some safety and efficacy endpoints, such as PedACR30, PedACR50, PedACR70, PedACR90 and incidence of treatment-emergent AEs (TEAEs), results will also be presented by the subgroups as listed below (at times, pooling across all baseline weight groups):

- Baseline age group:
  - 2-<6 years
  - 6-<12 years
  - 12-17 years
- ADAb titer classification (defined in Section 8.2 using RA0043 data):):
  - >= 0 to <= Quartile 1
  - > Quartile 1 to <= Quartile 2 (Median)
  - > Quartile 2 (Median) to <= Quartile 3
  - > Quartile 3
  - Missing
- Concomitant MTX use (distinct from Baseline MTX use presented in Section 6.1 and defined as any concomitant MTX use during the Treatment Period):
  - With concomitant MTX use
  - Without concomitant MTX use
- Gender
  - Female
  - Male

- Race
  - White
  - Non-white

For subgroup analyses of incidence of ADAb formation and CZP plasma concentrations, results will also be presented by Baseline age group. In addition, summaries will be provided by ADAb titer classification, ADAb participant status classification (defined in Section 8.2), and concomitant MTX use group in combination with Baseline weight group.

As specified in Section 3.3, Baseline for all subgroup analyses will always be the original Baseline (ie, prior to the 1st CZP Dose in this study).

In addition, selected outputs will only be summarized for the Any CZP Dose as specified in each relevant section.

Change #23

Section 5.1, Subject disposition

The number of screened study participants, and reasons for screen failure, will be summarized for all screened study participants.

The number and percentage of study participants who were treated, who completed the study, and who discontinued from the study, along with the discontinuation reasons, will be summarized for the Safety Set. For the Week 16, Week 24 and Week 56 interim analyses, number of study participants completing Week 16, Week 24 and Week 56 (respectively) will be added in addition to the number completing the study as appropriate. The number of study participants in each analysis set will be presented. Summaries will be provided for the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups.

Discontinuations due to AEs will be summarized separately for the SS, and will be provided for the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups.

The number and percentages of subjects impacted by COVID-19 will be presented for each visit, overall and by impact category, for each relationship to COVID-19 as well as any relationship, overall and by country, for all subjects in the SS. This data will be presented in subject data listings.

Was changed to:

The number of screened study participants, and reasons for screen failure, will be summarized for all screened study participants.

The number and percentage of study participants who were treated, who completed the study, and who discontinued from the study, along with the discontinuation reasons, will be summarized for the Safety Set by CZP Dose Regimen (Reduced, Original and Any) and Baseline weight group as well as by CZP Dose Regimen and ADAb titer classification. For the Week 16, Week 24 and other interim analyses, number of study participants completing Week 16, Week 24 and Week 48 (respectively) will be added in addition to the number completing the study as appropriate. The disposition of study participants in their initial

dosing phase, reduction phase and escalation dosing phase of the study will also be presented. The number of study participants in each analysis set will be presented.

Discontinuations due to AEs will be summarized separately for the SS, and will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups.

The number and percentages of subjects impacted by COVID-19 will be presented for overall and by impact visit, for any reason for all subjects in the SS. This data will be presented in subject data listings.

Change #24

Section 5.2, Protocol deviations

The number and percentage of study participants with important protocol deviations will be summarized by type for the SS for the Any CZP Dose Regimen. All important protocol deviations will also be listed.

Note that partial PK data exclusion is implemented due to certain protocol deviations (eg, incorrect treatment or dose, procedural noncompliance related to PK sampling), minor deviations from the planned treatment schedule (eg, delays or missing doses not considered as important protocol deviations), CZP interruption or CZP discontinuation due to AEs, TB prophylactic treatment, or clinical remission. These exclusions will be reviewed and identified at data cleaning meetings and are only applicable for group PK summary tables and graphs where the geometric mean for plasma concentration are calculated and displayed. However, all PK data will be included in listings and individual graphs. Study participants with at least one PK data exclusion are summarized and listed.

Was changed to:

The number and percentage of study participants with important protocol deviations will be summarized by type for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose. All important protocol deviations will also be listed.

Note that PK sample exclusion will be implemented due to certain protocol deviations; see Section 3.5. Study participants with at least one PK data exclusion are summarized and listed.

Change #25

Section 6.6, Rescue medications

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 nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, including as needed (PRN) use within 72 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).
- Higher than Baseline dose of analgesics or opioids including PRN use within 48 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).

- Any increase in dose of oral corticosteroids within 7 days prior to scheduled study visit (Note: The increase has to be higher than baseline).

In all cases, any medications recorded in the database will be classified as rescue medication only when JIA is listed as the indication for that medication. Rescue medication use and date of first usage will be confirmed during the data cleaning meetings prior to the database lock. Generally, the +1 day rule was applied to the first usage date when considering its impact on efficacy endpoints. Therefore, only efficacy data with dates after the first usage date of the rescue medication were impacted (using the nonresponder imputation (NRI) or LOCF imputation methods). Exceptions are nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, analgesics or opioids, or oral corticosteroids as specified above. The number and percentage of study participants of who used rescue medication up to the Week 16 visit and after the Week 16 visit will be summarized separately.

All summaries of rescue medications will be provided for the SS for the Reduced CZP Dose Regimen Overall, the Original CZP Dose Regimen Overall and the Any CZP Dose Regimen. All rescue medication will be listed.

Was changed to:

In all cases, any medications recorded in the database will be classified as rescue medication only when pJIA is listed as the indication for that medication. Rescue medication use and date of first usage will be confirmed during the data cleaning meetings prior to the database lock. Generally, the +1 day rule was applied to the first usage date when considering its impact on efficacy endpoints. Therefore, only efficacy data with dates after the first usage date of the rescue medication were impacted (using the non-responder imputation (NRI) method). The number and percentage of study participants of who used rescue medication up to the Week 16 visit and after the Week 16 visit will be summarized separately.

All summaries of rescue medications will be provided for the SS for the Reduced CZP Dose, the Original CZP Dose and the Any CZP Dose. All rescue medication will be listed.

Use of the following medications, which are not rescue medications, only results in efficacy data at the next scheduled visit being treated as missing/non-response:

- Higher than Baseline dose of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, including as needed (PRN) use within 72 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).
- Higher than Baseline dose of analgesics or opioids including PRN use within 48 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).
- Any increase in dose of oral corticosteroids within 7 days prior to scheduled study visit (Note: The increase has to be higher than baseline).

All medication data resulting in efficacy data being treated as missing/non-response will be flagged in the concomitant medication listing.

Change #26

Section 7, Measurements of treatment compliance

In addition, a study participant could change dose (or frequency of dosing if in 10-20kg group) if a study participant crossed into a new weight group, which is not considered in the above expected calculations of number of CZP administration since all expectations are based on baseline weight group dosing regimen regardless of weight change. This specifically applies to the change of dose frequency from Q4W to Q2W if a subject crossed into the 20 to <40kg weight group, which is not considered in the expected calculations. Note that the dose reduction of ongoing study participants following Protocol Amendment 4 is considered in the calculations. Note also the dose escalation of ongoing study participants following Protocol Amendment 9 is considered in the calculations.

Treatment compliance is provided for the SS for the Reduced CZP Dose Regimen Overall, Reduced CZP Dose Regimen, Original CZP Dose Regimen Prior to Dose Reduction or without Dose Reduction, Original CZP Dose Regimen Following Dose Reduction, Original CZP Dose Regimen Overall and Escalation CZP Dose Regimen.

Was changed to:

In addition, a study participant could change dose (or frequency of dosing if in 10-20kg group) if a study participant crossed into a new weight group, which is not considered in the above expected calculations of number of CZP administration; study participants are assigned dose groups (Reduced CZP Dose and Original CZP Dose) and Baseline weight group at baseline and do not change either for the entire analysis regardless of weight change and dose adjustments. This specifically applies to the change of dose frequency from Q4W to Q2W if a subject crossed into the 20 to <40kg weight group, which is not considered in the expected calculations. Note that the dose reduction of ongoing study participants following Protocol Amendment 4 is considered in the calculations. Note also the dose escalation of ongoing study participants following Protocol Amendment 9 is considered in the calculations.

For the Original CZP Dose and Reduced CZP Dose groups, treatment compliance is calculated from the first dose of CZP, for the entire time the study participant is taking study medication up to the dose change. For the results presented for Any CZP Dose, treatment compliance is calculated for the entire time the study participant is taking CZP from first dose until the last dose. Treatment compliance is summarized for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose.

Change #27

Section 8.1, CZP plasma concentriations

CZP plasma concentrations are measured at Baseline, Weeks 1, 4, 12, 16, 17, 24, 32, 40, 48, every 24 weeks thereafter, the Early Discontinuation/EOT Visit, and the Final Visit; for study participants enrolled prior to Protocol Amendment 8, samples were not collected after implementation of Protocol Amendment 8. CZP plasma concentrations will be summarized by CZP dose regimen (Original CZP Dose Regimen or Reduced CZP Dose Regimen) using geometric means, 95% CIs for the geometric mean, geometric CV, and the median, minimum and maximum concentrations.

The geometric CV will be calculated using the following formula:

$$geoCV(\%) = \sqrt{\exp(SD^2) - 1} * 100,$$

where SD=standard deviation from the log-transformed data.

For study participants enrolled prior to Amendment 9, who began treatment on the original CZP dose regimen, and whose PK samples are analyzed with the ECLIA method, plasma CZP concentrations will be summarized separately for samples obtained during the period of exposure to (1) the original CZP dose (all results before and through the dose reduction visit), and (2) the reduced CZP dose (all results from the initial dose reduction visit onward). Plasma concentrations at the visit where dose reduction was to be initiated will be included in summary (1) only. Concentrations from participants enrolled after Amendment 9 will be included in Summary (1).

For the summarization of geometric mean concentrations on the reduced CZP dose, visits will be identified as number of weeks relative to the dose reduction visit, regardless of the actual visit at which the dose reduction occurred. Study participants that reduce dose are thus expected to have plasma concentration results at the dose reduction visit, 4 weeks after dose reduction (identified as Week 4), 8 weeks after dose reduction (identified as Week 8), and 12 weeks after dose reduction (identified as Week 12). Any subsequent concentration results for the reduced dose period will also be similarly summarized (ie, concentration results 24 weeks after dose reduction will be summarized as Week 24 results).

Summaries of concentration results will be provided by Baseline weight group, as well as Baseline age group. In addition, summaries will be provided by TE ADAb status with titer classification (see 8.2) and concomitant MTX use in combination with Baseline weight group.

Geometric mean plasma concentration time curves will be provided separately for study participants according to the ECLIA assay and dosing scenarios outlined above for the tabular summaries. Geometric mean plots will be provided overall and by Baseline age stratum, Baseline weight group, TE ADAb status with titer classification (see 8.2), and concomitant MTX use.

In addition, observed plasma concentrations over time will be plotted for individual study participants, separately for each dose regimen whose samples have been analyzed with the ECLIA method. Plots of individual plasma concentrations will be provided by Baseline age stratum, Baseline weight group, TE ADAb status with titer classification (see 8.2), and concomitant MTX use.

Concentrations below the limit of quantification of 32.0 ng/mL (0.032µg/mL) (BLQ) will be replaced by the LLOQ divided by 2 for the calculation of descriptive statistics. The geometric mean and CV% will be derived when at least two-thirds of the concentrations at a certain visit are above the LLOQ. If that criteria are not met, only the maximum and minimum values will be shown. Similarly, the 95% CI of the geometric mean will be calculated if at least 5 samples are available at a time point.

All summaries will be provided for the PK-PP Set. All plasma concentration data will be listed.

Was changed to:

Only CZP plasma results analyzed using the ECLIA method will be summarized using the participants in the PK-PP set. CZP plasma concentrations are measured at Baseline, Weeks 1, 4, 12, 16, 17, 24, 32, 40, 48, every 24 weeks thereafter, the Early Discontinuation/EOT Visit, and the Final Visit; for study participants enrolled prior to Protocol Amendment 8, samples were not collected after implementation of Protocol Amendment 8. CZP plasma concentrations will be summarized by CZP dose (Original CZP Dose, Reduced CZP Dose) using geometric means, 95% CIs for the geometric mean, geometric CV, and the median, minimum and maximum concentrations.

The geometric CV will be calculated using the following formula:

$$geoCV(\%) = \sqrt{\exp(SD^2) - 1} * 100,$$

where SD=standard deviation from the log-transformed data.

For the two CZP Dose groups, summaries at all available visits and plots of plasma concentration results will be produced separately by Baseline weight group, Baseline age group, ADAb participant status classification, ADAb titer classification (see Section 8.2) and, concomitant MTX use in combination with Baseline weight group.

Line-plots will be produced to summarize geometric mean (+/- 95% CI) plasma concentration over time. On each plot there will be separate plot lines for each subgroup category as described above. Plasma concentration will be plotted on both linear and semi-logarithmic scales.

In addition, spaghetti plots of CZP plasma concentrations over time will be produced for individual study participants, separately for each CZP dose group. Plots will be provided by Baseline age group, Baseline weight group, concomitant MTX use in combination with Baseline weight group. In each plot, different symbols/colours will be used to identify subgroup categories.

Box plots of the PK concentrations at Weeks 12 and 24 will be presented by CZP dose group for Baseline weight group, Baseline age group, ADAb participant status classification, ADAb titer classification, and concomitant MTX use in combination with Baseline weight group.

Concentrations below the limit of quantification of 32.0 ng/mL (0.032µg/mL) (BLQ) will be replaced by the LLOQ divided by 2 for the calculation of descriptive statistics. The geometric mean and CV% will be derived when at least two-thirds of the concentrations at a certain visit are above the LLOQ. If the criteria are not met, only the maximum and minimum values will be shown. Similarly, the 95% CI of the geometric mean will be calculated if at least 5 samples are available at a time point.

All summaries will be provided for the PK-PP Set. All plasma concentration data will be listed.

Change #28

Section 8.2, Anti-ACZP antibodies

Immunogenicity will be assessed through listing of individual results by study participant and summary tables for data generated with the ECLIA method only. Immunogenicity data will be related to PK and efficacy readouts.

Anti-drug antibodies will be assessed by a three-tiered approach: screening (positive or negative screen), confirmatory (positive or negative immunodepletion) and titer assays, using ECLIA methods. Cut points will be determined during assay validation and used by the bioanalytical laboratory to determine the status of ADAb in the test samples.

The following definitions will be applied regarding classification of test samples:

· An ADAb status will be confirmed as positive for any sample with an ADAb level that is positive screen and positive immunodepletion.

· An ADAb status of negative will be concluded for any sample with an ADAb level that is either negative screen or positive screen and negative immunodepletion.

Confirmed positive samples will be titrated and the titer will be reported. The ADAb titer is presented in the listings and summaries including the minimum required dilution.

- If the titer for an ADAb level that is positive screen and positive immunodepletion is missing, then a conservative approach will be used and ADAb status will be considered as positive. No imputation rules apply for the missing titer.

  If the ADAb level is positive screen but no confirmatory result could be determined, then then a conservative approach will be used and ADAb status will be considered as positive.

Anomalous values will not be included in summaries/analysis but they will be reviewed and flagged by the study Clinical Pharmacologist.

Study participants will receive a treatment-emergent (TE) ADAb status and will be classified as follows based on the ADAb assay results:

- TE ADAb status positive is defined as either (i) baseline ADAb negative study participants having at least one ADAb confirmed positive sample post baseline or ii) baseline ADAb positive study participants with at least one post baseline sample with ≥minimum significant ratio (MSR) -fold increase from baseline on CZP treatment. The MSR will be defined during the process of sample analysis and is disease-specific.
- TE ADAb status negative is defined as having no samples either ADAb positive or with values ≥MSR -fold increase from baseline.

  Once determined positive, a study participant's highest titer is used to categorize ("titer classification") the study participant as follows:

  - Positive ≤32

- Positive >32 - ≤128
- Positive >128 - ≤512
- Positive >512 - ≤1024
- Positive >1024 - ≤4096
- Positive >4096.

All ADAb summaries will be provided for the SS Set. All ADAb data will be listed.

Summary of shift from Baseline ADAb status with titer classification to TE ADAb Status with titer classification for all study participants will be presented during the entire study, by visit. Summaries of ADAb data will be provided by Baseline weight group, as well as Baseline age group. In addition, summaries will be provided by concomitant MTX use in combination with Baseline weight group.

TE ADAbs will be presented separately (per ADAb status and titer classification) for the Original CZP Dose Regimen Overall and Reduced CZP Dose Regimen Overall (using the study Visit nomenclature previously outlined for PK concentrations), including the Final visit.

The time to achieving TE ADAb for all study participants will be analyzed based on Kaplan-Meier methods. Study participants will be considered to have an event at the time where treatment-emergent ADAb positive is first achieved during treatment period excluding Baseline/pre-treatment. Study participants classified as treatment-emergent ADAb negative will be censored at the time of last available ADAb result. The median and 95% CI based on the Kaplan-Meier estimation will also be presented. A plot of time to first ADAb positivity will be presented.

A scatter plot of CZP plasma concentrations and ADAb titer, separated by concomitant MTX use, will be presented. This plot will be repeated for separation by concomitant MTX use as well as Baseline body Weight group.

Was changed to:

Immunogenicity will be assessed through listing of individual results by study participant and summary tables and graphs for data generated with the ECLIA method only for the SS. Immunogenicity data will be related to PK (using the PK-PP set), efficacy (using the FAS) and safety (using the SS). All data including those results at the Final Visit will be used for analyses for the entire study.

Anti-drug antibodies will be assessed by a three-tiered approach: screening (positive or negative screen), confirmatory (positive or negative immuno-depletion) and titer assays, using ECLIA methods. Cut points will be determined during assay validation and used by the bioanalytical laboratory to determine the status of ADAb in the test samples as described in the table below.

Table 13–3: ADAb status at sample level

ADAb positive (ADAb+)	Sample values that are 'positive screen' and 'positive immuno-depletion.'
ADAb negative (ADAb-)	Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' if corresponding drug levels are equal or below the validated drug tolerance limit of the assay allowing detection of 100 ng/ml ADAb positive control or limit dictated by the ADAb assay and project needs (e.g. 250 ng/ml positive control).
ADAb inconclusive	Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' but with corresponding drug levels above the validated drug tolerance limit of the assay allowing detection of 100 ng/ml ADAb positive control or limit dictated by the ADAb assay and project needs (e.g. 250 ng/ml positive control).
Missing	Samples that were not collected per schedule or that could not be tested for ADAb status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc.

Confirmed positive samples will be titrated and the titer will be reported including the minimum required dilution (MRD) of the assay.

- If the titer, for an ADAb level that is 'positive screen' and 'positive immunodepletion' status, is missing, then ADAb status will be considered as positive and no imputation rules apply for the missing titer.

If the ADAb level is 'positive screen' but no confirmatory result could be determined, then a conservative approach will be used and ADAb status will be considered as positive. No imputation rules apply for the missing titer.

Change #29

Section 8.2.1, Participant ADAb classification was added

Study participants from the SS will be classified based on their pre and treatment ADAb status (see the table below). Classification will be done separately two ways: using the study participants' data for the entire study treatment period and using the study participants' data up to and including Week 24 (to facilitate comparison with adult RA data from study RA0138). Pre ADAb values are defined as the latest (not missing, not inconclusive and not anomalous) measurements up to and including the date of administration of first CZP treatment.

Table 13–4: ADAb status classification at participant level

1.	Pre ADAb negative and treatment emergent ADAb negative	Study participants who were negative at Baseline and negative at all sampling points post treatment until the time point of interest (eg. Data up to/including Week 24, data for the entire treatment period) [Note: study participants with baseline samples missing and negative ADAb status at all sampling points post treatment are included in this category because participants who are pre ADAb positive are expected to have ADAb positive samples post-dosing]
2.	Pre ADAb negative and treatment-(emergent) induced ADAb positive	Study participants who were negative at Baseline and positive at any sampling point post treatment until the timepoint of interest (eg. Data up to/including Week 24, data for the entire treatment period). This group also included study participants who had a missing Baseline sample with 1 or more positive post treatment samples.
3.	Pre ADAb positive and treatment-emergent reduced ADAb	Study participants who were positive at Baseline, and negative at all sampling points post treatment until the timepoint of interest (eg. Data up to/including Week 24, data for the entire treatment period).
4.	Pre ADAb positive and treatment-emergent unaffected ADAb positive	Study participants who were positive at Baseline and were positive at any sampling point post treatment with titer values of the same magnitude as Baseline (i.e., less than or equal to a predefined fold difference from the Baseline value of 2.10 which is defined with the validaton of the assay).
5.	Pre ADAb positive and treatment-emergent ADAb boosted positive	Study participants who were positive at Baseline and were positive at any sampling point post treatment with increased titer values compared to Baseline (greater than a predefined fold difference increase of 2.10 from Baseline value which is defined within the validation of the assay).
6.	ADAb inconclusive	Study participants who were positive at Baseline and some post-treatment samples were missing or inconclusive, while other post-treatment samples were negative.
7.	Treatment emergent ADAb positive	Study participants that were classified as 2 or 5.
8.	Pre-treatment ADAb positive	Study participants who are positive ADAb at baseline, so those classified as 3, 4, 5 or 6.

Table 13–4: ADAb status classification at participant level

9.	Missing	Study participants who were negative at Baseline or missing their Baseline assessment, were not positive at any post-Baseline visit, and have at least one missing/or inconclusive post-treatment scheduled assessment.
10	ADAb positive	Study participants who have a positive ADA sample status at any timepoint (either Baseline or post dose).

Change #30

Section 8.2.2, ADAb Titer Classification was added

To further evaluate the impact of ADAb on PK, efficacy and safety, grouped ADAb titer categories will be defined based on ADAb quartiles (see Section 4.7) observed in the study. Quartiles will be calculated separately for the entire treatment period, and then for the period up to and including Week 24, using each study participant's highest post-treatment ADAb titer (ADAb negative participants will be deemed to have zero titer levels for calculation purposes).

If interpretation of the grouped titer summaries is inconclusive or results from other studies suggest other groupings, additional post-hoc analyses may be conducted to further investigate.

Immunogenicity will be assessed through summary tables and figures and listing of individual results by study participant on the SS. Summaries will be by CZP dose (Reduced CZP Dose, Original CZP Dose) and each of Baseline weight group, Baseline age group, and concomitant MTX use, unless specified otherwise.

- All individual study participant-level ADAb results will be listed for all study participants. This will include the screening assay, confirmatory assay, and titer (if applicable). A separate listing showing CZP plasma concentrations, ADAb sample status classification, ADAb participant classification, ADAb titer, and ADAb titer classifications will be produced showing concentration and ADAb data in adjacent columns.
- Number and percentage of study participants with positive, negative, inconclusive or missing ADAb sample status (see Table 4) will be summarized at each visit and overall and by dose (Original CZP dose, Reduced CZP Dose).
- The number and percentage of study participants in each of the ADAb participant status categories (overall and up to Week 24 as defined according to Table 5) will be summarized. Percentages for the denominator will include all the participants that have been classified as per Table 5, so including missing /inconclusive participants.

Prevalence and incidence:

- Prevalence of pre ADAb positivity: number and percentage of study participants that have Baseline positive ADAb sample status, with the denominator for percentages defined as all participants having an evaluable (not missing, not inconclusive and not anomalous) Baseline ADAb sample.
- Incidence of treatment-emergent ADAb positivity: number and percentage of study participants with either treatment boosted ADAb or treatment induced ADAb, with the denominator for percentages all participants except those categorized as inconclusive or missing (overall for the entire treatment period and then up to and including Week 24).

Change #31

Section 8.2.3, Time to first occurrence of treatment-emergent ADAb positivity was added

Study participants will be considered to have an event at the first ADAb sampling time point with ADAb positive status if the participant is pre-ADAb negative or first ADAb sampling time point with fold difference increase from Baseline > 2.1 if participant is pre-ADAb positive. Study participants who are never treatment-emergent ADAb positive will be censored at the date of the last evaluable (not missing, not inconclusive and not anomalous) ADAb sample or on date of first CZP if no evaluable post-treatment ADAb samples. In case of pre-ADAb present in more than 10% of the study participants, the table will be produced separately for ADAb participant category 2 (induced) and 5 (boosted).

- Summary tables based on Kaplan-Meier (KM) estimates will be produced.

Kaplan-Meier plots of time to first treatment-emergent ADAb positivity will also be produced separately for the CZP doses (Original CZP dose, Reduced CZP dose). All available data timepoints will be included.

Change #32

Section 8.3, CZP plasma concentrations, anti-CZP antibody titers and PedACR response

Individual subject plots displaying log CZP plasma concentrations, log2 ADAb titers, JADAS-71 score and maximum PedACR response (the highest PedACR response at a given visit) will be produced by visit on the same plot. At each time point, the JADAS-71 score and maximum PedACR response at that visit will be plotted on a linear scale. A vertical line will be drawn at the time point of dose reduction (when applicable).
Spaghetti plots of ADAb titer on a log2 scale by week from CZP first dosing separated by concomitant MTX use and ADAb titer classification will be presented for study participants with PedACR0/30/50/70/90 at Week 16 as separate graphs. A listing of the corresponding data by visit, including CZP dose, will also be provided.

Was changed to:

Individual participants plots displaying CZP plasma concentrations, ADAb titers, JADAS-71 score and maximum PedACR response (the highest PedACR response at a given visit) will be produced by visit on the same plot. At each time point, the JADAS-71 score and maximum PedACR response at that visit will be plotted on a linear scale. CZP plasma concentration will be plotted on a (natural) log scale and ADAb titer will be plotted on a log 2 scale. CZP dosing and ADAb inconclusive values will be flagged in this plot. A vertical line will be

plotted when dose was changed for the participant. For each study participant, the category of ADAb participant status and demographic information at baseline (body weight and age) will be displayed.

Multi-panel spaghetti plots of individual participant (natural) log CZP plasma concentration by visit will be produced separately for each CZP dose (Original CZP dose, Reduced CZP dose) and ADAb titer classification and ADAb participant classification. Concomitant MTX use will be shown in different line colors and CZP concentrations for which ADAb positive samples were positive will be plotted with a red dot. These individual plots will be repeated replacing CZP plasma concentration with maximum PedACR response (linear scale).

Scatter plots of the plasma CZP concentration at each visit with different colors/symbols depending on ADAb participant classification and ADAb titer classification will be produced separately for the doses (Original CZP Dose, Reduced CZP Dose).

Change #33

Section 8.4, PopPK and PK-PD analyses

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. A graphical analysis of the relationship between PK and the clinical effect will be performed, and if data merits, a more formal modeling exercise will be performed. Details of the PopPK and PK-PD modeling procedures will be described in a separate data analysis plan.

Was changed to:

Plasma concentrations will be used to build a PopPK model with the nonlinear mixed-effect modeling (NONMEM) software. Details of the PopPK modeling procedures will be described in a separate data analysis plan.

Change #34

Section 9.1, Extent of exposure

The extent of exposure to study drug will be evaluated by summarizing the total amount of CZP received in mg and the total duration of exposure in days. Total duration of exposure will be calculated as the date of last dose of study medication – date of first dose of study medication + 14 if administration of CZP is Q2W, +28 if administration of CZP is Q4W.

Subject time at risk will also be calculated. Subject time at risk represents the time a subject is at risk for having an AE. Subject time (in days) at risk will generally be calculated as (date of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). However, the calculation of subject time at risk will be modified for study participants who change from original CZP dose regimen to reduced CZP dose regimen, or who dose escalate from reduced CZP dose regimen to the original CZP dose regimen. For the period of exposure prior to a dose change, subject time at risk ends on the date of dose change (ie, do not add 70 days). For the period of exposure on the final CZP dose regimen for a study participant, time at risk should include the additional 70 days. Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Duration of exposure and subject time at risk will be calculated as appropriate for each of the following CZP dose regimens:

- Reduced CZP Dose Regimen Overall: includes period of exposure to all CZP doses for all study participants enrolled on the reduced CZP dose regimen regardless to dose escalation
    - Reduced CZP Dose Regimen Prior to or without Dose Escalation: includes period of exposure to reduced CZP dose regimen only (ie, exposure period ends on the date of dose escalation)
- Original CZP Dose Regimen Overall: includes period of exposure to all CZP doses for all study participants enrolled on the original CZP dose regimen regardless of dose or subsequent dose reduction
    - Original CZP Dose Regimen Prior to or without Dose Reduction: includes period of exposure to original CZP dose regimen only (ie, exposure period ends on the date of dose reduction)
    - Original CZP Dose Regimen Following Dose Reduction: includes period of exposure to reduced CZP dose regimen only (ie, exposure period begins on the date of dose reduction)
- Any CZP Dose Regimen: includes all CZP doses for all treated study participants
- Escalation CZP Dose Regimen: includes period of exposure to an escalation CZP dose regimen only (ie, exposure period begins on the date of dose escalation for study participants from Reduced CZP Dose Regimen as well as Original CZP Dose Regimen Following Dose Reduction)

Study drug exposure will be summarized for the Reduced - Overall, Original - Overall, and Any CZP Dose Regimen groups. For study participants on the original CZP dose regimen, exposure will be summarized combining results prior to and following dose reduction. In addition, for study participants on the original CZP dose regimen, summaries of exposure will be produced separately for the period of exposure to (1) the original CZP dose (all exposure before the dose reduction visit or all exposure for study participants with no dose reduction), and (2) the reduced CZP dose (all exposure after the initial dose reduction visit). For study participants who dose escalate, exposure will be summarized.

Was changed to:

The extent of exposure to study drug will be evaluated by summarizing the total amount of CZP received in mg and the total duration of exposure in days. Total duration of exposure will be calculated as the date of last dose of study medication – date of first dose of study medication + 14 days if administration of CZP is Q2W, +28 days if administration of CZP is Q4W.

Subject time at risk will also be calculated. Subject time at risk represents the time a subject is at risk for having an AE. Subject time (in days) at risk will generally be calculated as (date of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). However, the calculation of subject time at risk will be

modified for study participants who change from Original CZP Dose to Reduced CZP Dose, or who dose escalate from Reduced CZP Dose to the Original CZP Dose. For the period of exposure prior to a dose change, subject time at risk ends on the date of dose change (ie, do not add 70 days). For the period of exposure on the final CZP dose for a study participant, time at risk should include the additional 70 days. Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Duration of exposure and subject time at risk will be calculated as appropriate for each of the following CZP dose groups:

- Reduced CZP Dose: includes period of exposure to the Reduced CZP Dose for all study participants enrolled on the Reduced CZP Dose; the exposure ends on the date of dose escalation or last dose of Reduced CZP Dose. The exposure calculation is Date of Dose Escalation or Last Dose of Reduced CZP – Date of First Dose + 14 or 28 days depending on administration of CZP.
- Original CZP Dose: includes period of exposure to the Original CZP Dose for all study participants enrolled on the Original CZP Dose; the exposure ends on the date of dose reduction or Last Dose of Original CZP. The exposure calculation is Date of Dose Reduction or Last Dose of Original CZP – Date of First Dose of CZP +14 or 28 days depending on administration of CZP.
- Any CZP Dose: includes the exposure to all CZP doses for all treated study participants; the exposure period is calculated using the formulas above depending on whether the subject took a Q2W or Q4W dose.

Study drug exposure will be summarized for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. Exposure will be presented as follows: >0 months, ≥6 months, ≥12 months, ≥24 months, ≥36 months, ≥48 months and ≥60 months.

Change #35

Section 9.1.1, Updated Week 24 Interim Analysis and other interim analyses was added

For interim analyses such as for the SSD, DMC and the Updated Week 24, the following modifications will be made to more accurately calculate exposure and time at risk.

For an interim analysis with a database cutoff date,

- if the study participant is ongoing, the exposure calculation is database cutoff date – date of first dose of study medication + 1 day. No data is presented in the analyses that is dated after the database cutoff date
- if the study participant is ongoing, the time at risk calculation is database cutoff date – date of first dose of study medication + 1 day.
- if the study participant has discontinued from the study >28 days before the database cutoff date and has Q4W dosing at the time of study discontinuation, then the exposure is date of last dose of study medication – date of first dose of study medication + 28 days

- if the study participant has discontinued from the study ≤28 days before the database cutoff date and has Q4W dosing at the time of study discontinuation, then the exposure is database cutoff date – date of first dose of study medication + 1 day
- if the study participant has discontinued from the study >14 days before the database cutoff date and has Q2W dosing at the time of study discontinuation, then the exposure is date of last dose of study medication – date of first dose of study medication + 14 days
- if the study participant has discontinued from the study ≤14 days before the database cutoff date and has Q2W dosing at the time of study discontinuation, then the exposure is database cutoff date – date of first dose of study medication + 1 day
- if the study participant has discontinued from the study >70 days before the database cutoff date, then the time at risk is date of last dose of study medication – date of first dose of study medication + 70 days

if the study participant has discontinued from the study ≤70 days before the database cutoff date, then the time at risk is the database cutoff date – date of first dose of study medication + 1 day.

Change #36

Section 9.2, Adverse events

Only treatment emergent adverse events (TEAE) will be included in the summary tables. Treatment emergent AEs are defined as AEs starting on or after the first administration of CZP and up to 70 days after the last dose of study medication. AEs that are pre-treatment or that start more than 70 days after the last dose of study medication will be flagged in the listing but excluded from summaries.

All AEs will be classified by SOC, HLT and PT according to the version of MedDRA® that is current to the sponsor at the time of data capture. A glossary for the TEAE listing will detail the verbatim terms that are coded to each SOC, HLT, and PT.

Treatment-related TEAEs are those with relationship to study medication of "Related" or "Possibly related" or those with a missing relationship. Severe TEAEs are those with an intensity of "Severe" or those with a missing intensity.

An overall summary of TEAEs overall and by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg) will include the number of events and number of study participants and percentage of study participants with:

- Any TEAE
- Any serious TEAE
- Any treatment-related TEAE
- Any severe TEAE
- Any TEAE leading to permanent withdrawal of IMP
- Any TEAE leading to discontinuation

- All deaths
- Any TEAE leading to death

Overall summaries of TEAEs will be provided for the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups. For study participants on the reduced CZP dose regimen overall, summaries will be provided for the TEAEs occurring during the period of exposure to reduced CZP dose only. For study participants on the original CZP dose regimen, summaries will be provided combining results prior to and following dose reduction. In addition, overall TEAE summaries for the original CZP dose regimen will be produced separately for TEAEs occurring during the period of exposure to (1) the original CZP dose (all results before the dose reduction visit or all results for study participants with no dose reduction), and (2) the reduced CZP dose (all results after the initial dose reduction visit). For study participants on either Reduced Overall or Original Overall, overall TEAE summaries will be produced for TEAEs occurring during the period of exposure to (3) the escalated CZP dose (all results after the initial dose escalation visit). TEAEs occurring on the day of dose reduction or dose escalation, respectively, will be reviewed by the study physician in order to assign events to the most appropriate time period (before or after dose reduction or dose escalation, respectively).

The overall summary of TEAEs will also be presented by Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), concomitant MTX use, ERA status (only for the Any CZP Dose Regimen), and anti-CZP antibody status pooling across all weight groups.

The following AE summaries will also be presented:

- All TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group*
- All TEAEs by primary SOC, HLT, and PT by Baseline age group
- All TEAEs by primary SOC, HLT, and PT by concomitant MTX use*
- All TEAEs by primary SOC, HLT, and PT by ERA status**
- All TEAEs by primary SOC, HLT, and PT by overall anti-CZP antibody status*
- All serious TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group*
- All TEAEs leading to study drug discontinuation by primary SOC, HLT, and PT, overall and by Baseline weight group*
- All TEAEs leading to death by primary SOC, HLT, and PT, overall and by Baseline weight group
- Injection reaction TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group, further subdivided into injection site reactions and systemic reactions, with systemic reactions further subdivided into acute vs. delayed systemic reactions
- All TEAEs by primary SOC, PT, and maximum intensity, overall and by Baseline weight group
- All TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group

- All serious TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- All non-serious TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- All fatal TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- Individual study participant numbers experiencing a given adverse event, grouped by SOC, PT, intensity, and relation to study drug**
- TEAEs occurring in at least 5% of study participants by primary SOC, HLT, and PT, overall and by Baseline weight group*
- Non-serious TEAEs occurring in more than 5% of study participants by primary SOC and PT, overall and by Baseline weight group**
- Non-serious TEAEs occurring in more than 5% of study participants by primary SOC, PT, and relationship, overall and by Baseline weight group**
- All non-serious TEAEs by primary SOC and PT, overall and by Baseline weight group**

For all of the summaries in the above list (except for the ones flagged with an asterisk (*) or double asterisks (**)), TEAEs will be summarized for the Reduced Overall, Original Overall, and Any CZP Dose Regimen groups. For the above summaries flagged with double asterisks (**), only the Any CZP Dose Regimen will be presented. For the above summaries flagged with an asterisk (*), TEAEs for the Original CZP Dose Regimen Overall group will also be summarized separately for events occurring during the period of exposure to (1) the original CZP dose (all results before the dose reduction visit or all results for study participants with no dose reduction), and (2) the reduced CZP dose (all results after the initial dose reduction visit); the Reduced Overall will summarize separately events occurring during the period of exposure to Reduced CZP Dose regimen; and study participants from either Reduced Overall and Original Overall will summarize separately events occurring during the period of the escalated CZP dose (all results after the initial dose escalation visit). As indicated above, TEAEs occurring on the day of dose reduction or dose escalation, respectively, will be reviewed by the study physician in order to assign events to the most appropriate time period (before or after dose reduction or dose escalation, respectively).

In addition, to assess TEAEs by duration of exposure, the frequency and percentage of TEAEs reported during the first 16 weeks of study medication exposure will be summarized separately for the 2 CZP dose regimens (original CZP dose regimen overall, reduced CZP dose regimen overall).

Data displayed will include the number of TEAEs, number of study participants experiencing the TEAEs and percentage of study participants with the TEAE (all occurrences of the same event will be counted under the number of TEAEs but the subject will only be counted once). Summaries of all TEAEs, serious TEAEs, TEAEs leading to death, TEAEs leading to permanent withdrawal of IMP, and TEAEs leading to study discontinuation will also include

the exposure-adjusted incidence rate (EAIR) with associated 95% confidence interval, and the exposure-adjusted event rate (EAER).

For EAIR, the numerator will be the total number of study participants experiencing a particular TEAE. The denominator will be 100 subject-years, ie, the total summation of individual subject-years at risk up to the first occurrence of the given TEAE for study participants with that TEAE, plus the total subject-years at risk for those study participants not experiencing that TEAE, divided by 100. Details regarding calculation of subject-years at risk are described in Section 9.1. EAIR will be presented with exact 95% confidence intervals based on the link between the chi-square distribution and the Poisson distribution (Ulm, 1990).

For EAER, the numerator will be the number of TEAEs including repeat occurrences in individual study participants. The denominator will be in 100 subject-years (total summation of individual subject-years at risk divided by 100). No confidence interval will be computed.

The following are TEAEs of interest for this study and will be summarized as described below:

1) Serious infections, including opportunistic infections. Serious infections will be summarized using the previously described All SAEs table. No separate table is planned. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.

2) Malignancies, including lymphoma. These will be presented in 2 tables using the criteria SMQ = “Malignant or unspecified tumours” and SMQ=”Malignant tumours”, respectively.

3) Congestive heart failure. These will be manually identified by the study physician from the previously described All TEAEs table. In addition, major adverse cardiac events (MACE) will be presented in a table using UCB-defined search criteria and will include fatal and serious non-fatal myocardial infarction, cerebrovascular events and congestive heart failure.

4) Demyelinating-like disorders. These will be manually identified by the study physician from the previously described All TEAEs table.

5) Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = “Haematopoietic cytopenias” in the subset of SAEs.

6) Serious bleeding events. These will be presented in a table using the criteria SMQ = “Haemorrhages” in the subset of SAEs.

7) Lupus and lupus-like illness. These will be manually identified by the study physician from the previously described All TEAEs table.

8) Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from the previously described All SAEs table.

The following is an AE of special interest for this study; the associated analysis will be described in the PDILI paragraph in Section 9.3:

Potential Hy's Law, defined as ≥3xULN alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (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.

Further information regarding search criteria and algorithms is provided in the guidance document "AEs of Interest – Cimzia Program".

The tables for 1, 2, 3, 5, and 6 above will be summarized by SOC, HLT, and PT and will include the number of events, the number and percentage of study participants with an event, the EAIR with associated 95% CIs and the EAER. TEAEs of interest tables will be provided for the Reduced CZP Dose Regimen Overall, Reduced CZP Dose Regimen, the Original CZP Dose Regimen Overall, the Original CZP Dose Regimen Prior to Dose Reduction or without Dose Reduction, the Original CZP Dose Regimen Following Dose Reduction, the Any CZP Dose Regimen, and the Escalation CZP Dose Regimen.

Was changed to:

Only treatment emergent adverse events (TEAE) will be included in the summary tables. Treatment emergent AEs are defined as AEs starting on or after the first administration of CZP and up to 70 days after the last dose of study medication. AEs that are pre-treatment or that start more than 70 days after the last dose of study medication will be flagged in the listing but excluded from summaries.

All AEs will be classified by SOC, HLT and PT according to the version of MedDRA® that is current to the sponsor at the time of data capture. A glossary for the TEAE listing will detail the verbatim terms that are coded to each SOC, HLT, and PT.

Treatment-related TEAEs are those with relationship to study medication of "Related" or "Possibly related" or those with a missing relationship. Severe TEAEs are those with an intensity of "Severe" or those with a missing intensity.

All TEAE summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. TEAEs occurring on the day of dose reduction or dose escalation, respectively, will be reviewed by the study physician in order to assign events to the most appropriate time period (before or after dose reduction or dose escalation, respectively).

The overview of the incidence of TEAEs, overall and by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg), will include the number of events and number of study participants and percentage of study participants with:

- Any TEAE
- Any serious TEAE
- Any treatment-related TEAE
- Any severe TEAE
- Any TEAE leading to permanent withdrawal of IMP

- Any TEAE leading to discontinuation
- All deaths
- Any TEAE leading to death

The overview of the incidence of TEAEs will also be presented by the following subgroups:

- Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years),
- concomitant MTX use,
- gender,

  race,
- ADAb participant status classification, and
- ADAb titer classification pooling across all Baseline weight groups.

The incidence and event rate (per 100 subject-years) of TEAEs will be presented as follows:

- All TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group
- All TEAEs by primary SOC, HLT, and PT by Baseline age group
- All TEAEs by primary SOC, HLT, and PT by concomitant MTX use
- All TEAEs by primary SOC, HLT, and PT by ADAb titer classification
- All TEAEs by primary SOC, HLT and PT by ADAb participant status classification
- All serious TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group
- All TEAEs leading to study drug discontinuation by primary SOC, HLT, and PT, overall and by Baseline weight group
- All TEAEs leading to death by primary SOC, HLT, and PT, overall and by Baseline weight group

The incidence of TEAEs will be presented as follows:

- Injection reaction TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group, further subdivided into injection site reactions and systemic reactions, with systemic reactions further subdivided into acute vs. delayed systemic reactions
- All TEAEs by primary SOC, PT, and intensity, overall and by Baseline weight group
- All TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- All serious TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- All non-serious TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group
- All fatal TEAEs by primary SOC, PT, and relationship, overall and by Baseline weight group

- TEAEs occurring in at least 5% of study participants by primary SOC, HLT, and PT, overall and by Baseline weight group
- Non-serious TEAEs occurring in more than 5% of study participants by primary SOC and PT, overall and by Baseline weight group

Incidence tables summarizing TEAEs will include the number of TEAEs, number of study participants experiencing the TEAEs and percentage of study participants with the TEAE (all occurrences of the same event will be counted under the number of TEAEs but the subject will only be counted once).

Incidence and event rate tables will include the descriptive statistics on the incidence table but also include the exposure-adjusted incidence rate (EAIR) with associated 95% confidence interval, and the exposure-adjusted event rate (EAER).

For EAIR, the numerator will be the total number of study participants experiencing a particular TEAE. The denominator will be 100 subject-years, ie, the total summation of individual subject-years at risk up to the first occurrence of the given TEAE for study participants with that TEAE, plus the total subject-years at risk for those study participants not experiencing that TEAE, divided by 100. Details regarding calculation of subject-years at risk are described in Section 9.1. EAIR will be presented with exact 95% confidence intervals based on the link between the chi-square distribution and the Poisson distribution (Ulm, 1990).

For EAER, the numerator will be the number of TEAEs including repeat occurrences in individual study participants. The denominator will be in 100 subject-years (total summation of individual subject-years at risk divided by 100). No confidence interval will be computed.

Listings:

Individual study participant numbers experiencing a given adverse event, grouped by SOC, PT, intensity, and relation to study drug

Change #37

Section 9.2.1, TEAEs of interest was added

The following are TEAEs of interest for this study and will be summarized in incidence and event rate tables (ie will include the number of events, the number and percentage of study participants with an event, the EAIR with associated 95% CIs and the EAER) as described below:

1) Serious infections, including opportunistic infections. Serious infections will be summarized using the previously described All SAEs table. No separate table is planned. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.

2) Malignancies, including lymphoma. These will be presented in 2 tables using the criteria SMQ = “Malignant or unspecified tumours” and SMQ=”Malignant tumours”, respectively.

3) Congestive heart failure. These will be manually identified by the study physician from the previously described All TEAEs table. In addition, major adverse cardiac events (MACE) will be presented in a table. using UCB-defined search criteria and will include fatal and serious non-fatal myocardial infarction, cerebrovascular events and congestive heart failure.

4) Demyelinating-like disorders. These will be presented in a table based on the SMQ=”Demyelination” in the TEAEs.

5) Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = “Haematopoietic cytopenias” in the subset of SAEs.

6) Serious bleeding events. These will be presented in a table using the criteria SMQ = “Haemorrhage terms (excl laboratory terms)” in the subset of SAEs.

7) Lupus and lupus-like illness. These will be manually identified by the study physician from the previously described All TEAEs table and not tabulated separately.

8) Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from the previously described All SAEs table and not tabulated separately.

9) Hepatic events. These will be summarized in a table that includes all TEAEs in the following SMQs: Cholestasis and jaundice of hepatic origin; hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions; hepatitis, noninfectious; liver-related investigations, signs and symptoms; liver-related coagulation and bleeding disturbances.

10)Hypersensitivity reactions. These will be determined from all TEAEs that either emerged on the same day as or next day after the administration of study medication injection and summarized in a table. The PTs are: administration site hypersensitivity, documented hypersensitivity to administered product, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis, infusion site hypersensitivity, injection site hypersensitivity, medical device site hypersensitivity, type II hypersensitivity, type IV hypersensitivity. reaction.

11) Anaphylactic reactions. These will be determined from all TEAEs that either emerged on the same day as or next day after the administration of study medication injection. Anaphylactic reactions will be summarized in a table using UCB-defined search criteria.

Further information regarding search criteria and algorithms is provided in the guidance document “AEs of Interest – Cimzia Program”.

Change #38

Section 9.2.2, AE of special interest was added

Potential Hy’s Law is an AE of special interest for this study; the definition is below. The occurrence of this AE of special interest is dependent upon laboratory parameters, given that, the associated analysis of these AEs will be described in the Clinical laboratory evaluations section, PDILI paragraph in Section 9.3:

Potential Hy's Law, defined as ≥3xULN alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (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 #39

Section 9.2.3, Covid vaccine sensitivity analysis was added

A summary of the incidence and event rate (per 100 subject-years) of TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group will be presented which will exclude TEAEs occurring up to and including 7 days from the date of covid vaccination. The list of TEAEs to be excluded if reported with Mild or Moderate intensity are:

Table 13–5: Covid vaccination related adverse events for sensitivity analysis

ARTHRALGIA	INJECTION SITE INDURATION
AXILLARY SWELLING	INJECTION SITE PAIN
AXILLARY TENDERNESS	INJECTION SITE WARMTH
BACKACHE	MYALGIA
BODY TEMPERATURE INCREASED	NAUSEA
CHILLS	PRURITUS
DIARRHOEA	RASH
FEVER	TENDERNESS
HEAD DISCOMFORT	URTICARIA
HEADACHE	VOMITING
INJECTION SITE ERYTHEMA	

Change #40

Section 9.3, Clinical laboratory evaluations

PDILI IMP discontinuation criteria as outlined in the Appendix of Protocol Amendment 9 will be evaluated at all laboratory assessments, for all study participants. The number and percentage of study participants with elevated liver function tests and meeting PDILI criteria will be presented. Any data that meets the PDILI criteria or is captured regarding PDILI will be listed.

Was changed to:

PDILI IMP discontinuation criteria as outlined in the Appendix of Protocol Amendment 9 will be evaluated at all laboratory assessments, for all study participants. The number and percentage of study participants meeting PDILI criteria will be presented. The following criteria will be presented:

- AST or ALT ≥ 3xULN and Total Bilirubin < 2xULN
- AST or ALT ≥ 3xULN and Total Bilirubin ≥ 2xULN
- AST or ALT ≥ 3xULN and Total Bilirubin ≥ 2xULN and Alkaline Phosphatase < 2xULN (Hy's Law if all criteria met at the same visit)
- AST or ALT ≥ 5xULN

Any data that meets the PDILI criteria or is captured regarding PDILI will be listed.

Change #41

Section 9.4.1, Vital signs

Vital signs will be measured within approximately 15 minutes prior to dosing, and in addition (following implementation of Protocol Amendment 3), pulse and blood pressure only will be measured approximately 30 minutes after dosing with study medication. Study participants should be sitting for at least 5 minutes prior to and during the collection of blood pressure and pulse rate measurements. Vital signs to be collected are pulse, systolic/diastolic blood pressure measurement, and temperature.

Descriptive statistics for observed values and change from pre-dose to post-dose pulse and blood pressure when available, will be presented for each visit for each vital sign parameter.

Vital signs summaries will be provided overall (ie, for the Any CZP Dose Regimen) and by Baseline weight group.

Was changed to:

Vital signs will be measured within approximately 15 minutes prior to dosing, and in addition (following implementation of Protocol Amendment 3), pulse and blood pressure only will be measured approximately 30 minutes after dosing with study medication. Study participants should be sitting for at least 5 minutes prior to and during the collection of blood pressure and pulse rate measurements. Vital signs to be collected are pulse, systolic/diastolic blood pressure measurement, and temperature.

For pre-dose measurements, if more than one results appears for a specific visit, then the pre-dose results are averaged. The same will occur for post dose measurements. All data will be listed, including the averages. If measurements are labeled as pre-dose in the CRF, but when compared to dosing, it is actually post-dose, the analysis label will reflect a post dose measurement. The same will occur for post-dose measurements.

Descriptive statistics for observed values and change from pre-dose to post-dose pulse and blood pressure when available, will be presented for each visit for each vital sign parameter.

Vital signs summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose) and by Baseline weight group.

A summary of the incidence of markedly abnormal vital signs results by visit will be presented for temperature, blood pressure, and pulse rate parameters. Details of markedly abnormal values will be listed by subject and parameter for which there is at least 1 markedly abnormal result recorded. Definitions of markedly abnormal values are given below in the table below.

Markedly abnormal high temperature is >40.0 degrees Celsius (>104.0 degrees Fahrenheit) while a markedly abnormal low temperature is 32 – 35 degrees Celsius (89.6 – 95 degrees Fahrenheit).

Table 13–6: Definitions of Markedly Abnormal Vital Signs Values

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	3y - <12y	<60 >130
	12y - <17y	≤50 ≥120
	≥17y	<60 >100
Systolic Blood Pressure (mmHg)	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	<90 >140 >160
Diastolic Blood Pressure (mmHg)	3y - <12y	<50 >80
	12y - <17y	≤50 ≥105
	≥17y	<50 >90 >100

Change #42

Section 10, Efficacy Analyses

Efficacy will be analyzed using the FAS. All efficacy results will be summarized overall and by Baseline weight group and will be provided for the Reduced CZP Dose Regimen Overall, the Original CZP Dose Regimen Overall, and the Any CZP Dose Regimen. For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and anti-CZP

antibody status will be presented pooling across all weight groups unless otherwise specified. In addition, selected summaries will also be presented by gender and race.

In addition to the efficacy summaries described below, all efficacy results will be listed by subject. However, some listings for study participants in Original CZP Dose Regimen may be grouped by study participants with dose reduction and study participants without dose reduction within each weight group.

Was changed to:

Efficacy will be analyzed using the FAS. All efficacy results will be summarized overall and by Baseline weight group and will be provided for the Original CZP Dose, Reduced CZP Dose, and the Any CZP Dose. For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and ADAb status will be presented pooling across all weight groups unless otherwise specified. In addition, selected summaries will also be presented by gender and race.

In addition to the efficacy summaries described below, all efficacy results will be listed by subject data listings.

In Section 10, the analyses described will be generated for the final analysis. For the Updated Week 24 Interim analysis, only efficacy data up to and including Week 24 will be presented in the analyses described in Section 10 for the following variables:

- PedACR30/50/70, 90
- Number of joints with active arthritis
- Number of joints with limitation of range of motion
- Physician's Global Assessment of Disease Activity
- Childhood Health Assessment Questionnaire
- Parent's Global Assessment of Overall Well-Being
- C-Reactive protein
- Juvenile Arthritis Disease Activity Score 71-joint

For the Updated Week 24 Interim analysis, all reported data for other efficacy variables will be listed only; any calculations described for the final analysis will not be performed. These include the following variables:

- Clinically Inactive Disease
- Clinical remission on medication
- Duration of Morning Stiffness
- Parent's Assessment of Arthritis Pain
- Faces Pain Scale Revised
- JIA Pain

- Fatigue Assessment Scale, and
- Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey.

Change #43

Section 10.2, Statistical analysis of the secondary efficacy variables

The frequency and percentage of study participants achieving a PedACR30, PedACR50, PedACR70, and PedACR90 response and associated 95% exact binomial CIs will be summarized for Week 16 as compared to Baseline. Results will be presented overall and by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg), as well as by Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), concomitant MTX use, overall anti-CZP antibody status, gender and race.

Was changed to:

The frequency and percentage of study participants achieving a PedACR30, PedACR50, PedACR70, and PedACR90 response and associated 95% exact binomial CIs will be summarized for Week 16. Results will be presented overall and by Baseline weight group (10 to <20kg, 20 to <40kg, and ≥40kg), as well as by Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), concomitant MTX use, ADAb titer classification, gender and race pooling across all Baseline weight groups.

Plots will be produced to show the percentage of PedACR30/50/70/90 responders by visit and ADAb titer classification.

Change #44

Section 10.3, Analysis of other efficacy variables

Continuous endpoints will be summarized using LOCF for missing values, unless otherwise specified, as for the Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey.

Was changed to:

Continuous endpoints will be summarized using observed case, as for the Physician's Global Assessment of Disease Activity.

Change #45

Section 10.3.1, PedACR30, PedACR50, PedACR70, and PedACR90, the following was added

Plots will be produced to show the percentage of PedACR30/50/70/90 responders by visit and ADAb titer classification.

Change #46

Section 10.3.5, Parent's Assessment of Arthritis Pain VAS

This section was updated to indicate that for the Updated Week 24 Interim Analysis, the data for this efficacy parameter would only be listed (not summarized).

Change #47

Section 10.3.9, Clinically Inactive Disease

This section was updated to indicate that for the Updated Week 24 Interim Analysis, the data for this efficacy parameter would only be listed (not summarized).

Change #48

Section 10.3.10, Clinical Remission on Medication

This section was updated to indicate that for the Updated Week 24 Interim Analysis, the data for this efficacy parameter would only be listed (not summarized).

Change #49

Section 10.3.11, Duration of morning stiffness

This section was updated to indicate that for the Updated Week 24 Interim Analysis, the data for this efficacy parameter would only be listed (not summarized).

Change #50

Section 10.3.12, Faces Pain Scale - Revised

This section was updated to indicate that for the Updated Week 24 Interim Analysis, the data for this efficacy parameter would only be listed (not summarized).

Change #51

Section 10.3.13, Patient's Assessment of Arthritis Pain VAS

This section was updated to indicate that for the Updated Week 24 Interim Analysis, the data for this efficacy parameter would only be listed (not summarized).

Change #52

Section 10.3.14, FASCA – Fatigue Assessment Analysis

This section was updated to indicate that for the Updated Week 24 Interim Analysis, the data for this efficacy parameter would only be listed (not summarized).

Change #53

Section 10.3.15, Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey

This section was updated to indicate that for the Updated Week 24 Interim Analysis, the data for this efficacy parameter would only be listed (not summarized).

Change #54

Section 12.1, Comparisons with RA0138 data was added

Comparisons between RA0043 and RA0138 data will focus on common timepoints (Weeks 12 and 24).

Separate boxplots will be performed for Week 12 and Week 24 showing plasma CZP concentrations for the two CZP dose groups (Original or Reduced) for RA0043 and the single CZP dose group for RA0138 in the same plot. The plots will be repeated separately by Baseline weight group, Baseline age group and concomitant MTX use.

Separate plots of individual participant (natural) log CZP plasma concentration versus log2 ADAb titer will be produced for Week 12 and Week 24 data for both studies. In these plots, participants study (RA0043 or RA0138) and CZP dose group (Original or Reduced) will be shown as a different symbol/color to aid comparison. In addition, for RA0138 only, plots of individual participant area under the plasma concentration curve over the 2-week dosing interval (AUC0-tau) versus log2 ADAb titer at Week 12 will be produced.

If there are signs that higher titer levels are associated with lower plasma concentrations, further investigations will be performed to attempt to determine at which titer levels differences are observed and to assess the impact on efficacy and safety.

Further analyses may be defined in the integrated summary of immunogenicity including comparisons of ADAb titer levels between studies (no pooling of studies across indications are planned) allowing us to put the pJIA/RA data in context of the AS and PSO indications.

13.5 AMENDMENT 5

Rationale for the amendment

The primary reasons for this SAP amendment were to:

- Include additional exposure, CZP plasma concentration, ADAb and treatment-emergent adverse event analyses on Complete Reduced CZP and Complete Original CZP doses, in line with [redacted] response,
- Update analysis concepts in regards to the PK and ADAb analyses, and
- Clarify and update other analysis concepts.

Modifications and changes

Global changes

Three dose groups are now referenced for analysis: Original CZP Dose, Reduced CZP Dose and Any CZP Dose. The FDA has requested two additional dose groups – Complete Reduced CZP dose (which will show data captured at the time a study participant was taking Reduced CZP dose, regardless of dose switching) and Complete Original CZP dose (which will show data captured while a study participant was taking Original CZP dose, regardless of dose switching). Only specific tables for exposure, PK, ADAb and adverse events will present data summarized using these two new treatment groups.

Specific changes

Change #1

SAP/Amendment	Date

Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016
SAP Amendment 3	30 Jun 2021
SAP Amendment 4	8 Dec 2022

Has been changed to:

SAP/Amendment	**Date**
Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016
SAP Amendment 3	30 Jun 2021
SAP Amendment 4	8 Dec 2022
SAP Amendment 5	21 Jun 2023

Change #2

List of abbreviations include ED and ELISA.

Change #3

Section 2, Protocol Summary

Results of a planned interim PopPK analysis conducted suggested that while observed CZP plasma concentrations with the original dose regimen administration remained in the adult range, they were at the upper end of the distribution. 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. Based on interactions with FDA, Amendment 9 re-introduced the original dose regimen for 30 new participants and the option to increase to this dose for ongoing participants that had been receiving the reduced dose.

Was changed to:

Study participants, prior to Protocol Amendment 4, were enrolled on the Original CZP Dose. Results of a planned interim PopPK analysis conducted suggested that while observed CZP plasma concentrations with the Original Dose administration remained in the adult range, they were at the upper end of the distribution. Based on these findings, the dosing was

changed with Protocol Amendments 4 and 5, and the doses to be administered were reduced by 50% for all weight groups, Reduced CZP Dose, see Table 2–3. 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. Based on interactions with FDA, Amendment 9 allowed 30 new participants to be enrolled taking Original CZP Dose; for the study participants who were taking Reduced CZP Dose, it introduced the option to increase to the Original CZP Dose.

Study participants will be summarized by the following 5 dose groups:

- Any CZP Dose – includes all data from all study participants while being treated in the study
- Original CZP Dose – includes all data for study participants enrolled on Original CZP Dose prior to the first change in dosage
- Reduced CZP Dose – includes all data for study participants enrolled on Reduced CZP Dose prior to the first change in dosage
- Complete Original CZP Dose – includes all data for study participants who took Original CZP Dose prior to the first change in dosage as well as the data from when study participants increased their dosage to Original CZP after taking Reduced CZP Dose
- Complete Reduced CZP Dose – includes all data for study participants who took Reduced CZP Dose prior to the first change in dosage as well as the data from when study participants took Reduced CZP Dose after taking Original CZP Dose

Change #4

Section 2.3 Study design and conduct

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 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.

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 (except the 10 to < 20kg group on the reduced dose will be administered 50mg Q4W).

Was changed to:

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 are intended to be enrolled on the Original CZP Dose 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.

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 (except the 10 to < 20kg group on the Reduced CZP Dose will be administered 50mg Q4W).

Change #5

Section 2.4 Determination of sample size

With Protocol Amendment 9, an additional 30 study participants will be enrolled on the original dose 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).

Was changed to:

With Protocol Amendment 9, an additional 30 study participants will be enrolled 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 #6

Section 2.5 Study RA0138

RA0138 is an open-label study in 30 adult study participants with RA. This study was conducted to generate PK and ADAb data using the same ECLIA assay as used in RA0043 to form the basis of "PK-matching" for CZP approval. The PK and ADAb data from RA0138 will be analyzed and displayed in the same manner as data from RA0043 so that comparisons and conclusions can be made. Those details will be presented in the Appendix, Section 12.1.

Was changed to:

RA0138 is an open-label study in 33 adult study participants with RA who took 400mg loading dose (Weeks 0, 2, and 4), followed by 200mg CZP Q2W. This study was conducted to generate PK and ADAb data using the same ECLIA assay as used in RA0043 to form the basis of "PK-matching" for CZP approval. The PK and ADAb data from RA0138 will be analyzed and displayed in the same manner as data from RA0043 so that comparisons and conclusions can be made. Those details will be presented in the Appendix, Section 12.1.

Change #7

Section 3.1 General presentation of summaries and analyses

Generally, data will be summarized by the Original CZP Dose, Reduced CZP Dose, and Any CZP Dose groups. For PK and ADA analyses, data will be summarized by Original CZP Dose and Reduced Dose only.

Further details regarding these displays based upon dose groups can be found in the respective PK, safety and efficacy analysis sections below.

Was changed to:

The planned data summaries using dose groups of Original CZP Dose and Reduced CZP Dose are designed to allow for the most relevant comparison of PK data and PK extrapolation using only data collected from study participants while receiving one consistent dosing regimen of CZP. This assignment of treatment groups will allow for a pure comparison of PK of the Original CZP Dose and the Reduced CZP Dose between pediatrics and adults without

the potential of confounding differences in CZP plasma concentrations due to dose switching. Additionally, these dose groupings allow for the continuity of safety, immunogenicity, and open label efficacy analyses for the Original CZP Dose and Reduced CZP Dose.

Generally, data will be summarized by the Original CZP Dose, Reduced CZP Dose, and Any CZP Dose groups. For PK and ADAb analyses, data will be summarized by Original CZP Dose and Reduced CZP Dose only.

Following recommendations received from [redacted], a few data summaries will be organized by "Complete" CZP dose groups defined below, which will allow assessment of exposure and safety for all time that study participants were receiving the specified dose regardless of dose switching:

- Complete Original CZP Dose: includes all study participants who began treatment in accordance with the Original CZP Dose, as well as study participants who began treatment in accordance with the Reduced CZP Dose and then later dose escalated to the Original CZP Dose.

  Only data obtained while the study participant was receiving the Original CZP Dose will be included in summaries of the Complete Original CZP Dose. For study participants who began treatment with the Original CZP Dose, this includes time on the Original CZP Dose prior to first change in dosage, as well as time after returning to Original CZP Dose after a previous dose reduction. For study participants who began treatment with the Reduced CZP Dose, this includes only time after dose escalation to the Original CZP Dose.

- Complete Reduced CZP Dose: includes all study participants who began treatment in accordance with the Reduced CZP Dose, as well as study participants who began treatment in accordance with the Original CZP Dose and later dose reduced to the Reduced CZP Dose.

  Only data obtained while the study participant was receiving the Reduced CZP Dose will be included in summaries of the Complete Reduced CZP Dose. For study participants who began treatment with the Reduced CZP Dose, this includes time on the Reduced CZP Dose prior to first change in dosage. For study participants who began treatment with the Original CZP Dose, this includes only time after dose reduction to the Reduced CZP Dose, and prior to any potential later dose escalation back to the Original CZP Dose.

Selected exposure and TEAE summaries will be produced on Complete Original CZP Dose and Complete Reduced CZP Dose in order to answer specific agency questions. Similarly, summaries of the proportion of PK and ADAb samples and participants that have been reanalyzed with the ECLIA assay will also be produced with this treatment association.

Further details regarding these displays based upon dose groups can be found in the respective PK, safety and efficacy analysis sections below.

Change #8

Section 3.2.5 Week 24 was added:

Week 24 is defined as the visit labeled as Week 24 or Visit 10 in the data.

Change #9

Section 3.2.6 Entire treatment period was added:

The entire treatment period is the same as the entire exposure period which includes all data while the study participant is taking study medication.

Change #10

Section 3.4.1 PK protocol deviations was renamed to Exclusion of PK data points

Exclusion of specific PK data points will be done for that PK data presented in the subset of tables and figures where geometric means are calculated and displayed. These exclusions will not occur in the PK data presented in spaghetti plots or individual profile figures. The reasons why PK data points may be excluded are the following:

- Study participant taking an incorrect treatment or dose,
- Study participant's discontinuation of CZP,
- Study participant being in Clinical remission (and not taking CZP),
- Study participant having deviations where CZP dosings occur outside the scheduled CZP dosing window, and
- Study participant is procedurally non-compliant in having PK samples taken at the appropriate time points.

PK data that is excluded due to the above reasons will be flagged on the analysis PK dataset. The flagging will allow the data to be excluded from geometric mean calculations which could be more affected by instances of treatment and procedure non-compliance.

Was changed to:

Exclusion of specific PK data points will be done for that CZP plasma concentration data presented in the subset of tables and figures where geometric means are calculated and displayed. These exclusions will not occur in the CZP plasma concentration data presented in spaghetti plots or individual profile figures. The reasons why CZP plasma concentration data points may be excluded are the following:

- Study participant taking an incorrect treatment or dose,
- Study participant's discontinuation of CZP,
- Study participant being in Clinical remission (and not taking CZP),
- Study participant having deviations where CZP dosings occur outside the scheduled CZP dosing window, and
- Study participant is procedurally non-compliant, in not having plasma concentration samples taken at the appropriate time points.

CZP plasma concentration data that is excluded due to the above reasons will be flagged on the analysis PK dataset. The flagging will allow the data to be excluded from geometric mean calculations which could be more affected by instances of treatment and procedure non-compliance.

Change #11

Section 3.4.1.1 Rules for exclusions of specific PK samples

The PK sample results taken at a specific visit will be excluded from analysis for the following reasons:

- For study participants in documented clinical remission (and not taking CZP), any study participant's PK sample results during clinical remission (after CZP dose is stopped) are excluded,
  - For study participants returning to CZP dosing after having stopped taking CZP (eg. when in clinical remission), a study participant's PK sample result will be included in summaries if the prior 3 consecutive CZP doses are present,
- If the study participant's PK sample was taken at a visit where the prior 2 consecutive CZP doses were missed, then the study participant's PK sample is excluded,
- If in the 168 days prior to the study participant's PK sample, there were >3 CZP doses missed, then that study participant's PK sample is excluded,
- If the PK sample is taken following the study participant's noncompliance in CZP dosing as indicated by an important protocol deviation, then the study participant's affected PK sample (the one following that noncompliant dose) will be excluded,
- If a study participant is on a Q2W CZP dosing interval, and the study participant's PK sample is taken <9 days or >19 days from the last CZP dosing, then it is excluded,
- If a study participant is on a Q4W CZP dosing interval, and the study participant's PK sample is taken <23 days or >33 days from the last CZP dosing, then it is excluded,
- For the Week 1 PK sample, if a study participant's PK sample is taken (too soon) <4 days after or (too late) >10 days after the Week 0 CZP dose, it is excluded, or
- For the Week 17 PK sample, if a study participant's PK sample is taken (too soon) <4 days after or (too late) >10 days after the Wk 16 CZP dose, it is excluded.

Was changed to:

The PK sample results taken at a specific visit will be excluded from analysis for the following reasons:

- If the study participant's CZP plasma concentration sample was taken at a visit where the prior 2 consecutive CZP doses were missed, then the study participant's CZP plasma concentration sample is excluded,
  - For study participants returning to CZP dosing, a study participant's CZP plasma concentration result will be included in summaries if the prior 3 consecutive CZP doses are present.

- If in the 168 days prior to the study participant's CZP plasma concentration sample, there were >3 CZP doses missed, then that study participant's CZP plasma concentration sample is excluded,
  - For study participants returning to CZP dosing, a study participant's CZP plasma concentration result will be included in summaries if the prior 3 consecutive CZP doses are present.
- If a study participant is on a Q2W CZP dosing interval, and the study participant's CZP plasma concentration sample is taken <9 days or >19 days from the last CZP dosing, then it is excluded,
- If a study participant is on a Q4W CZP dosing interval, and the study participant's CZP plasma concentration sample is taken <23 days or >33 days from the last CZP dosing, then it is excluded,
- For the Week 1 CZP plasma concentration sample, if a study participant's sample is taken (too soon) <4 days after or (too late) >10 days after the Week 0 CZP dose, it is excluded, or
- For the Week 17 CZP plasma concentration sample, if a study participant's sample is taken (too soon) <4 days after or (too late) >10 days after the Week 16 CZP dose, it is excluded.

  In addition, CZP plasma concentrations that have been analyzed outside the stability coverage of the ECLIA assay have also been excluded. In this latter case from all tables and figures and only will appear in the listings with a flag for out of stability.

Change #12

Section 3.5 Analysis sets

The efficacy variables will be summarized using the Full Analysis Set (FAS). All safety and immunogenicity analyses will be based on the Safety Set (SS). Plasma concentration data and PK parameters will be summarized using the Pharmacokinetic Per-Protocol Set (PK-PP). Pharmacokinetic-pharmacodynamic modeling will be based upon the Pharmacokinetic-Pharmacodynamic (PK-PD) Set.

Was changed to:

The efficacy variables will be summarized using the Full Analysis Set (FAS). All safety and immunogenicity analyses will be based on the Safety Set (SS). Plasma concentration data will be summarized using the Pharmacokinetic Per-Protocol Set (PK-PP).

Change #13

Section 3.5.4 Pharmacokinetic Per-Protocol (PK-PP) Set

The Pharmacokinetic Per-Protocol (PK-PP) Set 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 and analyzed using the ECLIA method) on at least 1 occasion and who had no important protocol deviations affecting the PK parameters, as

confirmed during data cleaning meetings prior to locking the database. The PK-PP Set will be used for the PopPK model that will be described in a separate data analysis plan (DAP)and for all presentations of plasma concentration.

Was changed to:

The Pharmacokinetic Per-Protocol (PK-PP) Set is a subset of the SS consisting of those study participants who took at least 1 dose of study medication, provided measurable plasma CZP concentration samples (with recorded sampling date/time or for which date/time can be reasonably assumed and it was analyzed using the ECLIA method) on at least 1 occasion. The PK-PP Set will be used for the PopPK model that will be described in a separate data analysis plan (DAP) and for all presentations of plasma concentration.

Change #14

Section 3.8 Coding dictionaries

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA® version 18.1) according to UCB standard operating procedures (SOP). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD version dated Sep 2013) according to UCB SOPs.

Was changed to:

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA® version 23.1) according to UCB standard operating procedures (SOP). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD version dated Sep 2020 B3) according to UCB SOPs.

Change #15

Section 3.9 Changes to protocol-defined analyses

The definition for the PK-PP has been clarified that study participants in this set must have PK data analyzed using the ECLIA method.

Was changed to:

The definition for the PK-PP has been clarified such that study participants in this set must have PK data analyzed using the ECLIA method.

In line with [redacted] response, additional analyses have been added to

- summarize exposure and treatment-emergent adverse events for when study participants were taking Complete Original CZP Dose and Complete Reduced CZP Dose.
  - Complete Original CZP Dose includes all data for study participants who took Original CZP Dose prior to the first change in dosage as well as the data from when study participants increased their dosage to Original CZP after taking Reduced CZP Dose.

  - Complete Reduced CZP Dose includes all data for study participants who took Reduced CZP Dose prior to the first change in dosage as well as the data from when study participants took Reduced CZP Dose after taking Original CZP Dose.

- the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples initially analyzed with the ELISA method will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples analyzed with the ECLIA method (either originally or via re-analysis) will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples initially analyzed with the ELISA method will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- Additionally, the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples analyzed with the ECLIA method (either originally or vis re-analysis) will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.

Change #16

Section 3.9 Changes to protocol-defined analyses

This analysis plan includes plots of CZP plasma concentrations, ADAb titers, JADAS-71 and maximum PedACR response for individual study participants by visit. Box plots of the PK distribution as Weeks 12 and 24 stratified by Baseline weight group, Baseline age group, concomitant MTX use and participant ADAb classification will be performed as a basis of the comparison with the adult RA PK exposures in RA0138; this comparison of observed PK data will be covered in Appendix Section 12.1. Plots of PK and ADAb data were not pre-specified in the study protocol.

It is not planned to perform a population PKPD modeling analysis of RA0043 data to explore the exposure-response relationship in JIA pediatric population for the following reasons: i) the purpose of the RA0043 study is to support the efficacy extrapolation to the pediatric population by PK matching with respect to RA adult PK, and thus the main aim of the analysis that will be performed by nonlinear mixed effect modeling is to characterize the PK in JIA pediatrics with precise parameter estimates; and ii) the W24 interim analyses performed and submitted in 2016 (BLA 125160-275) included PedACR and JADAS-71 graphical explorations by dose regimen which concluded that a substantial improvement of the PedACR and JADAS-71 responses across both dosing regimens investigated in Study RA0043 was observed, with no differences between these, that would support a pop-PKPD analysis. Hence the PK-PD Set was removed as no analysis are planned for this population.

In the protocol it was stated that continuous efficacy endpoints would be presented using both last observation carried forward (LOCF) and observed case (OC) analyses. Instead, only observed case summaries of continuous efficacy endpoints will be presented since efficacy is not the primary objective of this study and little difference is expected between the two different analyses.

For the Updated Week 24 Interim Analysis, the efficacy data will be summarized and plotted up to and including Week 24; all efficacy data will be included in listings. Efficacy analyses will not be submitted for the 120 Day Safety Update.

Was changed to:

This analysis plan includes plots of CZP plasma concentrations, ADAb titers, and maximum PedACR response for individual study participants by visit. Box plots of the PK distribution at Weeks 12 and 24 stratified by Baseline weight group, Baseline age group, concomitant MTX use and participant ADAb classification will be performed as a basis of the comparison with the adult RA PK exposures in RA0138; this comparison of observed PK data will be covered in Appendix Section 12.1. Plots of PK and ADAb data were not pre-specified in the study protocol.

It is not planned to perform a population PKPD modeling analysis of RA0043 data to explore the exposure-response relationship in JIA pediatric population for the following reasons: i) the purpose of the RA0043 study is to support the efficacy extrapolation to the pediatric population by PK matching with respect to RA adult PK, and thus the main aim of the analysis that will be performed by nonlinear mixed effect modeling is to characterize the PK in JIA pediatrics with precise parameter estimates; and ii) the W24 interim analyses performed and submitted in 2016 (BLA 125160-275) included PedACR and JADAS-71 graphical explorations by dose which concluded that a substantial improvement of the PedACR and JADAS-71 responses across both doses investigated in Study RA0043 was observed, with no differences between these, that would support a pop-PKPD analysis. Hence the PK-PD Set was removed as no analyses are planned for this population.

In the protocol it was stated that continuous efficacy endpoints would be presented using both last observation carried forward (LOCF) and observed case (OC) analyses. Instead, only observed case summaries of continuous efficacy endpoints will be presented since efficacy is not the primary objective of this study and little difference is expected between the two different analyses.

For the Updated Week 24 Interim Analysis, the efficacy data will be summarized and plotted up to and including Week 24; all efficacy data will be included in listings and displayed on a small subset of figures.

Change #17

Section 4.2 Handling of dropouts or missing data

For all binary efficacy endpoints assessing response (PedACR30, PedACR50, PedACR70, PedACR90, CID, CRM), a subject having missing data for the time point assessed will be conservatively counted as a non-remitter or non-responder. This will be done whether the

data is missing, the subject discontinued the study prior to the time point assessed, or the data is considered missing due to use of prohibited or rescue medication.

For all non-missed visits, if any of the PedACR core set measures are missing then those scores will be considered as not having met the criteria for improvement in the PedACR30, PedACR50, PedACR70 and PedACR90 response analyses. PedACR30, PedACR50, PedACR70, and PedACR90 responses will be derived if a single core set measure is missing. However, if 2 or more core set measures are missing, the corresponding PedACR30, PedACR50, PedACR70 and PedACR90 responses will in general be treated as missing.

All efficacy data collected at any visits after the use of rescue medications, or prohibited medications that could impact efficacy, will be treated as missing for continuous endpoints and non-response for binary endpoints in all analyses except where specifically stated otherwise. See Section 6.6 for a list of medications which would result in all efficacy data at only the next scheduled visit (and not all subsequent visits) being treated as missing/non-response. Any joint receiving intra-articular corticosteroids will be treated as missing with respect to assessments of that joint for 3 months (91 days).

For continuous efficacy endpoints, missing assessments will not be imputed. For all analyses, the data will be analyzed as observed cases without any imputation. For the non-responder imputation (NRI) calculations for binary efficacy outcomes, the data beyond Week 56 will be analyzed as observed cases without any imputation while the data up to and including Week 56, NRI will only be applied to study participants who have discontinued early prior to reaching Week 56.

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

Was changed to:

For all binary efficacy endpoints assessing response (PedACR30, PedACR50, PedACR70, PedACR90, CID, CRM), a study participant having missing data for the time point assessed will be conservatively counted as a non-remitter or non-responder. This will be done whether the data is missing, the study participant discontinued the study prior to the time point assessed, or the data is considered missing due to use of prohibited or rescue medication.

For all non-missed visits, if any of the PedACR core set measures are missing then those scores will be considered as not having met the criteria for improvement in the PedACR30, PedACR50, PedACR70 and PedACR90 response analyses. PedACR30, PedACR50, PedACR70, and PedACR90 responses will be derived if a single core set measure is missing. However, if 2 or more core set measures are missing, the corresponding PedACR30, PedACR50, PedACR70 and PedACR90 responses will in general be treated as missing.

Derived binary efficacy endpoints at visits affected by the use of rescue medications, or prohibited medications, will be treated as non-response. See Section 6.7 for a list of medications which would result in all efficacy data at only the next scheduled visit (and not all subsequent visits) being treated as missing/non-response. Any joint receiving intra-articular corticosteroids will be treated as missing with respect to assessments of that joint for 3 months (91 days).

For continuous efficacy endpoints, missing assessments will not be imputed..

For the non-responder imputation (NRI) calculations for binary efficacy outcomes,

- the study participants who discontinued up to and including Week 56, NRI will be imputed up to Week 56,
- the study participants who discontinued after Week 56, no imputation will be performed after the last visit,
- for study participants who take rescue and prohibited medications (see Section 6.6),
  - for visits up to and including Week 56, the outcomes are imputed as NRI up to Week 56
  - for visits after Week 56, the outcomes are imputed as NRI if medication initiation is before or on Week 56
- for the initiation of rescue, short-acting or prohibited medications after Week 56, then the NRI imputation is not applied.

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

Change #18

Section 4.3 Interim analyses and data monitoring

Based on results of this interim PopPK analysis, the doses 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 the previous study in adult study participants with RA (study C87050). However, it was later determined that there were deficiencies detected with in the bioanalytical assay used within RA0043, which rendered the PK data for the PopPK analysis and simulations that informed the dose reduction in Protocol Amendments 4 and 5 were not up to current standards and FDA guidelines; therefore, those data were not able to support the regulatory filing.

<u>Interim analyses of PK, immunogenicity, safety, and efficacy endpoints</u>

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; this is referred to as the 2016 Week 24 interim analysis. 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; this will be referred to as the Updated Week 24 Interim analysis to be used in support of the re-submission of BLA 125160-275.

Was changed to:

Based on results of this interim PopPK analysis, the doses were 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 the previous study in adult study participants with RA (study C87050).

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; this is referred to as the 2016 Week 24 interim analysis. However, it was then determined that there were deficiencies with the bioanalytical assay used within RA0043, which rendered the PK data for the PopPK analysis and simulations not up to current standards and FDA guidelines; therefore those data were not able to support the regulatory filing.

At the time of Protocol Amendment 9, a new assay had been developed and would be used to analyze samples from the 30 new subjects enrolled on the original dose as well as any old samples with sufficient volume remaining. 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; this will be referred to as the Updated Week 24 Interim analysis to be used in support of the re-submission of BLA 125160-275.

Change #19

Section 5.2 Protocol deviations

Note that PK sample exclusion will be implemented due to certain protocol deviations; see Section 3.5. Study participants with at least one PK data exclusion are summarized and listed.

Was changed to:

Note that PK sample exclusion will be implemented due to certain protocol deviations; see Section 3.5. Study participants with at least one PK data exclusion from scheduled visits are summarized and listed.

Change #20

Section Demographics, the variable ERA Status (present, absent) and the following sentence was added:

Demographics information will be listed.

Change #21

Section 6.2 Other baseline characteristics, the following sentence was added:

Other baseline characteristics information will be listed.

Change #22

Section 6.3 Medical history and concomitant diseases, the following sentence was added:

Medical history, JIA history and a glossary of medical history conditions will be listed.

Change #23

Section 6.4 Prior and concomitant medications

All prior medications will be summarized by anatomical therapeutic chemical (ATC) classification level 3 (Pharmacological Subgroup) and WHO-DD generic name. In addition, past DMARDs will be summarized separately by ATC level 3 and WHO-DD generic name. These summaries will be provided for the SS for the Reduced CZP Dose, the Original CZP Dose and the Any CZP Dose.

Concomitant medications will be summarized for all medications, and separately for DMARDs, systemic corticosteroids, and intra-articular corticosteroid injections. DMARDs and corticosteroids will be identified through ATC codes and medical review. Concomitant medications will be summarized by ATC level 3 and WHO-DD generic name. All summaries of concomitant medications will be provided for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups.

Listings of all prior and concomitant medications will be provided.

Was changed to:

All prior medications will be summarized by anatomical therapeutic chemical (ATC) classification level 3 (Pharmacological Subgroup) and WHO-DD generic name. The number of DMARDs stopped prior to Baseline and not re-initiated during the study will be assessed and summarized. For those study participants with these stopped DMARDs, the WHO-DD generic name will be summarized. These summaries will be provided for the SS for the Reduced CZP Dose, the Original CZP Dose and the Any CZP Dose.

Concomitant medications will be summarized for all medications, and separately for DMARDs, systemic corticosteroids, and intra-articular corticosteroid injections. DMARDs and corticosteroids will be identified through ATC codes and medical review. Concomitant medications will be summarized by ATC level 3 and WHO-DD generic name. All summaries of concomitant medications will be provided for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups.

Listings of all prior and concomitant medications will be provided as well as a glossary of the concomitant medications.

Medications related to triamcinolone with the following WHO-DD generic names will be grouped and appear in summaries as "Triamcinolone" with the ATC3 level label of "UCB Triamcinolone ATC3": triamcinolone, triamcinolone acetonide, triamcinolone hexacetonide, triamcinolone acetate, triamcinolone diacetate, triamcinolone acetonide dipotassium phosphate.

Medications related to prednisone with the following WHO-DD generic names will be grouped and appear in summaries as "Prednisone" with the ATC3 level label of "UCB Prednisone ATC3": prednisone, prednisolone, prednisolone acetate, prednisolone sodium

phosphate, methylprednisolone, methylprednisolone acetate.

Medications related methotrexate with the following WHO-DD generic names will be grouped and appear in summaries as "Methotrexate" with the ATC3 level label of "UCB Methotrexate ATC3": methotrexate, methotrexate sodium.

Change #24

Section 6.5 Prohibited medications, the following sentence was added:

Prohibited medication usage will be listed.

Change #25

Section 6.6 Rescue medications

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

Was changed to:

The following medications are defined as rescue medication when initiated in the first 56 weeks of the study:

Change #26

Section 6.6 Rescue medications

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

Was changed to:

The following medications are defined as rescue medication when initiated at any time up to Week 56 during the study:

Change #27

Section 6.6 Rescue medications

Any joint injected with ia corticosteroids that does not satisfy the criteria for rescue medication (ie, isolated cases of ia corticosteroids) will be excluded from the efficacy analysis for a period of 3 months (91 days).

Was changed to:

Any joint injected with ia corticosteroids will be excluded from the efficacy analysis for a period of 3 months (91 days).

Change #28

Section 6.7 Short-acting medications was made a subsection containing the following unedited text:

Use of the following medications, which are not rescue medications, only results in efficacy data at the next scheduled visit being treated as missing/non-response:

- Higher than Baseline dose of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, including as needed (PRN) use within 72 hours

prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).

- Higher than Baseline dose of analgesics or opioids including PRN use within 48 hours prior to scheduled study visit (Note: No intake at baseline is considered equivalent to a baseline dose of 0).
- Any increase in dose of oral corticosteroids within 7 days prior to scheduled study visit (Note: The increase has to be higher than baseline).

All medication data resulting in efficacy data being treated as missing/non-response will be flagged in the concomitant medication listing.

Change #29

Section 6.8 Medical procedure history and concomitant medical procedures was added:

All medical procedures, in history or concomitant, will be presented in data listings. The historical procedures with no start date will be assigned to Reduced CZP dose (for those study participants who started the study taking Reduced CZP) or Original CZP dose (for those study participants who started the study taking Original CZP).

Change #30

Section 7 Measurements of treatment compliance

Treatment compliance is summarized for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose.

Was changed to:

Treatment compliance will be summarized and listed for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose for the final analysis; for the Updated week 24 Interim Analysis, treatment compliance will be summarized and listed for the SS for the Reduced CZP Dose and Original CZP Dose.

Change #31

Section 8 Pharmacokinetics and immunological procedures

Data from the ECLIA methods will constitute the study's main PK and ADAb evaluations.

Was changed to:

Data from the ECLIA methods, that are within the stability coverage of the assay, will constitute the study's main PK and ADAb evaluations; all reported ECLIA assay results will be listed.

Change #32

Section 8 Pharmacokinetics and immunological procedures

Box plots of the PK concentrations at Weeks 12 and 24 will be presented by CZP dose group for Baseline weight group, Baseline age group, ADAb participant status classification, ADAb titer classification, and concomitant MTX use in combination with Baseline weight group.

Concentrations below the limit of quantification of 32.0 ng/mL (0.032µg/mL) (BLQ) will be replaced by the LLOQ divided by 2 for the calculation of descriptive statistics.

Was changed to:

Concentrations below the limit of quantification of 320.0 ng/mL (0.32µg/mL) (BLQ) will be replaced by the LLOQ divided by 2 for the calculation of descriptive statistics.

Change #33

Section 8.1.1 ECLIA vs ELISA samples was added:

In line with [redacted] response, the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples initially analyzed with the ELISA method will be summarized.

First, the number and percentage of study participants with at least one PK sample re-analyzed using the ECLIA method (after previous analysis using the ELISA method) will be presented. For this percentage, the denominator is the number of study participants with at least one non-missing PK result from the ELISA method, and the numerator is the number of study participants with at least one non-missing PK result from the ECLIA method that had also been analyzed with the ELISA method previously. (Below LLOQ is considered a non-missing result.)

Second, the number and percentage of post-baseline PK samples that were re-analyzed using the ECLIA method (after previous analysis using the ELISA method) will be presented. For this percentage, the denominator is the number of post-baseline PK samples with non-missing ELISA results. The numerator is the number of post-baseline PK samples with non-missing ECLIA results where the same PK sample had previously been analyzed using the ELISA method. (Below LLOQ is considered a non-missing result.)

Additionally, the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples analyzed with the ECLIA method (either originally or via re-analysis) will be summarized.

First, the number and percentage of study participants with at least one PK sample re-analyzed using the ECLIA method (after previous analysis using the ELISA method) will be presented. For this percentage, the denominator is the number of study participants with at least one non-missing PK sample that was analyzed using the ECLIA method (either originally or via re-analysis). The numerator is the number of study participants with at least one non-missing PK result from the ECLIA method for a sample that had also been analyzed with the ELISA method previously. Also, the number and percentage of study participants that did not have any PK sample re-analyzed with the ECLIA method will be presented. The denominator is the same, but the numerator is the number of study participants for whom all non-missing PK results obtained using the ECLIA method were on samples that had never been analyzed using the ELISA method. (Below LLOQ is considered a non-missing result.)

Second, the number and percentage of post-baseline PK samples that were re-analyzed using the ECLIA method (after previous analysis using the ELISA method) will be presented. For this percentage, the denominator is the number of non-missing post-baseline PK results that

were obtained using the ECLIA method (either originally or via re-analysis). The numerator is the number of those non-missing post-baseline PK results that were obtained by re-analysis with the ECLIA method, after having also been analyzed by the ELISA method previously. Also, the number and percentage of those post-baseline samples that were not re-analyzed with the ECLIA method (out of those analyzed with ECLIA method) will be presented. The denominator is the same, but the numerator is the number of those non-missing post-baseline PK results for samples that were only ever analyzed using the ECLIA method. (Below LLOQ is considered a non-missing result.)

All summaries will be provided for the Safety Set and presented for Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose and Complete Reduced CZP Dose by baseline weight.

Change #34

Section 8.2.1 Partcipant ADAb classification

Study participants from the SS will be classified based on their pre and treatment ADAb status (Table 8–2). Classification will be done separately two ways: using the study participants' data for the entire study treatment period and using the study participants' data up to and including Week 24 (to facilitate comparison with adult RA data from study RA0138). Pre ADAb values are defined as the latest (not missing, not inconclusive and not anomalous) measurements up to and including the date of administration of first CZP treatment.

Table 13–7: ADAb status classification at participant level

1.	Pre ADAb negative and treatment-emergent ADAb negative	Study participants who were negative at Baseline and negative at all sampling points post treatment until the time point of interest (eg. Data up to/including Week 24, data for the entire treatment period) [Note: study participants with baseline samples missing and negative ADAb status at all sampling points post treatment are included in this category because participants who are pre ADAb positive are expected to have ADAb positive samples post-dosing]
2.	Pre ADAb negative and treatment-(emergent) induced ADAb positive	Study participants who were negative at Baseline and positive at any sampling point post treatment until the timepoint of interest (eg. Data up to/including Week 24, data for the entire treatment period). This group also included study participants who had a missing Baseline sample with 1 or more positive post treatment samples.
3.	Pre ADAb positive and treatment-emergent reduced ADAb	Study participants who were positive at Baseline, and negative at all sampling points post treatment until the timepoint of interest (eg. Data up to/including Week 24, data for the entire treatment period).

Table 13–7: ADAb status classification at participant level

4.	Pre ADAb positive and treatment-emergent unaffected ADAb positive	Study participants who were positive at Baseline and were positive at any sampling point post treatment with titer values of the same magnitude as Baseline (i.e., less than or equal to a predefined fold difference from the Baseline value of 2.10 which is defined with the validation of the assay).
5.	Pre ADAb positive and treatment-emergent ADAb boosted positive	Study participants who were positive at Baseline and were positive at any sampling point post treatment with increased titer values compared to Baseline (greater than a predefined fold difference increase of 2.10 from Baseline value which is defined within the validation of the assay).
6.	ADAb inconclusive	Study participants who were positive at Baseline and some post-treatment samples were missing or inconclusive, while other post-treatment samples were negative.
7.	Treatment emergent ADAb positive	Study participants that were classified as 2 or 5.
8.	Pre-treatment ADAb positive	Study participants who are positive ADAb at baseline, so those classified as 3, 4, 5 or 6.
9.	Missing	Study participants who were negative at Baseline or missing their Baseline assessment, were not positive at any post-Baseline visit, and have at least one missing/or inconclusive post-treatment scheduled assessment.
10	ADAb positive	Study participants who have a positive ADA sample status at any timepoint (either Baseline or post dose).

Was changed to:

Study participants from the SS will be classified based on their baseline and treatment-emergent ADAb status (Table 8–2). Classification will be done separately for two time periods of interest: (1) using the study participants' data for the entire study treatment period and (2) using the study participants' data up to and including Week 24 (to facilitate comparison with adult RA data from study RA0138). Baseline ADAb values are defined as the latest (not missing, not inconclusive) measurements up to and including the date of administration of first CZP treatment.

Table 13–8: ADAb status classification at participant level

1.	Baseline ADAb negative and treatment-emergent ADAb negative	Study participants who were negative at Baseline and negative at all sampling points post treatment until the time point of interest [Note: study participants with Baseline samples missing and negative ADAb status at all sampling points post treatment are included in this category because participants

Table 13–8: ADAb status classification at participant level

		who are pre ADAb positive are expected to have ADAb positive samples post-dosing]
2.	Baseline ADAb negative and treatment-(emergent) induced ADAb positive	Study participants who were negative at Baseline and positive at any sampling point post treatment until the timepoint of interest. This group also included study participants who had a missing Baseline sample with 1 or more positive post treatment samples.
3.	Baseline ADAb positive and treatment-emergent reduced ADAb	Study participants who were positive at Baseline and negative at all sampling points post treatment until the timepoint of interest.
4.	Baseline ADAb positive and treatment-emergent unaffected ADAb positive	Study participants who were positive at Baseline and were positive at any sampling point post treatment until the timepoint of interest with all titer values of the same magnitude as Baseline (i.e., less than or equal to a predefined fold increase from the Baseline value of 2.10 which is defined with the validation of the assay).
5.	Baseline ADAb positive and treatment-emergent ADAb boosted positive	Study participants who were positive at Baseline and were positive at any sampling point post treatment until the timepoint of interest with any increased titer values compared to Baseline (greater than a predefined fold increase of 2.10 from Baseline value which is defined within the validation of the assay).
6.	ADAb inconclusive	Study participants who were positive at Baseline and some post-treatment samples until the timepoint of interest were missing or inconclusive, while other post-treatment samples until the timepoint of interest were negative. [Note: study participants who were positive at Baseline and all post-treatment samples up to the timepoint of interest were missing or inconclusive are also included in this category.]
7.	Treatment emergent ADAb positive	Study participants that were classified as 2 or 5.
8.	Baseline treatment ADAb positive	Study participants who are positive ADAb at baseline, so those classified as 3, 4, 5 or 6.
9.	Missing	Study participants who were negative at Baseline or missing their Baseline assessment, were not positive at any post-Baseline visit, and have at least one missing/or inconclusive post-treatment scheduled assessment (until the timepoint of interest).
10	ADAb positive	Study participants who have a positive ADAb sample status at any timepoint (either Baseline or post dose).

Unscheduled visits including early discontinuation visits (ED) or Final visits with missing results are disregarded. Thus, study participants who had missing ADAb measurements at ED but were ADAb negative at all other post-treatment visits will be classified in category 1 above . Study participants who were negative at Baseline or missing their Baseline assessment and whose only post-treatment ADAb assessment was at ED and was missing will be classified in category 9 above. Study participants who were positive at Baseline and whose only post-treatment assessment was at ED and was missing will be classified in category 6 above. Only positive data at unscheduled visits will be used for classification.

Table 13–9: Aid to Programming ADAb participant status category

ADAb Participant Status Category	Post-Treatment ADAb Sample Status[a]		
Baseline ADAb Sample Status	**Any Positive**	**All Scheduled Negative**	**Some/ All Scheduled Missing[b]**
Missing	2	1	9
Negative	2	1	9
Positive	4 or 5[c]	3	6

[a] Unscheduled (including withdrawal visits) with missing data disregarded. Missing data at other (scheduled) visits considered.
[b] And no positive ADAb samples post-treatment (including positive in either scheduled or unscheduled).
[c] Highest ADAb titer used to determine category.

Post-treatment ADAb sample status categories are mutually exclusive and applied left to right. Thus study participants with both positive and missing post-treatment ADAb samples are considered in the "Any Positive" category.

Time point of interest is the entire treatment period including SFU and the treatment period up to Week 24.

Change #35

Section 8.2.2 ADAb Titer Classification

To further evaluate the impact of ADAb on PK, efficacy and safety, grouped ADAb titer categories will be defined based on ADAb quartiles (see Section 4.7) observed in the study. Quartiles will be calculated separately for the entire treatment period, and then for the period up to and including Week 24, using each study participant's highest post-treatment ADAb titer (ADAb negative participants will be deemed to have zero titer levels for calculation purposes).

If interpretation of the grouped titer summaries is inconclusive or results from other studies suggest other groupings, additional post-hoc analyses may be conducted to further investigate.

Immunogenicity will be assessed through summary tables and figures and listing of individual results by study participant on the SS. Summaries will be by CZP dose (Reduced

CZP Dose, Original CZP Dose) and each of Baseline weight group, Baseline age group, and concomitant MTX use, unless specified otherwise.

- All individual study participant-level ADAb results will be listed for all study participants. This will include the screening assay, confirmatory assay, and titer (if applicable). A separate listing showing CZP plasma concentrations, ADAb sample status classification, ADAb participant classification, ADAb titer, and ADAb titer classifications will be produced showing concentration and ADAb data in adjacent columns.
- Number and percentage of study participants with positive, negative, inconclusive or missing ADAb sample status (Table 8–1) will be summarized at each visit and overall and by dose (Original CZP dose, Reduced CZP Dose).
- The number and percentage of study participants in each of the ADAb participant status categories (overall and up to Week 24 as defined according to Table 8–2) will be summarized. Percentages for the denominator will include all the participants that have been classified as per Table 8–2, so including missing /inconclusive participants.

Prevalence and incidence:

- Prevalence of pre ADAb positivity: number and percentage of study participants that have Baseline positive ADAb sample status, with the denominator for percentages defined as all participants having an evaluable (not missing, not inconclusive and not anomalous) Baseline ADAb sample.

Incidence of treatment-emergent ADAb positivity: number and percentage of study participants with either treatment boosted ADAb or treatment induced ADAb, with the denominator for percentages all participants except those categorized as inconclusive or missing (overall for the entire treatment period and then up to and including Week 24).

Was changed to:

To further evaluate the impact of ADAb on PK, efficacy and safety, grouped ADAb titer categories will be defined based on ADAb quartiles (see Section 4.7) observed in the study. Quartiles will be calculated separately for the entire treatment period, and then for the period up to and including Week 24, using each study participant's highest post-treatment ADAb titer (ADAb negative participants will be deemed to have zero titer levels for calculation purposes). If all post-baseline scheduled visit results are Negative, then the study participant will be assigned to the lowest titer classification (lowest quartile); unscheduled visits with missing results are disregarded. If a study participant doesn't have any positive results at post-baseline scheduled visits and any of the results at scheduled visits are deemed missing or inconclusive, then the study participant will be assigned to "Missing".

If interpretation of the grouped titer summaries is inconclusive or results from other studies suggest other groupings, additional post-hoc analyses may be conducted to further investigate.

Immunogenicity will be assessed through summary tables and figures and listing of individual results by study participant on the SS. Summaries will be by CZP dose (Reduced

CZP Dose, Original CZP Dose) and each of Baseline weight group, Baseline age group, and concomitant MTX use, unless specified otherwise.

- All individual study participant-level ADAb results will be listed for all study participants. This will include the screening assay, confirmatory assay, and titer (if applicable). A separate listing showing CZP plasma concentrations, ADAb sample status classification, ADAb participant classification, ADAb titer, and ADAb titer classifications will be produced showing concentration and ADAb data in adjacent columns.
- Number and percentage of study participants with positive, negative, inconclusive or missing ADAb sample status (Table 8–1) will be summarized at each visit and overall and by dose (Original CZP dose, Reduced CZP Dose).
- The number and percentage of study participants in each of the ADAb participant status categories (overall and up to Week 24 as defined according to Table 8–2) will be summarized. Percentages for the denominator will include all the participants that have been classified as per Table 8–2, so including missing /inconclusive participants.

Prevalence and incidence:

- Prevalence of Baseline ADAb positivity: number and percentage of study participants that have Baseline positive ADAb sample status, with the denominator for percentages defined as all participants having an evaluable (not missing, not inconclusive) Baseline ADAb sample.

Incidence of treatment-emergent ADAb positivity: number and percentage of study participants with either treatment boosted ADAb or treatment induced ADAb, with the denominator for percentages all participants except those categorized as inconclusive or missing (overall for the entire treatment period and then up to and including Week 24).

Change #36

Section 8.2.3 Time to first occurrence of treatment-emergent ADAb positivity

Study participants will be considered to have an event at the first ADAb sampling time point with ADAb positive status if the participant is pre-ADAb negative or first ADAb sampling time point with fold difference increase from Baseline > 2.1 if participant is pre-ADAb positive. Study participants who are never treatment-emergent ADAb positive will be censored at the date of the last evaluable (not missing, not inconclusive and not anomalous) ADAb sample or on date of first CZP if no evaluable post-treatment ADAb samples. In case of pre-ADAb present in more than 10% of the study participants, the table will be produced separately for ADAb participant category 2 (induced) and 5 (boosted).

Was changed to:

Study participants will be considered to have an event at the first ADAb sampling time point with ADAb positive status in the entire treatment period if the participant is Baseline ADAb negative or first ADAb sampling time point with fold difference increase from Baseline > 2.1 if participant is Baseline ADAb positive. Study participants who are never treatment-emergent ADAb positive will be censored at the date of the last evaluable (not missing, not

inconclusive) ADAb sample or on date of first CZP if no evaluable post-treatment ADAb samples. In case of Baseline ADAb positivity present in more than 10% of the study participants, the table will be produced separately for ADAb participant category 2 (induced) and 5 (boosted).

Change #37

Section 8.2.4 ECLIA vs ELISA samples was added:

In line with [redacted] response, the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples initially analyzed with the ELISA method will be summarized.

First, the number and percentage of study participants with at least one ADAb sample re-analyzed using the ECLIA method (after previous analysis using the ELISA method) will be presented. For this percentage, the denominator is the number of study participants with at least one non-missing ADAb result from the ELISA method and the numerator is the number of study participants with at least one non-missing ADAb result from the ECLIA method that had also been analyzed with the ELISA method previously. (BLQ is considered a non-missing result.)

Second, the number and percentage of baseline and post-baseline ADAb samples that were re-analyzed using the ECLIA method (after previous analysis using the ELISA method) will be presented separately. For the percentage of baseline and post-baseline re-analyzed ADAb samples, the denominator is the number of baseline or post-baseline ADAb samples with non-missing ELISA results, respectively. The numerator is the number of baseline or post-baseline ADAb samples, respectively, with non-missing ECLIA results previously where the same ADAb sample had previously been analyzed with the ELISA method. (Below LLOQ is considered a non-missing result.)

Additionally, the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples analyzed with the ECLIA method (either originally or via re-analysis) will be summarized.

First, the number and percentage of study participants with at least one ADAb sample re-analyzed using the ECLIA method (after previous analysis using the ELISA method) will be presented. For this percentage, the denominator is the number of study participants with at least one non-missing ADAb sample that was analyzed using the ECLIA method (either originally or via re-analyses). The numerator is the number of study participants with at least one non-missing ADAb result from the ECLIA method for a sample that had also been analyzed with the ELISA method previously. Also, the number and percentage of study participants that did not have any ADAb sample re-analyzed with the ECLIA method will be presented. The denominator is the same, but the numerator is the number of study participants for whom all non-missing ADAb results obtained using the ECLIA method were on samples that had never been analyzed using the ELISA method. (Below LLOQ is considered a non-missing result.)

Second, the number and percentage of baseline and post-baseline ADAb samples that were analyzed using the ECLIA method (after previous analysis using the ELISA method) will be

presented. For this percentage, the denominator is the number of non-missing baseline or post-baseline ADAb results, respectively, that were obtained using the ECLIA method (either originally or via re-analysis). The numerator is the number of those non-missing baseline or post-baseline ADAb results, respectively, that were obtained by re-analysis with the ECLIA method, after having been analyzed by the ELISA method previously. Also, the number and percentage of those baseline or post-baseline samples, respectively, that were not re-analyzed with the ECLIA method (out of those analyzed with the ECLIA method) will be presented. The denominator is the same for each, respectively, but the numerator is the number of those non-missing baseline or post-baseline ADAb results, respectively, for samples that were only ever analyzed using the ECLIA method. (Below LLOQ is considered a non-missing result.)

All summaries will be provided for the Safety Set and presented for Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose and Complete Reduced CZP Dose by baseline weight.

Change #38

Section 8.3 CZP plasma concentrations, anti-CZP antibody titers, and PedACR response

The plots described in this section will be generated on the FAS. Individual participants plots displaying CZP plasma concentrations, ADAb titers, JADAS-71 score and maximum PedACR response (the highest PedACR response at a given visit) will be produced by visit on the same plot. At each time point, the JADAS-71 score and maximum PedACR response at that visit will be plotted on a linear scale. CZP plasma concentration will be plotted on a (natural) log scale and ADAb titer will be plotted on a log 2 scale. CZP dosing and ADAb inconclusive values will be flagged in this plot. A vertical line will be plotted when dose was changed for the participant. For each study participant, the category of ADAb participant status and demographic information at baseline (body weight and age) will be displayed.

Multi-panel spaghetti plots of individual participant (natural) log CZP plasma concentration by visit will be produced separately for each CZP dose (Original CZP dose, Reduced CZP dose) and ADAb titer classification and ADAb participant classification. Concomitant MTX use will be shown in different line colors and CZP concentrations for which ADAb positive samples were positive will be plotted with a red dot. These individual plots will be repeated replacing CZP plasma concentration with maximum PedACR response (linear scale).

Scatter plots of the plasma CZP concentration at each visit with different colors/symbols depending on ADAb participant classification and ADAb titer classification will be produced separately for the doses (Original CZP Dose, Reduced CZP Dose).

Was changed to:

The plots described in this section that include an efficacy endpoint will be generated on the FAS, otherwise on the PK-PPS. Individual participants plots displaying CZP plasma concentrations, ADAb titers, and maximum PedACR response (the highest PedACR response at a given visit) will be produced by visit on the same plot. At each time point, the maximum PedACR response at that visit will be plotted on a linear scale. CZP plasma concentration will be plotted on a (natural) log scale and ADAb titer will be plotted on a log 2 scale. CZP dosing and ADAb inconclusive values will be flagged in this plot. A vertical line will be plotted when dose was changed for the study participant. For each study participant, the

category of ADAb participant status and demographic information at baseline (body weight and age) will be displayed.

Multi-panel spaghetti plots of individual participant (natural) log CZP plasma concentration by visit will be produced separately for each CZP dose (Original CZP dose, Reduced CZP dose) and ADAb titer classification and ADAb participant classification for the PK-PPS. Concomitant MTX use will be shown in different line colors and CZP concentrations for which ADAb positive samples were positive will be plotted with a red dot. These individual plots will be repeated replacing CZP plasma concentration with maximum PedACR response (linear scale) on the FAS.

Scatter plots of the plasma CZP concentration at each visit with different colors/symbols depending on ADAb participant classification and ADAb titer classification will be produced separately for the doses (Original CZP Dose, Reduced CZP Dose) for the PK-PPS.

Change #39

The section name for Section 8.4 PopPK and PK-PD analyses

Was changed to:

Section 8.4 PopPK analyses

Change #40

Section 9.1 Extent of exposure

The extent of exposure to study drug will be evaluated by summarizing the total amount of CZP received in mg and the total duration of exposure in days. Total duration of exposure will be calculated as the date of last dose of study medication – date of first dose of study medication + 14 days if administration of CZP is Q2W, +28 days if administration of CZP is Q4W.

Subject time at risk will also be calculated. Subject time at risk represents the time a subject is at risk for having an AE. Subject time (in days) at risk will generally be calculated as (date of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). However, the calculation of subject time at risk will be modified for study participants who change from Original CZP Dose to Reduced CZP Dose, or who dose escalate from Reduced CZP Dose to the Original CZP Dose. For the period of exposure prior to a dose change, subject time at risk ends on the date of dose change (ie, do not add 70 days). For the period of exposure on the final CZP dose for a study participant, time at risk should include the additional 70 days. Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Duration of exposure and subject time at risk will be calculated as appropriate for each of the following CZP dose groups:

- Reduced CZP Dose: includes period of exposure to the Reduced CZP Dose for all study participants enrolled on the Reduced CZP Dose; the exposure ends on the date of dose escalation or last dose of Reduced CZP Dose. The exposure calculation is Date of Dose Escalation or Last Dose of Reduced CZP – Date of First Dose + 14 or 28 days depending on administration of CZP.

- Original CZP Dose: includes period of exposure to the Original CZP Dose for all study participants enrolled on the Original CZP Dose; the exposure ends on the date of dose reduction or Last Dose of Original CZP. The exposure calculation is Date of Dose Reduction or Last Dose of Original CZP – Date of First Dose of CZP +14 or 28 days depending on administration of CZP.
- Any CZP Dose: includes the exposure to all CZP doses for all treated study participants; the exposure period is calculated using the formulas above depending on whether the subject took a Q2W or Q4W dose.

Study drug exposure will be summarized for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. Exposure will be presented as follows: >0 months, ≥6 months, ≥12 months, ≥24 months, ≥36 months, ≥48 months and ≥60 months.

Was changed to:

Over the course of the RA0043 study, study participants follow one of 5 dosing scenarios for CZP exposure:

Table 13–10: Dosing periods

Starting the study taking:	1st dosing period (of variable length)	2nd dosing period (of variable length)	3rd dosing period (of variable length)
Reduced CZP dose	Reduced CZP (A)		
	Reduced CZP (B) ->	Original CZP (E)	
Original CZP dose	Original CZP (F)		
	Original CZP (G) ->	Reduced CZP (C)	
	Original CZP (H) ->	Reduced CZP (D) - >	Original CZP (J)

The extent of exposure to study drug will be evaluated by summarizing the total amount of CZP received in mg and the total duration of exposure in days. Total duration of exposure will be calculated using this general formula as: the Date of Last Dose of study medication – Date of First Dose of study medication + 14 days if administration of CZP is Q2W, +28 days if administration of CZP is Q4W.

Duration of exposure will be calculated as appropriate for each of the following dosing periods:

A: use the general formula;

B: Date of Escalation – Date of First Dose;

C: Date of Last Dose – Date of Dose Reduction +14 or 28 days depending on administration of CZP;

D: Date of Escalation – Date of Reduction;

E: Date of Last Dose – Date of Dose Escalation + 14 or 28 days depending on administration of CZP;

F: use the general formula;

G: Date of Dose Reduction – Date of First Dose;

H: Date of Dose Reduction – Date of First Dose;

J: Date of Last Dose – Date of Dose Escalation + 14 or 28 days depending on administration of CZP

Duration of exposure will be calculated as appropriate for each of the following CZP Dose groups:

- Any CZP Dose: includes the exposure to all CZP doses for all treated study participants; the exposure period is calculated using the general formula.
- Reduced CZP Dose: includes period of exposure to the Reduced CZP Dose for all study participants enrolled on the Reduced CZP dose; use the following formulas:
  - Period A - for study participants without dose escalation; and
  - Period B - for study participants with dose escalation.
- Original CZP Dose: includes period of exposure to the Original CZP Dose for all study participants enrolled on the Original CZP Dose; use the following formulas:
  - Period F - for study participants without dose reduction;
  - Period G - for study participants with dose reduction and without dose escalation; and
  - Period H - for study participants with dose reduction and dose escalation.
- Complete Reduced CZP Dose: includes all periods of exposure to Reduced CZP Dose for all study participants (periods A, B, C and D); use the following formulas:
  - Period A - for study participants enrolled on Reduced CZP Dose without dose escalation;
  - Period B - for study participants enrolled on Reduced CZP Dose with dose escalation;
  - Period C - for study participants enrolled on Original CZP Dose with dose reduction and without dose escalation; and
  - Period D - for study participants enrolled on Original CZP Dose with dose reduction and dose escalation.
- Complete Original CZP Dose: includes all periods of exposure to Original CZP dose for all study participants (periods E, F, G H and J); use the following formulas:
  - Period E - for study participants enrolled on Reduced CZP Dose with dose escalation;
  - Period F - for study participants enrolled on Original CZP Dose without dose reduction;
  - Period G - for study participants enrolled on Original CZP Dose with dose reduction and without dose escalation; and

- Period H+J - for study participants enrolled on Original CZP Dose with dose reduction and dose escalation.

13.5.1 Subject time at risk

Subject time at risk will also be calculated. Subject time at risk represents the time a study participant is at risk for having an AE. Subject time (in days) at risk will generally be calculated using this general formula: (date of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). However, the calculation of subject time at risk will be modified for study participants who change from Original CZP Dose to Reduced CZP Dose, or who dose escalate from Reduced CZP Dose to the Original CZP Dose. For the period of exposure prior to a dose change, subject time at risk ends on the date of dose change (ie, do not add 70 days). For the period of exposure on the final CZP dose for a study participant, time at risk should include the additional 70 days. Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Subject time at risk will be calculated as appropriate for each of the following CZP dosing periods:

A: use the general formula;

B: Date of Escalation – Date of First Dose;

C: Date of Last Dose – Date of Dose Reduction +70 days;

D: Date of Escalation – Date of Reduction;

E: Date of Last Dose – Date of Dose Escalation + 70 days;

F: use the general formula;

G: Date of Dose Reduction – Date of First Dose;

H: Date of Dose Reduction – Date of First Dose;

J: Date of Last Dose – Date of Dose Escalation + 70 days;

Subject time at risk will be calculated as appropriate for each of the following CZP Dose groups;

- Any CZP Dose: includes the time at risk to all CZP doses for all treated study participants; the time at risk is calculated using the general formula.
- Reduced CZP Dose: includes time at risk during the exposure to the Reduced CZP Dose for all study participants enrolled on the Reduced CZP dose up to the first dose change; use the following formulas:
  - Period A - for study participants without dose escalation; and
  - Period B - for study participants with dose escalation.
- Original CZP Dose: includes time at risk during the exposure to the Original CZP Dose for all study participants enrolled on the Original CZP Dose up to the first dose change; use the following formulas:
  - Period F - for study participants without dose reduction;

  - Period G - for study participants with dose reduction and without dose escalation; and
  - Period H - for study participants with dose reduction and dose escalation.
- Complete Reduced CZP Dose: includes time at risk during all periods of exposure to Reduced CZP Dose for all study participants (periods A, B, C and D); use the following formulas:
  - Period A - for study participants enrolled on Reduced CZP Dose without dose escalation;
  - Period B - for study participants enrolled on Reduced CZP Dose with dose escalation;
  - Period C - for study participants enrolled on Original CZP Dose with dose reduction and without dose escalation; and
  - Period D - for study participants enrolled on Original CZP Dose with dose reduction and dose escalation.
- Complete Original CZP Dose: includes all time at risk during all periods of exposure to Original CZP dose for all study participants (periods E, F, G H and J); use the following formulas:
  - Period E - for study participants enrolled on Reduced CZP Dose with dose escalation;
  - Period F - for study participants enrolled on Original CZP Dose without dose reduction;
  - Period G - for study participants enrolled on Original CZP Dose with dose reduction and without dose escalation; and
  - Period H+J - for study participants enrolled on Original CZP Dose with dose reduction and dose escalation.

The extent of study drug exposure will be summarized for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. Exposure over time will be presented as follows: >0 months, ≥6 months, ≥12 months, ≥24 months, ≥36 months, ≥48 months, ≥60 months, ≥72months, ≥84 months, and ≥96 months. In line with [redacted] response, the extent of study drug exposure as well as exposure over time will be presented by Complete Original CZP Dose and Complete Reduced CZP Dose.

Study medication administration will be listed.

Change #41

Section 9.2 Adverse events

All AEs will be classified by SOC, HLT and PT according to the version of MedDRA® that is current to the sponsor at the time of data capture. A glossary for the TEAE listing will detail the verbatim terms that are coded to each SOC, HLT, and PT.

Treatment-related TEAEs are those with relationship to study medication of "Related" or "Possibly related" or those with a missing relationship. Severe TEAEs are those with an intensity of "Severe" or those with a missing intensity.

All TEAE summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. TEAEs occurring on the day of dose reduction or dose escalation, respectively, will be reviewed by the study physician in order to assign events to the most appropriate time period (before or after dose reduction or dose escalation, respectively).

Was changed to:

A glossary for the TEAE listing will detail the verbatim terms that are coded to each SOC, HLT, and PT.

Treatment-related TEAEs are those with relationship to study medication of "Related" or "Possibly related" or those with a missing relationship. Severe TEAEs are those with an intensity of "Severe" or those with a missing intensity.

All TEAE summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose groups. TEAEs occurring on the day of dose reduction or dose escalation, respectively, will be summarized in the dose groups that it appears.

Change #42

Section 9.2 Adverse events, the following sentence was added:

In line with [redacted] response, incidence tables of TEAEs will be presented by primary SOC, PT, overall and Baseline weight group by Original CZP, Reduced CZP, Any CZP, Complete Original CZP and Complete Reduced CZP doses.

Change #43

Section 9.2.1 Adverse events

2) Malignancies, including lymphoma. These will be presented in 2 tables using the criteria SMQ = "Malignant or unspecified tumours" and SMQ="Malignant tumours", respectively.

Was changed to:

2) Malignancies, including lymphoma. These will be presented in 2 tables using the criteria SMQ = "Malignant or unspecified tumours" and its subset, SMQ="Malignant tumours", respectively.

Change #44

Section 9.2.3 Covid vaccine sensitivity analysis

The list of TEAEs to be excluded if reported with Mild or Moderate intensity are:

Was changed to:

The list of the PTs of these TEAEs to be excluded if reported with Mild or Moderate intensity are:

Change #45

Section 9.3 Clinical laboratory evaluations

All laboratory summaries described in this section will be provided for Reduced CZP Dose, Original CZP Dose, and Any CZP Dose) and by Baseline weight group.

Descriptive statistics for observed values and change from Baseline will be presented for each visit for the following hematology and biochemistry parameters:

- Hematology: RBC, hemoglobin, hematocrit, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
- Biochemistry: sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphorus, creatinine kinase, glucose, creatinine, uric acid, urea, total protein, albumin, ALP, gamma glutamyl transferase (γ-GT), AST, ALT, lactate dehydrogenase, bilirubin, and total cholesterol.

The following urinalysis parameters will be tested locally only: pH, protein, glucose, and blood. If abnormalities are found from the dipstick test, microscopy (WBC, RBC, casts, crystals, and bacteria) will be performed, and these results will be listed. A summary of the shift from Baseline to end of treatment will also be provided for hematology and biochemistry parameters. Results will be classified as low, normal, or high based on the normal ranges provided by the central laboratory.

A summary of the incidence of markedly abnormal laboratory results by visit will be presented for hematology and biochemistry parameters. Details of markedly abnormal values will be listed by subject and parameter for hematology and biochemistry variables for which there is at least 1 markedly abnormal result recorded. Definitions of markedly abnormal values are adopted from the UCB Central Nervous System Clinical and Laboratory Possibly Clinically Significant Treatment Emergent Criteria and are given below Table 9–3 for markedly abnormal hematology values and Table 9–4 for markedly abnormal biochemistry values).

Was changed to:

All laboratory summaries described in this section will be provided for Reduced CZP Dose, Original CZP Dose, and Any CZP Dose and by Baseline weight group. All laboratory data will be listed.

Descriptive statistics for observed values and change from Baseline will be presented for each visit for the following hematology and biochemistry parameters:

- Hematology: RBC, hemoglobin, hematocrit, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
- Biochemistry: sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphorus, creatinine kinase, glucose, creatinine, uric acid, urea, total protein, albumin, ALP, gamma glutamyl transferase (GGT), AST, ALT, lactate dehydrogenase, bilirubin, and total cholesterol.

The following urinalysis parameters will be tested locally only: pH, protein, glucose, and blood. If abnormalities are found from the dipstick test, microscopic analysis (WBC, RBC, casts, crystals, and bacteria) will be performed, and these results will be listed. A summary of

the shift from Baseline to end of treatment will also be provided for hematology and biochemistry parameters. Results will be classified as low, normal, or high based on the normal ranges provided by the central laboratory.

A summary of the incidence of markedly abnormal laboratory results by visit will be presented for hematology and biochemistry parameters. Details of markedly abnormal values will be listed by study participant and parameter for hematology and biochemistry variables for which there is at least 1 markedly abnormal result recorded. Definitions of markedly abnormal values are adopted from the UCB Therapeutic Area: Central Nervous System : Clinical and Laboratory Markedly Abnormal (MA) Values and are given below Table 9–3 for markedly abnormal hematology values and Table 9–4 for markedly abnormal biochemistry values).

Change #46

Section 9.3 Clinical laboratory evaluations, the following sentence was added:

Any data that is captured as being a suspected hepatic event will be listed.

Change #47

Section 9.4.1 Vital signs

A summary of the incidence of markedly abnormal vital signs results by visit will be presented for temperature, blood pressure, and pulse rate parameters. Details of markedly abnormal values will be listed by subject and parameter for which there is at least 1 markedly abnormal result recorded. Definitions of markedly abnormal values are given below in Table 9–5.

Markedly abnormal high temperature is >40.0 degrees Celsius (>104.0 degrees Fahrenheit) while a markedly abnormal low temperature is 32 – 35 degrees Celsius (89.6 – 95 degrees Fahrenheit).

Was changed to:

A summary of the incidence of markedly abnormal vital signs results by post-baseline scheduled visit will be presented for temperature, blood pressure, and pulse rate parameters. Details of markedly abnormal values will be listed by study participant and parameter for which there is at least 1 markedly abnormal result recorded. Definitions of markedly abnormal values are given below in Table 9–5.

Markedly abnormal high temperature is >40.0 degrees Celsius (>104.0 degrees Fahrenheit) while a markedly abnormal low temperature is 32 – 35 degrees Celsius (89.6 – 95 degrees Fahrenheit). Vital signs data will be listed, including the flagging of markedly abnormal values.

Change #48

Section 9.4.2.2 Tanner stages

A summary of shift table of Tanner stages from baseline to relevant post-treatment visit(s) (eg., 48 week) by age and gender will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose.

Was changed to:

A summary of shift table of Tanner stages from baseline to relevant post-treatment visit(s) (48 week, 96 week, etc) by age and gender will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose.

Change #49

Section 9.4.2.5 Autoantibodies

Autoantibodies (ANA and anti-dsDNA) will be assessed at Baseline, Weeks 16 and 48, and Early Discontinuation/EOT. For ANA antibodies, normal corresponds to dilutions of <1:160 and antibodies present corresponds to dilutions of 1:160 or higher. A summary of the cumulative shift from the Baseline through the Early Discontinuation/EOT Visit will be summarized for both the ANA and anti-dsDNA antibodies.

All autoantibodies summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose) and by Baseline weight group.

Was changed to:

Autoantibodies (ANA and anti-dsDNA) will be assessed at Baseline, Weeks 16 and 48, and Early Discontinuation/EOT. For ANA antibodies, normal corresponds to dilutions of <1:160 and antibodies present corresponds to dilutions of 1:160 or higher. A summary of the maximum shift from the Baseline to anytime while on CZP treatment will be summarized for both the ANA and anti-dsDNA antibodies.

All autoantibodies summaries will be provided for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose) and by Baseline weight group. All autoantibody assay data will be listed.

Change #50

Section 10 Efficacy analyses

For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and ADAb status will be presented pooling across all weight groups unless otherwise specified.

Was changed to:

For subgroup efficacy analyses, summaries by Baseline age group, concomitant MTX use, and ADAb titer classification will be presented pooling across all weight groups unless otherwise specified.

Change #51

Section 10.3.13.2 Final Analysis

Descriptive statistics of the observed values and change from Baseline will be presented separately for the acute and standard versions for each of the specified visits.

Was changed to:

Descriptive statistics of the observed values and change from Baseline will be presented separately for the acute and standard versions (See Protocol Amendment 9, Section 11.13) for each of the specified visits.

Change #52

Section 12.1 Comparisons with RA0138 data

Comparisons between RA0043 and RA0138 data will focus on common timepoints (Weeks 12 and 24).

Separate boxplots will be performed for Week 12 and Week 24 showing plasma CZP concentrations for the two CZP dose groups (Original or Reduced) for RA0043 and the single CZP dose group for RA0138 in the same plot. The plots will be repeated separately by Baseline weight group, Baseline age group and concomitant MTX use.

Was changed to:

Comparisons between RA0043 and RA0138 data will focus on common timepoints (Weeks 12 and 24). The dose groups that will be compared are the Original CZP Dose and the Reduced CZP Dose from RA0043 (Section 3.1) and the 200 mg Q2W maintenance dose from RA0138.

Separate boxplots will be performed for Week 12 and Week 24 showing plasma CZP concentrations for the two CZP dose groups (Original CZP Dose or Reduced CZP Dose) for RA0043 and the single CZP dose group for RA0138 in the same plot. Box plots of the PK concentrations at Weeks 12 and 24 will be presented by CZP dose group for Baseline weight group, Baseline age group, ADAb participant status classification, ADAb titer classification, and concomitant MTX use in combination with Baseline weight group. In the box plots the 5th and 95th percentiles of the concentrations distribution will be shown.

13.6 AMENDMENT 6

Rationale for the amendment

The primary reasons for this SAP amendment was to:

- pJIA was changed to pcJIA throughout the SAP,
- Update clarifications as to which analyses were done for the Updated Week 24 Interim Analysis vs the Final Analysis,
- In demographics, add a summary by country of enrollment,
- Clarify the algorithm for calculating treatment compliance (adjusting calculation for when study participants are in clinical remission),
- Clarify how data will be treated when study participants have large gaps in study medication dosing (eg TEAEs, time at risk),
- Clarify the algorithm for flagging important and non-important protocol deviations when study participants are off study medication,

- Clarify that only data for n≥20 study participants for the Any CZP Dose group will be shown in by visit (week) summaries for all three dose groups
- Add a new AE table, AE listings and an additional laboratory test listing, and
- Update as to which questions from the Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey will be summarized in tables,

Modifications and changes

Global changes

pJIA was changed to pcJIA thoughout the SAP. Analyses that were completed for the Updated Week 24 Interim Analysis were indicated when they would not be repeated for the final analysis.

Specific changes

Change #1

SAP/Amendment	Date
Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016
SAP Amendment 3	30 Jun 2021
SAP Amendment 4	8 Dec 2022
SAP Amendment 5	21 Jun 2023

Has been changed to:

SAP/Amendment	Date
Final SAP	23 Jun 2015
SAP Amendment 1	29 Sep 2015
SAP Amendment 2	24 Jun 2016
SAP Amendment 3	30 Jun 2021
SAP Amendment 4	8 Dec 2022
SAP Amendment 5	21 Jun 2023
SAP Amendment 6	23 May 2024

Change #2

CRM	clinical remission on medication

was changed to:

CRM	derived clinical remission (previously referred to as clinical remission on medication)

Change #3

Section 1 Introduction

This document describes the planned analyses and summary tables, figures, and listings to be included in the final clinical study report (CSR) for RA0043 as well as for the Updated Week 24 interim analysis and other analyses supporting marketing applications. Note that the Week 16 interim analysis and the 2016 Week 24 interim analyses were completed as specified in SAP Amendment 1 and text about these analyses will be kept as is.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this statistical analysis plan (SAP) will be amended accordingly. If, after the final database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP, but they will be identified in the CSR. Any deviations from this SAP will be documented in the CSR.

Was changed to:

This document describes the planned analyses and summary tables, figures, and listings to be included in the final clinical study report (CSR) for RA0043 as well as for the Updated Week 24 Interim Analysis and other analyses supporting marketing applications; specific analyses added just for the Updated Week 24 Interim Analysis have been updated to say that they were only generated for that analysis Note that the Week 16 interim analysis and the 2016 Week 24 interim analyses were completed as specified in SAP Amendment 1 and text about these analyses will be kept as is.

If, after the final database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP, but they will be identified in the CSR. Any deviations from this SAP will be documented in the CSR.

Change #4

Section 2 Protocol Summary

- Reduced CZP Dose – includes all data for study participants enrolled on Reduced CZP Dose prior to the first change in dosage
- Complete Original CZP Dose – includes all data for study participants who took Original CZP Dose prior to the first change in dosage as well as the data from when study participants increased their dosage to Original CZP after taking Reduced CZP Dose

Was changed to:

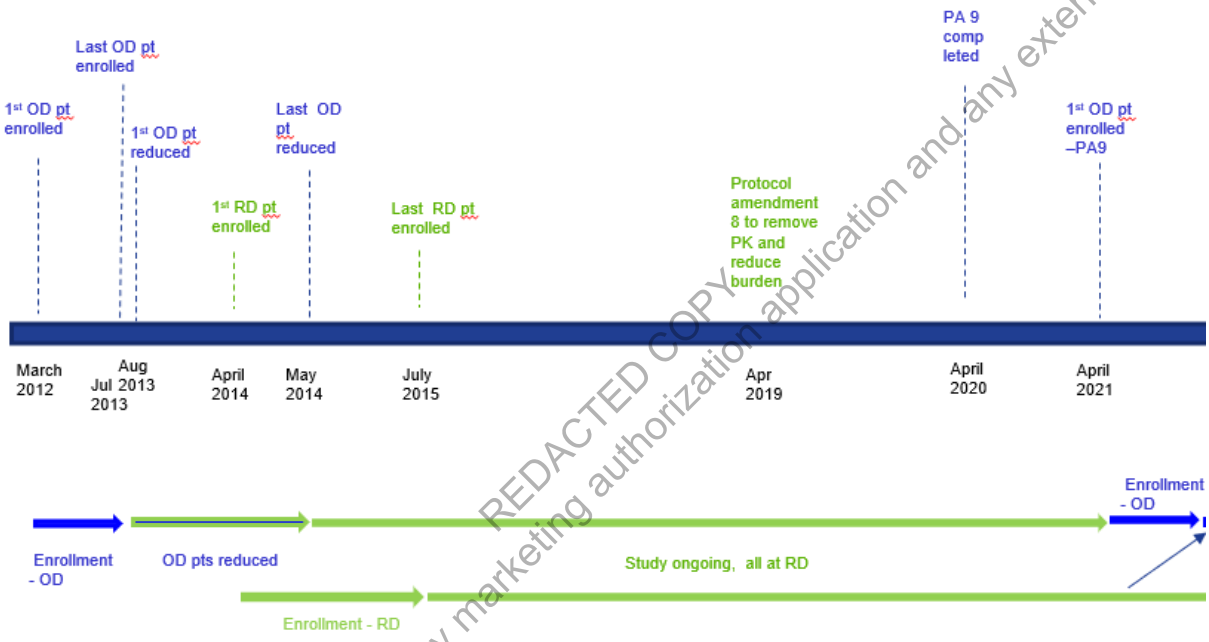
- Reduced CZP Dose – includes all data for study participants enrolled on Reduced CZP Dose prior to the first change in dosage

For the Updated Week 24 Interim Analysis only, study participants were also summarized by the following 2 dose groups:

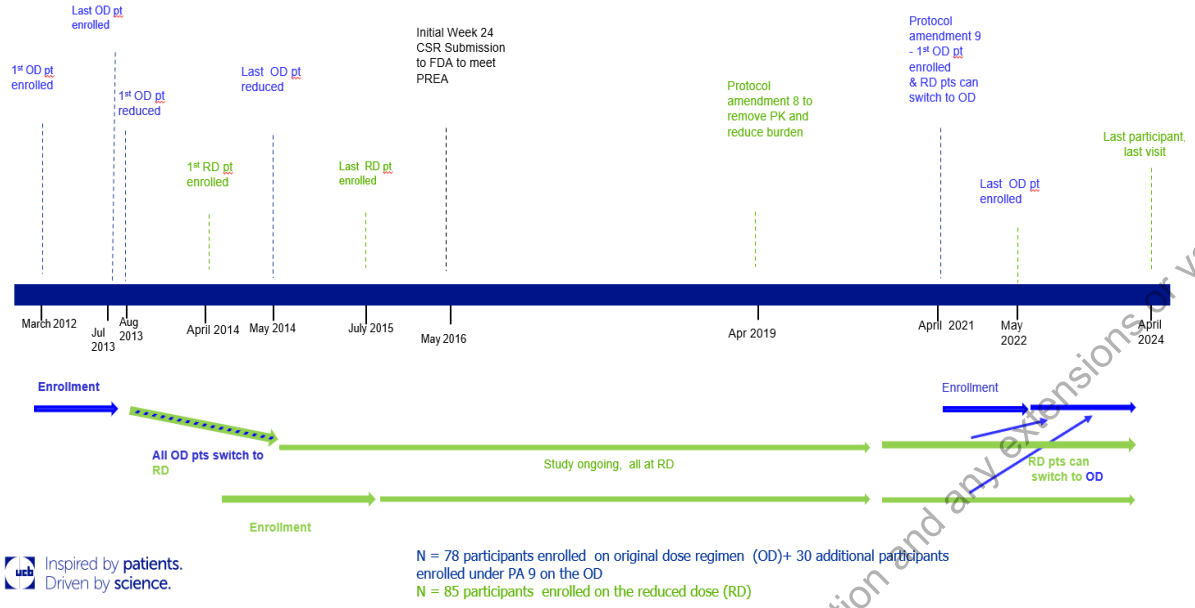
- Complete Original CZP Dose – includes all data for study participants who took Original CZP Dose prior to the first change in dosage as well as the data from when study participants increased their dosage to Original CZP after taking Reduced CZP Dose

Change #5

Section 2, Protocol Summary



Was changed to:



Change #6

Section 2.2.3.4 Additional other variables

Additional variables that were covered under other variables that will be specifically analyzed and intended to be used for comparison purposes to support the regulatory submission include:

Was changed to:

Additional variables that were covered under other variables that were specifically analyzed in the Updated Week 24 Interim Analysis only and were used for comparison purposes to support the regulatory submission include:

Change #7

Section 2.3 Study design and conduct

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 pJIA 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.

Was changed to:

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 pcJIA in the study participant's country or region

or closing the study by UCB. A Final Visit will be conducted 12 weeks after last dose of study medication.

Change #8

Table 2-3: Dosing administration of CZP: the following footnote was added to the table:

[b]Note that for Reduced Dose, 10 to <20kg study participants, maintenance dosing started at Week 8.

Change #9

Section 2.3 Study design and conduct

A validated ECLIA method that meets the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics will be used for any new analyses, including re-analysis of archived samples collected before Protocol Amendment 9 and for the analysis of bio-samples collected from the additional 30 study participants after Protocol Amendment 9.

Was changed to:

A validated ECLIA method that meets the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics was introduced after Protocol Amendment 9, it has been used for all new analyses, including re-analysis of archived samples collected before Protocol Amendment 9 and for the analysis of bio-samples collected from the additional 30 study participants after Protocol Amendment 9.

Change #10

Section 2.3 Study design and conduct

Therefore, in order to adequately assess the exposure levels and clinical experience of CZP in pJIA at both the Reduced and Original CZP Doses and support the safety for the Original CZP Dose, 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 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 ADAb 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.

Full interim analyses were performed in 2016 after all active study participants completed the Week 24 (Visit 10) assessments. Week 24 full interim analyses were completed as described in SAP Amendment 1. SAP Amendment 4 comprises the analyses to be completed for an Updated Week 24 (Visit 10) interim analysis including the 30 new study participants enrolled after Protocol Amendment 9, any interim analyses to support marketing applications and the final analysis of the study.

Was changed to:

Therefore, in order to adequately assess the exposure levels and clinical experience of CZP in pcJIA at both the Reduced and Original CZP Doses and support the safety for the Original CZP Dose, as more of the safety data collected in the study prior to Amendment 9 were on the reduced dose, 30 additional study participants have been enrolled on the Original CZP Dose 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 ADAb 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 PK analysis, and was the basis for the modeling and simulation work that supported the interim PK analysis in 2023 and the 2024 submission.

Full interim analyses were performed in 2016 after all active study participants completed the Week 24 (Visit 10) assessments. Week 24 full interim analyses were completed as described in SAP Amendment 1. An Updated Week 24 (Visit 10) interim analysis, including the 30 new study participants enrolled after Protocol Amendment 9, was completed as described in SAP Amendments 4, 5, and 6. The final analysis will be completed as described in SAP Amendment 6.

Change #11

Section 2.4 Determination of sample size

Available ECLIA-based data from all study participants will be included in the final PopPK analysis as described in a separate Data Analysis Plan and reported separately, and therefore should allow CL/F and V/F to be determined with sufficient precision.

Was changed to:

Available ECLIA-based data from all study participants were included in the final PopPK analysis as described in a separate Data Analysis Plan and reported separately for the Updated Week 24 Interim Analysis only.

Change #12

Section 2.5 Study RA0138

RA0138 is an open-label study in 33 adult study participants with RA who took 400mg loading dose (Weeks 0, 2, and 4), followed by 200mg CZP Q2W. This study was conducted to generate PK and ADAb data using the same ECLIA assay as used in RA0043 to form the basis of "PK-matching" for CZP approval. The PK and ADAb data from RA0138 will be analyzed and displayed in the same manner as data from RA0043 so that comparisons and conclusions can be made. Those details will be presented in the Appendix, Section 12.1.

Was changed to:

RA0138 is an open-label study in 33 adult study participants with RA who took 400mg loading dose (Weeks 0, 2, and 4), followed by 200mg CZP Q2W. This study was conducted to generate PK and ADAb data using the same ECLIA assay as used in RA0043 to form the basis of "PK-matching" for CZP approval. For Updated Week 24 Interim Analysis, the PK

and ADAb data from RA0138 was analyzed and displayed in the same manner as data from RA0043; comparisons and conclusions were made. Those details are presented in the Appendix, Section 12.1.

Change #13

Section 3.1 General presentation of summaries and analyses

Generally, data will be summarized by the Original CZP Dose, Reduced CZP Dose, and Any CZP Dose groups. For PK and ADAb analyses, data will be summarized by Original CZP Dose and Reduced CZP Dose only.

Following recommendations received from [redacted], a few data summaries will be organized by "Complete" CZP dose groups defined below, which will allow assessment of exposure and safety for all time that study participants were receiving the specified dose regardless of dose switching:

- Complete Original CZP Dose: includes all study participants who began treatment in accordance with the Original CZP Dose, as well as study participants who began treatment in accordance with the Reduced CZP Dose and then later dose escalated to the Original CZP Dose.

  Only data obtained while the study participant was receiving the Original CZP Dose will be included in summaries of the Complete Original CZP Dose. For study participants who began treatment with the Original CZP Dose, this includes time on the Original CZP Dose prior to first change in dosage, as well as time after returning to Original CZP Dose after a previous dose reduction. For study participants who began treatment with the Reduced CZP Dose, this includes only time after dose escalation to the Original CZP Dose.

- Complete Reduced CZP Dose: includes all study participants who began treatment in accordance with the Reduced CZP Dose, as well as study participants who began treatment in accordance with the Original CZP Dose and later dose reduced to the Reduced CZP Dose.

  Only data obtained while the study participant was receiving the Reduced CZP Dose will be included in summaries of the Complete Reduced CZP Dose. For study participants who began treatment with the Reduced CZP Dose, this includes time on the Reduced CZP Dose prior to first change in dosage. For study participants who began treatment with the Original CZP Dose, this includes only time after dose reduction to the Reduced CZP Dose, and prior to any potential later dose escalation back to the Original CZP Dose.

Selected exposure and TEAE summaries will be produced on Complete Original CZP Dose and Complete Reduced CZP Dose in order to answer specific agency questions. Similarly, summaries of the proportion of PK and ADAb samples and participants that have been reanalyzed with the ECLIA assay will also be produced with this treatment association.

Further details regarding these displays based upon dose groups can be found in the respective PK, safety and efficacy analysis sections below.

Categorical data will be presented as summary tables. A missing category will be included as applicable.

Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum. For CZP plasma concentrations and CRP, the geometric mean and geometric coefficient of variation (CV) will be presented.

Was changed to:

Generally, data will be summarized by the Original CZP Dose, Reduced CZP Dose, and Any CZP Dose groups. For PK and ADAb analyses, data will be summarized by Original CZP Dose and Reduced CZP Dose only. For the Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey, data will be summarized by Any CZP Dose group only.

Following recommendations received from [redacted], a few data summaries were organized for the Updated Week 24 Interim Analysis only, by "Complete" CZP dose groups defined below, which allowed assessment of exposure and safety for all time that study participants were receiving the specified dose regardless of dose switching:

- Complete Original CZP Dose: included all study participants who began treatment in accordance with the Original CZP Dose, as well as study participants who began treatment in accordance with the Reduced CZP Dose and then later dose escalated to the Original CZP Dose.

  Only data obtained while the study participant was receiving the Original CZP Dose was included in summaries of the Complete Original CZP Dose. For study participants who began treatment with the Original CZP Dose, this included time on the Original CZP Dose prior to first change in dosage, as well as time after returning to Original CZP Dose after a previous dose reduction. For study participants who began treatment with the Reduced CZP Dose, this included only time after dose escalation to the Original CZP Dose.

- Complete Reduced CZP Dose: included all study participants who began treatment in accordance with the Reduced CZP Dose, as well as study participants who began treatment in accordance with the Original CZP Dose and later dose reduced to the Reduced CZP Dose.

  Only data obtained while the study participant was receiving the Reduced CZP Dose was included in summaries of the Complete Reduced CZP Dose. For study participants who began treatment with the Reduced CZP Dose, this included time on the Reduced CZP Dose prior to first change in dosage. For study participants who began treatment with the Original CZP Dose, this included only time after dose reduction to the Reduced CZP Dose, and prior to any potential later dose escalation back to the Original CZP Dose.

Selected exposure and TEAE summaries were produced on Complete Original CZP Dose and Complete Reduced CZP Dose in order to answer specific agency questions. Similarly,

summaries of the proportion of PK and ADAb samples and participants that have been reanalyzed with the ECLIA assay were also produced with this treatment association.

Further details regarding these displays based upon dose groups can be found in the respective PK, safety and efficacy analysis sections below.

Categorical data will be presented as summary tables. A missing category will be included as applicable.

Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum. For CZP plasma concentrations and CRP, the geometric mean and geometric coefficient of variation (CV) will be presented.

Due to shifts in visit schedules per protocol amendments that were adopted at different times for different sites and study participants, some visits/ time points had very few study participants assessed. For categorical and continuous efficacy variables presented by visit/time point, if the visit/time point for the Any CZP Dose group contains 19 or fewer study participants with non-missing data, those visits/ time points will not be displayed in the efficacy tables or plotted in figures for Reduced CZP Dose, Original CZP Dose and Any CZP Dose groups. All information will appear in the listings.

Change #14

Section 3.2.2 Relative day

Relative day after last dose will have the prefix "+", and will be calculated from the date of last CZP administration (date X - date of last CZP administration). Relative day will not be calculated when any part of a corresponding date is missing, and will not be included in corresponding datasets, tables and listings.

Was changed to:

Relative day after last dose will have the prefix "+",and will be calculated from the date of last CZP administration (date X - date of last CZP administration). Relative day will not be calculated when any part of a corresponding date is missing,and will not be included in corresponding tables and listings.

Change #15

Section 3.4 Protocol deviations, the following was added:

Study participants, if taking CZP Q2W, should be dosed 9 to 19 days from the previous dosing; if taking CZP Q4W, study participants should be dosed 23 to 33 days from the previous dosing. Study participants who are taking CZP Q2W, if they have instances where they take their study medication > 42 days from the last dosing, or for those who are taking CZP Q4W, if they have instances where they take their study medication > 84 days from the last dosing, these instances will be flagged as important protocol deviations. For study participants not in derived CRM and taking CZP Q2W, gaps less than 9 days or >19 to 42 days will be considered as protocol deviations. For study participants not in derived CRM and taking CZP Q4W, gaps less than 23 days or >33 to 84 days will be considered as protocol deviations.

Change #16

Section 3.5 Exclusion of PK data points

- Study participant being in Clinical remission (and not taking CZP),

Was changed to:

- Study participant being in derived CRM (and not taking CZP),

Change #17

Section 3.5.4 Pharmacokinetic Per-Protocol (PK-PP) Set

The Pharmacokinetic Per-Protocol (PK-PP) Set is a subset of the SS consisting of those study participants who took at least 1 dose of study medication, provided measurable plasma CZP concentration samples (with recorded sampling date/time or for which date/time can be reasonably assumed and it was analyzed using the ECLIA method) on at least 1 occasion. The PK-PP Set will be used for the PopPK model that will be described in a separate data analysis plan (DAP) and for all presentations of plasma concentration.

Was changed to:

The Pharmacokinetic Per-Protocol (PK-PP) Set is a subset of the SS consisting of those study participants who took at least 1 dose of study medication, provided measurable plasma CZP concentration samples (with recorded sampling date/time or for which date/time can be reasonably assumed and it was analyzed using the ECLIA method) on at least 1 occasion. The PK-PP Set will be used for presentations of plasma concentration. The PK-PP Set was used for the PopPK model that was described in a separate data analysis plan (DAP) to support the marketing application in 2024.

Change #18

Section 3.10 Changes to protocol-defined analyses

In line with [redacted] response, additional analyses have been added to

- summarize exposure and treatment-emergent adverse events for when study participants were taking Complete Original CZP Dose and Complete Reduced CZP Dose.
  - Complete Original CZP Dose includes all data for study participants who took Original CZP Dose prior to the first change in dosage as well as the data from when study participants increased their dosage to Original CZP after taking Reduced CZP Dose.
  - Complete Reduced CZP Dose includes all data for study participants who took Reduced CZP Dose prior to the first change in dosage as well as the data from when study participants took Reduced CZP Dose after taking Original CZP Dose.
- the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples initially analyzed with the ELISA method will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.

- the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples analyzed with the ECLIA method (either originally or via re-analysis) will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples initially analyzed with the ELISA method will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- Additionally, the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples analyzed with the ECLIA method (either originally or vis re-analysis) will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.

In the statistical section of the protocol, it is stated that the AEs will be summarized separately for the periods of exposure to Original CZP Dose and the Reduced CZP Dose, in addition to exposure for study participants that switched from the Reduced CZP Dose to the Original CZP Dose following Protocol Amendment 9. The analysis of AEs after a study participant changes doses will not be separately identified and presented in the Updated Week 24 Interim Analysis although the AEs that occur after dose changes will be summarized in the Any CZP Dose group.

In the statistical section of the protocol, it is stated that the frequency and percentage of AEs reported during the first 16 weeks of study medication exposure will be summarized separately for the 2 CZP doses (the Original CZP Dose, the Reduced CZP Dose), and that this analysis will be repeated, excluding any study participants who switched from the original to the reduced CZP dose prior to Week 16. The protocol-specified safety Week 16 analyses generated for prior interim analyses will not be included in the Updated Week 24 Interim Analysis or any later analyses.

Exposure-adjusted event rates (EAER) are added to selected TEAE tables.

This analysis plan includes plots of CZP plasma concentrations, ADAb titers, and maximum PedACR response for individual study participants by visit. Box plots of the PK distribution at Weeks 12 and 24 stratified by Baseline weight group, Baseline age group, concomitant MTX use and participant ADAb classification will be performed as a basis of the comparison with the adult RA PK exposures in RA0138; this comparison of observed PK data will be covered in Appendix Section 12.1. Plots of PK and ADAb data were not pre-specified in the study protocol.

It is not planned to perform a population PKPD modeling analysis of RA0043 data to explore the exposure-response relationship in JIA pediatric population for the following reasons: i) the purpose of the RA0043 study is to support the efficacy extrapolation to the pediatric population by PK matching with respect to RA adult PK, and thus the main aim of the analysis that will be performed by nonlinear mixed effect modeling is to characterize the PK in JIA pediatrics with precise parameter estimates; and ii) the W24 interim analyses

performed and submitted in 2016 (BLA 125160-275) included PedACR and JADAS-71 graphical explorations by dose which concluded that a substantial improvement of the PedACR and JADAS-71 responses across both doses investigated in Study RA0043 was observed, with no differences between these, that would support a pop-PKPD analysis. Hence the PK-PD Set was removed as no analyses are planned for this population.

In the protocol it was stated that continuous efficacy endpoints would be presented using both last observation carried forward (LOCF) and observed case (OC) analyses. Instead, only observed case summaries of continuous efficacy endpoints will be presented since efficacy is not the primary objective of this study and little difference is expected between the two different analyses.

For the Updated Week 24 Interim Analysis, the efficacy data will be summarized and plotted up to and including Week 24; all efficacy data will be included in listings and displayed on a small subset of figures.

Was changed to:

In line with [redacted] response, for the Updated Week 24 Interim Analysis only, additional analyses were added to:

- summarize exposure and treatment-emergent adverse events for when study participants were taking Complete Original CZP Dose and Complete Reduced CZP Dose.
  - Complete Original CZP Dose included all data for study participants who took Original CZP Dose prior to the first change in dosage as well as the data from when study participants increased their dosage to Original CZP after taking Reduced CZP Dose.
  - Complete Reduced CZP Dose included all data for study participants who took Reduced CZP Dose prior to the first change in dosage as well as the data from when study participants took Reduced CZP Dose after taking Original CZP Dose.
- summarize the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples initially analyzed with the ELISA method were summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- summarize the proportion of study participants and the proportion of PK samples with sufficient volume for re-analysis with the ECLIA method out of all PK samples analyzed with the ECLIA method (either originally or via re-analysis) will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- summarize the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all ADAb samples initially analyzed with the ELISA method will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.
- Additionally, to summarize the proportion of study participants and the proportion of ADAb samples with sufficient volume for re-analysis with the ECLIA method out of all

ADAb samples analyzed with the ECLIA method (either originally or vis re-analysis) will be summarized by Original CZP Dose, Reduced CZP Dose, Complete Original CZP Dose, and Complete Reduced CZP Dose.

In the statistical section of the protocol, it is stated that the AEs will be summarized separately for the periods of exposure to Original CZP Dose and the Reduced CZP Dose, in addition to exposure for study participants that switched from the Reduced CZP Dose to the Original CZP Dose following Protocol Amendment 9. The analysis of AEs after a study participant changes doses will not be separately identified and presented in the Updated Week 24 Interim Analysis or the final analysis although the AEs that occur after dose changes will be summarized in the Any CZP Dose group.

In the statistical section of the protocol, it is stated that the frequency and percentage of AEs reported during the first 16 weeks of study medication exposure will be summarized separately for the 2 CZP doses (the Original CZP Dose, the Reduced CZP Dose), and that this analysis will be repeated, excluding any study participants who switched from the original to the reduced CZP dose prior to Week 16. The protocol-specified safety Week 16 analyses generated for prior interim analyses will not be included in the Updated Week 24 Interim Analysis or any later analyses.

Exposure-adjusted event rates (EAER) are added to selected TEAE tables.

This analysis plan, for the Updated Week 24 Interim Analysis only, includes plots of CZP plasma concentrations, ADAb titers, and maximum PedACR response for individual study participants by visit. Box plots of the PK distribution at Weeks 12 and 24 stratified by Baseline weight group, Baseline age group, concomitant MTX use and participant ADAb classification will be performed as a basis of the comparison with the adult RA PK exposures in RA0138; this comparison of observed PK data will be covered in Appendix Section 12.1. Plots of PK and ADAb data were not pre-specified in the study protocol.

It is not planned to perform a population PKPD modeling analysis of RA0043 data to explore the exposure-response relationship in pcJIA pediatric population for the following reasons: i) the purpose of the RA0043 study is to support the efficacy extrapolation to the pediatric population by PK matching with respect to RA adult PK, and thus the main aim of the analysis that will be performed by nonlinear mixed effect modeling is to characterize the PK in pcJIA pediatrics with precise parameter estimates; and ii) the W24 interim analyses performed and submitted in 2016 (BLA 125160-275) included PedACR and JADAS-71 graphical explorations by dose which concluded that a substantial improvement of the PedACR and JADAS-71 responses across both doses investigated in Study RA0043 was observed, with no differences between these, that would support a pop-PKPD analysis. Hence the PK-PD Set was removed as no analyses are planned for this population.

In the protocol it was stated that continuous efficacy endpoints would be presented using both last observation carried forward (LOCF) and observed case (OC) analyses. Instead, only observed case summaries of continuous efficacy endpoints will be presented since efficacy is not the primary objective of this study and little difference is expected between the two different analyses.

For the Updated Week 24 Interim Analysis, the efficacy data were summarized and plotted up to and including Week 24; all efficacy data were included in listings. For the Final Analysis, all data will be summarized and plotted, by visit (week) when there are 20 or more study participants with non-missing data, as applicable; all efficacy data will be included in listings.

Change #19

Section 4.2.1 Incomplete dates for adverse events and concomitant medications

Partial adverse event (AE) and concomitant medication start dates will be imputed as follows:

Was changed to:

Partial adverse event (AE), medical procedures, and concomitant medication start dates will be imputed as follows:

Change #20

Section 4.3 Interim analyses and data monitoring

At the time of Protocol Amendment 9, a new assay had been developed and would be used to analyze samples from the 30 new subjects enrolled on the original dose as well as any old samples with sufficient volume remaining. 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; this will be referred to as the Updated Week 24 Interim analysis to be used in support of the re-submission of BLA 125160-275.

Was changed to:

At the time of Protocol Amendment 9, a new assay had been developed and was used to analyze samples from the 30 new study participants enrolled on the original dose as well as any old samples with sufficient volume remaining. An interim analysis, including all enrolled study participants, for all PK, immunogenicity, safety, and efficacy endpoints was performed after all active study participants, including those enrolled following the implementation of Protocol Amendment 9, completed the Week 24 (Visit 10) assessments; this is referred to as the Updated Week 24 Interim analysis that was used in support of the re-submission of BLA 125160-275.

Change #21

Section 5.1 Study participant disposition

The number and percentage of study participants who were treated, who completed the study, and who discontinued from the study, along with the discontinuation reasons, will be summarized for the Safety Set by CZP Dose (Reduced, Original and Any) and Baseline weight group as well as by CZP Dose and ADAb titer classification. For the Week 16, Week 24 and other interim analyses, number of study participants completing Week 16, Week 24 and Week 48 (respectively) will be added in addition to the number completing the study as appropriate. The disposition of study participants in their initial dosing phase, reduction phase

and escalation dosing phase of the study will also be presented. The number of study participants in each analysis set will be presented.

Was changed to:

The number and percentage of study participants who were treated, and who discontinued from the study, along with the discontinuation reasons, will be summarized for the Safety Set by CZP Dose (Reduced, Original and Any) and Baseline weight group as well as by CZP Dose and ADAb titer classification; because the study was closed, every ongoing study participant is discontinued from the study. For the Week 16, the number of study participants completing Week 16 was added. For the Updated Week 24 Interim Analysis, the number of study participants completing Week 24 was added. For the Final Analysis, the number of study participants completing Week 24 and Week 48, respectively, will be added. The disposition of study participants in their initial dosing phase, reduction phase and escalation dosing phase of the study will also be presented. The number of study participants in each analysis set will be presented.

Change #22

Section 5.2 Protocol deviations, the following was removed:

When applicable, exclusion from analysis set will also be summarized and listed.

Change #23

Section 6.1 Demographics

The following categorical variables will be summarized by Baseline weight group and ADAb titer classification: gender (male, female), racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, Not Hispanic or Latino), Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), ERA status (present, absent), Baseline MTX use group (with, without) and Concomitant MTX Use (with, without). Demographics information will be listed.

Was changed to:

The following categorical variables will be summarized by Baseline weight group and ADAb titer classification: gender (male, female), racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, Not Hispanic or Latino), Country (Argentina, Brazil, Canada, Chile, Mexico, Russia, and USA), Baseline age group (2 to 5 years, 6 to 11 years, and 12 to 17 years), Baseline MTX use group (with, without) and Concomitant MTX Use (with, without). Demographics information will be listed.

Change #24

Section 7 Measurements of Treatment Compliance

Descriptive statistics will be presented for the compliance ratio defined as total number of CZP administrations received/total number of CZP administrations expected for the SS. Total number of CZP administrations expected differs depending on the loading phase or maintenance phase as well as depends on the different dosing scheduling of the 3 different

weight groups. For example, in the Original CZP Dose, a study participant is expected to receive 3 loading CZP administrations and then a maintenance dose of CZP Q2W through the Early Discontinuation/EOT Visit, with the exception of following implementation of Protocol Amendment 4; study participants in the 10 to <20kg weight group change from Q2W to a maintenance dose of CZP Q4W.

In addition, a study participant could change dose (or frequency of dosing if in 10-20kg group) if a study participant crossed into a new weight group, which is not considered in the above expected calculations of number of CZP administration; study participants are assigned dose groups (Reduced CZP Dose and Original CZP Dose) and Baseline weight group at baseline and do not change either for the entire analysis regardless of weight change and dose adjustments. This specifically applies to the change of dose frequency from Q4W to Q2W if a study participant crossed into the 20 to <40kg weight group, which is not considered in the expected calculations. Note that the dose reduction of ongoing study participants following Protocol Amendment 4 is considered in the calculations. Note also the dose escalation of ongoing study participants following Protocol Amendment 9 is considered in the calculations.

For the Original CZP Dose and Reduced CZP Dose groups, treatment compliance is calculated from the first dose of CZP, for the entire time the study participant is taking study medication up to the dose change. For the results presented for Any CZP Dose, treatment compliance is calculated for the entire time the study participant is taking CZP from first dose until the last dose. Treatment compliance will be summarized and listed for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose for the final analysis; for the Updated week 24 Interim Analysis, treatment compliance will be summarized and listed for the SS for the Reduced CZP Dose and Original CZP Dose.

Was changed to:

Compliance with study drug administration will be based upon comparing the actual number of injections administered $N_{inj.actual}$ with the expected number of injected administered $N_{inj.expected}$. If a study participants is in derived CRM and is not dosed, then no doses are expected for the compliance calculation. Since study participants are dosed on a Q2W or Q4W schedule, the week number of the visit is used to identify weeks where doses are expected starting with Week 0 (Baseline).

$$CR = \frac{N\ inj.actual}{N\ inj.expected}$$

Descriptive statistics will be presented for the compliance ratio for the SS. Total number of CZP administrations expected differs depending on the loading phase or maintenance phase as well as depends on the different dosing scheduling of the 3 different weight groups. For example, in the Original CZP Dose, a study participant is expected to receive 3 loading CZP administrations and then a maintenance dose of CZP Q2W through the Early Discontinuation/EOT Visit, with the exception of following implementation of Protocol Amendment 4; study participants in the 10 to <20kg weight group change from Q2W to a maintenance dose of CZP Q4W.

In addition, a study participant could change dose (or frequency of dosing if in 10-20kg group) if a study participant crossed into a new weight group, which is considered in the above expected calculations of number of CZP administration If a study participant crossed into the 20 to <40kg weight group, the calculations are updated to reflect the weight change. Note that the dose reduction of ongoing study participants following Protocol Amendment 4 is considered in the calculations. Note also the dose escalation of ongoing study participants following Protocol Amendment 9 is considered in the calculations.

For the Original CZP Dose and Reduced CZP Dose groups, treatment compliance is calculated from the first dose of CZP, for the entire time the study participant is taking study medication up to the dose change. For the results presented for Any CZP Dose, treatment compliance is calculated for the entire time the study participant is taking CZP from first dose until the last dose.

The ratios of compliance will be summarized as a continuous variable and categorically (eg. 0 - <0.80, 0.8 - 1.0 and >1.0). Treatment compliance will be summarized and listed for the SS for the Reduced CZP Dose, Original CZP Dose, and Any CZP Dose for the final analysis; for the Updated week 24 Interim Analysis, treatment compliance was summarized and listed for the SS for the Reduced CZP Dose and Original CZP Dose.

Change #25

Section 8.1 CZP plasma concentrations

Concentrations below the limit of quantification of 320.0 ng/mL (0.32µg/mL) (BLQ) will be replaced by the LLOQ divided by 2 for the calculation of descriptive statistics. The geometric mean and CV% will be derived when at least two-thirds of the concentrations at a certain visit are above the LLOQ. If the criteria are not met, only the maximum and minimum values will be shown. Similarly, the 95% CI of the geometric mean will be calculated if at least 5 samples are available at a time point.

All summaries will be provided for the PK-PP Set. All plasma concentration data will be listed.

Was changed to:

Concentrations below the limit of quantification of 320.0 ng/mL (0.32µg/mL) (BLQ) will be replaced by the LLOQ divided by 2 for the calculation of descriptive statistics. The geometric mean and CV% will be derived when at least two-thirds of the concentrations at a certain visit are above the LLOQ and not missing. A minimum of 3 values are required to calculate summary statistics. If only 2 values are available then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-") When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ value replaced by half the LLOQ value". If the criteria are not met, only the maximum and minimum values will be shown. Similarly, the 95% CI of the geometric mean will be calculated if at least 5 samples are available at a time point.

All summaries will be provided for the PK-PP Set. All plasma concentration data will be listed. Concentrations should be listed to the same number of significant figures supplied by

the bioanalytical laboratory. For listings concentrations below the limit of quantification should be reported as BLQ (below the limit of quantification).

Change #26

Section 8.4 PopPK analyses

Plasma concentrations will be used to build a PopPK model with the nonlinear mixed-effect modeling (NONMEM) software. Details of the PopPK modeling procedures will be described in a separate data analysis plan.

Was changed to:

Plasma concentrations will be used to build a PopPK model with the nonlinear mixed-effect modeling (NONMEM) software. Details of the PopPK modeling procedures will be described in a separate data analysis plan. This analysis was generated for the Updated Week 24 Interim analysis only.

Change #27

Section 9.1 Extent of exposure

The extent of exposure to study drug will be evaluated by summarizing the total amount of CZP received in mg and the total duration of exposure in days. Total duration of exposure will be calculated using this general formula as: the Date of Last Dose of study medication – Date of First Dose of study medication + 14 days if administration of CZP is Q2W, +28 days if administration of CZP is Q4W.

Was changed to:

The extent of exposure to study drug will be evaluated by summarizing the total amount of CZP received in mg and the total duration of exposure in days. Total duration of exposure will be calculated using this general formula as: the Date of Last Dose of study medication – Date of First Dose of study medication + 14 days if administration of CZP is Q2W, +28 days if administration of CZP is Q4W. Dosing gaps (which occur between 2 CZP doses) are not considered in (does not reduce) the duration of exposure calculation.

Change #28

Section 9.1 Extent of exposure

Duration of exposure will be calculated as appropriate for each of the following CZP Dose groups:

Was changed to:

Duration of exposure was calculated as appropriate for each of the following CZP Dose groups for the Updated Week 24 Interim Analysis but will only be calculated for Any CZP Dose, Reduced CZP Dose and Original CZP Doze for the final analysis:

Change #29

Section 9.1.1 Subject time at risk

Subject time at risk will also be calculated. Subject time at risk represents the time a study participant is at risk for having an AE. Subject time (in days) at risk will generally be

calculated using this general formula: (date of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). However, the calculation of subject time at risk will be modified for study participants who change from Original CZP Dose to Reduced CZP Dose, or who dose escalate from Reduced CZP Dose to the Original CZP Dose. For the period of exposure prior to a dose change, subject time at risk ends on the date of dose change (ie, do not add 70 days). For the period of exposure on the final CZP dose for a study participant, time at risk should include the additional 70 days. Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Was changed to:

Subject time at risk will also be calculated. Subject time at risk represents the time a study participant is at risk for having an AE while taking CZP. Subject time (in days) at risk will generally be calculated using this general formula: (date of the last dose of study medication – date of the first dose of study medication + 70 days) (70 days = 5 CZP half-lives). However, the calculation of subject time at risk will be modified for study participants who change from Original CZP Dose to Reduced CZP Dose, or who dose escalate from Reduced CZP Dose to the Original CZP Dose; the subject time at risk will further be modified for study participants who have dosing gaps > 70 days during the study – eg. meaning if a study participant has 100 consecutive day dosing gap, only the first 70 days will be included in the subject time at risk. For the period of exposure prior to a dose change, subject time at risk ends on the date of dose change (ie, do not add 70 days). For the period of exposure on the final CZP dose for a study participant, time at risk should include the additional 70 days. Subject years at risk will be calculated as subject time at risk (in days) divided by 365.25.

Change #30

Section 9.1.1 Subject time at risk

Subject time at risk will be calculated as appropriate for each of the following CZP Dose groups;

Was changed to:

Subject time at risk was calculated as appropriate for each of the following CZP Dose groups for the Updated Week 24 Interim Analysis but will only be calculated for Any CZP Dose, Reduced CZP Dose and Original CZP Doze for the final analysis:

Change #31

Section 9.2 Adverse events

Only treatment emergent adverse events (TEAE) will be included in the summary tables. Treatment emergent AEs are defined as AEs starting on or after the first administration of CZP and up to 70 days after the last dose of study medication. AEs that are pre-treatment or that start more than 70 days after the last dose of study medication will be flagged in the listing but excluded from summaries.

Was changed to:

Only treatment emergent adverse events (TEAE) will be included in the summary tables. Treatment emergent AEs are defined as AEs starting on or after the first administration of

CZP and up to 70 days after the last (most recent) dose of study medication; then only the adverse events occurring up to 70 days after the last (most recent) dose of study medication will be counted as treatment emergent; all other adverse events occurring after first dose will not be flagged as treatment emergent. AEs that are pre-treatment or that start more than 70 days after the last (most recent) dose of study medication will be in the listing but excluded from summaries.

Change #32

Section 9.2 Adverse events, the following was added:

- Injection reaction TEAEs by primary SOC, HLT, and PT, overall and by Baseline weight group, further subdivided into injection site reactions and systemic reactions, with systemic reactions further subdivided into acute vs. delayed systemic reactions

as well as:

For disclosure on public registries (eg, ClinicalTrials.gov), information from the incidence tables of TEAEs and treatment-emergent SAEs will be published.

Change #33

Section 9.2 Adverse events

In line with [redacted] response, incidence tables of TEAEs will be presented by primary SOC, PT, overall and Baseline weight group by Original CZP, Reduced CZP, Any CZP, Complete Original CZP and Complete Reduced CZP doses.

Incidence and event rate tables will include the descriptive statistics on the incidence table but also include the exposure-adjusted incidence rate (EAIR) with associated 95% confidence interval, and the exposure-adjusted event rate (EAER).

For EAIR, the numerator will be the total number of study participants experiencing a particular TEAE. The denominator will be 100 subject-years, ie, the total summation of individual subject-years at risk up to the first occurrence of the given TEAE for study participants with that TEAE, plus the total subject-years at risk for those study participants not experiencing that TEAE, divided by 100. Details regarding calculation of subject-years at risk are described in Section 9.1. EAIR will be presented with exact 95% confidence intervals based on the link between the chi-square distribution and the Poisson distribution (Ulm, 1990).

For EAER, the numerator will be the number of TEAEs including repeat occurrences in individual study participants. The denominator will be in 100 subject-years (total summation of individual subject-years at risk divided by 100). No confidence interval will be computed.

Listings:

- Individual study participant numbers experiencing a given adverse event, grouped by SOC, PT, intensity, and relation to study drug

Was changed to:

For the Updated Week 24 Interim Analysis only, in line with [redacted] response, incidence tables of TEAEs were presented by primary SOC, HLT, and PT, overall and Baseline weight group by Original CZP, Reduced CZP, Any CZP, Complete Original CZP and Complete Reduced CZP doses. Also, incidence and event rate tables of TEAEs up to Week 24 were presented by primary SOC, HLT, and PT, overall and by Baseline weight group for Reduced CZP and Original CZP dose groups.

For the final analysis, incidence tables of TEAEs will be presented by primary SOC, HLT, and PT, overall and by Baseline weight group by Original CZP, Reduced CZP and Any CZP doses. The incidence and event rate tables of TEAEs up to Week 24 will not be presented for the final analysis.

Incidence and event rate tables will include the descriptive statistics on the incidence table but also include the exposure-adjusted incidence rate (EAIR) with associated 95% confidence interval, and the exposure-adjusted event rate (EAER).

For EAIR, the numerator will be the total number of study participants experiencing a particular TEAE. The denominator will be 100 subject-years, ie, the total summation of individual subject-years at risk up to the first occurrence of the given TEAE for study participants with that TEAE, plus the total subject-years at risk for those study participants not experiencing that TEAE, divided by 100. Details regarding calculation of subject-years at risk are described in Section 9.1. EAIR will be presented with exact 95% confidence intervals based on the link between the chi-square distribution and the Poisson distribution (Ulm, 1990).

For EAER, the numerator will be the number of TEAEs including repeat occurrences in individual study participants. The denominator will be in 100 subject-years (total summation of individual subject-years at risk divided by 100). No confidence interval will be computed.

Listings:

- Individual study participant numbers experiencing a given adverse event, grouped by SOC, PT, intensity, and relation to study drug
- Individual study participant numbers experiencing a serious treatment emergent adverse event, grouped by SOC, PT, intensity, and relation to study drug
- Individual study participant numbers experiencing a TEAE leading to study drug discontinuation, grouped by SOC, PT, intensity and relation to study drug

Individual study participant numbers experiencing an AE leading to death, grouped by SOC, PT, intensity and relation to study drug

Change #34

Section 9.3 Clinical laboratory evaluations, the following was added:

A listing of when blood and urine samples were taken as well as serum pregnancy tests were performed will also be produced.

Change #35

Section 10 Efficacy analyses

In Section 10, the analyses described will be generated for the final analysis. For the Updated Week 24 Interim analysis, only efficacy data up to and including Week 24 will be presented in the analyses described in Section 10 for the following variables:

- PedACR30/50/70, 90
- Number of joints with active arthritis
- Number of joints with limitation of range of motion
- Physician's Global Assessment of Disease Activity
- Childhood Health Assessment Questionnaire
- Parent's Global Assessment of Overall Well-Being
- C-Reactive protein
- Juvenile Arthritis Disease Activity Score 71-joint

For the Updated Week 24 Interim analysis, all reported data for other efficacy variables will be listed only; any calculations described for the final analysis will not be performed. These include the following variables:

- Clinically Inactive Disease
- Clinical remission on medication
- Duration of Morning Stiffness

Was changed to:

In Section 10, the analyses described for all efficacy variables below will be generated for the final analysis. For the Updated Week 24 Interim analysis, only efficacy data up to and including Week 24 was presented in the analyses described in Section 10 for the following variables:

- PedACR30/50/70/90
- Number of joints with active arthritis
- Number of joints with limitation of range of motion
- Physician's Global Assessment of Disease Activity
- Childhood Health Assessment Questionnaire
- Parent's Global Assessment of Overall Well-Being
- C-Reactive protein
- Juvenile Arthritis Disease Activity Score 71-joint

For the Updated Week 24 Interim analysis, all reported data for other efficacy variables were listed only; any calculations described for the final analysis were not performed. These included the following variables:

- Clinically Inactive Disease

- CRM
- Duration of Morning Stiffness

Change #36

Section 10.3.1 PedACR30, PedACR50, PedACR70, PedACR90

In addition to the Week 16 summary described above, the PedACR30, PedACR50, PedACR70, and PedACR90 response rates as compared to Baseline at every other visit except the Final Visit will also be summarized. Plots of PedACR30, PedACR50, PedACR70 and PedACR90 response rates (combined on the same plot) by visit will be provided by the same CZP dose groups as in the summary tables above, overall and by Baseline weight group.

Was changed to:

The PedACR30, PedACR50, PedACR70, and PedACR90 response rates as compared to Baseline at every visit (including Week 16) except the Final Visit will be summarized. Plots of PedACR30, PedACR50, PedACR70 and PedACR90 response rates (combined on the same plot) by visit will be provided by the same CZP dose groups as in the summary tables above, overall and by Baseline weight group.

Change #37

Section 10.3.9.2 Final Analysis

If any of the 6 criteria cannot be assessed due to missing data, the study participant will be assumed not to have achieved CID at the corresponding visit.

CID will be assessed at every post-Baseline visit except the Final Visit.

The n and percentage of study participants with CID will be summarized for each post-Baseline visit. The exact 95% CI for the percentage will also be presented.

Time to initial CID in days will be calculated as date of first visit where CID is achieved – date of first dose of study medication + 1 day. Time to initial CID in days will be presented using Kaplan-Meier product limit estimation. Study participants that discontinue without achieving CID will be censored at the time of discontinuation; ongoing study participants that have not achieved CID at the time of interim analyses (Week 24 and other interim analyses) and the final analysis will be censored at the time of the last available assessment. The median and 95% CI for the time to initial CID will be presented. The 95% CI for the median will be based on the method of Brookmeyer and Crowley. Kaplan-Meier product limit survival estimates of the cumulative proportion of study participants with CID (1 minus the product limit estimate of the proportion of study participants without CID) will also be presented. Kaplan-Meier plots of time to CID will be presented overall and by Baseline weight group.

Both summaries of CID and time to CID will be provided.

Was changed to:

The 6 criteria above will be used to derive CID. If any of the 6 criteria cannot be assessed due to missing data, the study participant will be assumed not to have achieved derived CID at the corresponding visit.

Derived CID will be assessed at every post-Baseline visit except the Final Visit.

The n and percentage of study participants with derived CID will be summarized for each post-Baseline visit. The exact 95% CI for the percentage will also be presented.

Time to initial derived CID in days will be calculated as date of first visit where derived CID is achieved – date of first dose of study medication + 1 day. Time to initial derived CID in days will be presented using Kaplan-Meier product limit estimation. Study participants that discontinue without achieving derived CID will be censored at the time of discontinuation; ongoing study participants that have not achieved derived CID at the time of interim analyses (Week 24 and other interim analyses) and the final analysis will be censored at the time of the last available assessment. The median and 95% CI for the time to initial derived CID will be presented. The 95% CI for the median will be based on the method of Brookmeyer and Crowley. Kaplan-Meier product limit survival estimates of the cumulative proportion of study participants with derived CID (1 minus the product limit estimate of the proportion of study participants without derived CID) will also be presented. Kaplan-Meier plots of time to CID will be presented overall and by Baseline weight group.

Both summaries of derived CID and time to derived CID will be provided as well as listed.

Change #38

Section 10.3.10.2 Final Analysis

CRM is defined as criteria for CID achieved for at least 6 continuous months. CRM will be considered achieved at a given visit if the study participant has CID at the visit and if the time from the first visit where CID is achieved to the given visit is ≥ 6 months (182 days) and the study participant had CID at all visits in between. CRM is defined as criteria for CID achieved for at least 6 continuous months.

CRM will be assessed at every post-Baseline visit from Week 24 onwards, except the Final Visit.

The n and percentage of study participants with CRM will be summarized for each post-Baseline visit starting at Week 24. The exact 95% CI for the percentage will also be presented.

Time to initial CRM in days will be calculated as date of first visit where CRM is achieved – date of first dose of study medication + 1 day. Time to CRM in days will be presented using Kaplan-Meier product limit estimation. Study participants that discontinue without achieving CRM will be censored at the time of discontinuation; ongoing study participants that have not achieved CRM at the time of interim analyses (Week 24 and other interim analyses) and the final analysis will be censored at the time of the last available assessment. The median and 95% CI for the time to initial CRM in days calculated using Kaplan-Meier product limit estimators will be presented. The 95% CI for the median will be based on the method of Brookmeyer and Crowley. Kaplan-Meier product limit survival estimates of the cumulative proportion of study participants in CRM (1 minus the product limit estimate of the proportion

of study participants without CRM) from 6 months onwards will also be presented. Kaplan-Meier plots of time to CRM will be presented overall and by Baseline weight group.

Both summaries of CRM and time to CRM will be provided.

Was changed to:

CRM as indicated by the PI in the eCRF will only be listed.

Derived CRM is defined as achieving the criteria for derived CID for at least 6 continuous months; study participants who reach derived CRM can either stay on CZP or stop taking CZP; so being in derived CRM is not an indicator of whether the study participant is taking CZP while in derived CRM. Derived CRM will be considered achieved at a given visit if the study participant has derived CID at the visit and if the time from the first visit where derived CID is achieved to the given visit is ≥ 6 months (182 days) and the study participant had derived CID at all attended visits in between; if missed visits occur between visits where derived CID is achieved, then derived CID will be assumed for the missed visits. Derived CRM is defined as criteria for derived CID achieved for at least 6 continuous months.

Derived CRM will be assessed at every post-Baseline visit from Week 24 onwards, except the Final Visit.

The n and percentage of study participants with derived CRM will be summarized for each post-Baseline visit starting at Week 24. The exact 95% CI for the percentage will also be presented.

Time to initial derived CRM in days will be calculated as date of first visit where derived CRM is achieved – date of first dose of study medication + 1 day. Time to derived CRM in days will be presented using Kaplan-Meier product limit estimation. Study participants that discontinue without achieving derived CRM will be censored at the time of discontinuation; ongoing study participants that have not achieved derived CRM at the time of interim analyses (Week 24 and other interim analyses) and the final analysis will be censored at the time of the last available assessment. The median and 95% CI for the time to initial derived CRM in days calculated using Kaplan-Meier product limit estimators will be presented. The 95% CI for the median will be based on the method of Brookmeyer and Crowley. Kaplan-Meier product limit survival estimates of the cumulative proportion of study participants in derived CRM (1 minus the product limit estimate of the proportion of study participants without derived CRM) from 6 months onwards will also be presented. Kaplan-Meier plots of time to derived CRM will be presented overall and by Baseline weight group.

Both summaries of derived CRM and time to derived CRM will be provided as well as listings.

Change #39

Section 10.3.13.2 Final Analysis, the following was added:

Study participants who are past 17 years old while still on the study will continue to be administered the JIA Pain VAS.

Change #40

Section 10.3.15.2 Final Analysis

The n and percentages for each of the question responses will be summarized for the following categorical questions: 1 – 4, 6, 10-13. Descriptive statistics for the responses to the remaining quantitative questions will be summarized.

Was changed to:

The following analysis will be presented for the Any CZP dose only. The n and percentages for each of the question responses will be summarized for the following categorical questions: 6, 10-12. Descriptive statistics for the responses to the quantitative questions (8-9, 14-20) will be summarized.

Change #41

Section 12.1 Comparisons with RA0138 data

Comparisons between RA0043 and RA0138 data will focus on common timepoints (Weeks 12 and 24). The dose groups that will be compared are the Original CZP Dose and the Reduced CZP Dose from RA0043 (Section 3.1) and the 200 mg Q2W maintenance dose from RA0138.

Separate boxplots will be performed for Week 12 and Week 24 showing plasma CZP concentrations for the two CZP dose groups (Original CZP Dose or Reduced CZP Dose) for RA0043 and the single CZP dose group for RA0138 in the same plot. Box plots of the PK concentrations at Weeks 12 and 24 will be presented by CZP dose group for Baseline weight group, Baseline age group, ADAb participant status classification, ADAb titer classification, and concomitant MTX use in combination with Baseline weight group. In the box plots the 5th and 95th percentiles of the concentrations distribution will be shown.

Separate plots of individual participant (natural) log CZP plasma concentration versus log2 ADAb titer will be produced for Week 12 and Week 24 data for both studies. In these plots, participants study (RA0043 or RA0138) and CZP dose group (Original or Reduced) will be shown as a different symbol/color to aid comparison. In addition, for RA0138 only, plots of individual participant area under the plasma concentration curve over the 2-week dosing interval (AUC0-tau) versus log2 ADAb titer at Week 12 will be produced.

If there are signs that higher titer levels are associated with lower plasma concentrations, further investigations will be performed to attempt to determine at which titer levels differences are observed and to assess the impact on efficacy and safety.

Further analyses may be defined in the integrated summary of immunogenicity including comparisons of ADAb titer levels between studies (no pooling of studies across indications are planned) allowing us to put the pJIA/RA data in context of the AS and PSO indications.

Was changed to:

The following analysis was only completed for the Updated Week 24 Interim Analysis; it will not be regenerated for the final analysis.

Comparisons between RA0043 and RA0138 data focused on common timepoints (Weeks 12 and 24). The dose groups that were compared are the Original CZP Dose and the Reduced

CZP Dose from RA0043 (Section 3.1) and the 200 mg Q2W maintenance dose from RA0138.

Separate boxplots were generated for Week 12 and Week 24 showing plasma CZP concentrations for the two CZP dose groups (Original CZP Dose or Reduced CZP Dose) for RA0043 and the single CZP dose group for RA0138 in the same plot. Box plots of the PK concentrations at Weeks 12 and 24 were presented by CZP dose group for Baseline weight group, Baseline age group, ADAb participant status classification, ADAb titer classification, and concomitant MTX use in combination with Baseline weight group. In the box plots the 5th and 95th percentiles of the concentrations distribution were shown.

Separate plots of individual participant (natural) log CZP plasma concentration versus log2 ADAb titer were produced for Week 12 and Week 24 data for both studies. In these plots, participants study (RA0043 or RA0138) and CZP dose group (Original or Reduced) were shown as a different symbol/color to aid comparison. In addition, for RA0138 only, plots of individual participant area under the plasma concentration curve over the 2-week dosing interval (AUC0-tau) versus log2 ADAb titer at Week 12 were produced.

If there were signs that higher titer levels were associated with lower plasma concentrations, further investigations were performed to attempt to determine at which titer levels differences are observed and to assess the impact on efficacy and safety.

Further analyses were defined in the integrated summary of immunogenicity including comparisons of ADAb titer levels between studies (no pooling of studies across indications are planned) allowing us to put the pcJIA/RA data in context of the AS and PSO indications.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

Name: ra0043-sap-amend6

Version: 1.0

Document Number: CLIN-000248991

Title: RA0043 SAP Amendment 6

Approved Date: 24 May 2024

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 23-May-2024 20:16:12 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 23-May-2024 22:39:00 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Document Author Date of Signature: 24-May-2024 14:28:40 GMT+0000