NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	125160/S-275
Priority or Standard	Standard
Submit Date(s)	March 14, 2024 (Resubmission, Class 2)
Received Date(s)	March 14, 2024
PDUFA Goal Date	September 14, 2024
Division/Office	Division of Rheumatology and Transplant Medicine
Review Completion Date	See stamp date
Established/Proper Name	Certolizumab pegol (CZP)
(Proposed) Trade Name	Cimzia
Pharmacologic Class	Tumor necrosis factor alpha (TNFα) inhibitor
Applicant	UCB, Inc.
Dosage form	(b) (4) 200 mg/1 mL prefilled syringe 200 mg lyophilized powder in a single-dose vial
Applicant proposed Dosing Regimen	• Body weight group 10 kg to <20 kg: loading doses of CZP 100 mg at Weeks 0, 2, and 4, followed by CZP 50 mg every 2 weeks from Week 6 onwards • Body weight group 20 kg to <40 kg: loading doses of CZP 200 mg at Weeks 0, 2, and 4, followed by CZP 100 mg every 2 weeks from Week 6 onwards • Body weight group ≥40 kg: loading doses of CZP 400 mg at Weeks 0, 2, and 4, followed by CZP 200 mg every 2 weeks from Week 6 onwards
Applicant Proposed Indication(s)/Population(s)	Treatment of (b) (4) active polyarticular (b) (4) (b) (4) Juvenile Idiopathic Arthritis (b) (4) in patients 2 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	None
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Polyarticular juvenile idiopathic arthritis

Recommended Dosing Regimen	• Body weight group 10 kg to <20 kg: loading doses of CZP 100 mg at Weeks 0, 2, and 4, followed by CZP 50 mg every 2 weeks from Week 6 onwards • Body weight group 20 kg to <40 kg: loading doses of CZP 200 mg at Weeks 0, 2, and 4, followed by CZP 100 mg every 2 weeks from Week 6 onwards • Body weight group ≥40 kg: loading doses of CZP 400 mg at Weeks 0, 2, and 4, followed by CZP 200 mg every 2 weeks from Week 6 onwards

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CS	corticosteroids
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Certolizumab pegol (CZP, CIMZIA) is a humanized fragment antigen binding prime (Fab') conjugated to polyethylene glycol (PEG) which targets tumor necrosis alpha (TNFα). CZP neutralizes human TNFα bioactivity and also inhibits the production of inflammatory cytokines by monocytes. Because it does not include an Fc region, it does not induce complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, or other cytotoxicity such as apoptosis and degranulation. CZP is approved in the United States (US) for the treatment of adults with Crohn's disease (CD), rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), and psoriasis (PsO). It is currently available as a single-use vial (lyophilized powder for reconstitution, 200 mg) or a pre-filled syringe (200 mg/mL) for subcutaneous (SC) injection.

UCB, Inc. (Applicant) is re-submitting Supplement 275 (S-275) to Biologics License Application (BLA) 125160 for CZP for the treatment of polyarticular course juvenile idiopathic arthritis (pcJIA). This supplement originally received a Complete Response (CR) for this population on March 22, 2017. A history of the previous submission and other pertinent regulatory history is provided in Section 3.

The Applicant proposes a weight-tiered dosing regimen:

- Body weight group 10 kg to <20 kg: loading doses of CZP 100 mg at Weeks 0, 2, and 4, followed by CZP 50 mg every 2 weeks from Week 6 onwards
- Body weight group 20 kg to <40 kg: loading doses of CZP 200 mg at Weeks 0, 2, and 4, followed by CZP 100 mg every 2 weeks from Week 6 onwards
- Body weight group ≥40 kg: loading doses of CZP 400 mg at Weeks 0, 2, and 4, followed by CZP 200 mg every 2 weeks from Week 6 onwards

With this supplement, [redacted] (b) (4) Thus, no changes to the currently marketed presentations are being proposed in this supplemental BLA (sBLA). Discussion of the proposed and available presentations for the lower weight categories is located in the review (Sections 3 and 6).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval of Cimzia (also referred to as certolizumab pegol [CZP], the naming convention used in this review) for the following indication:

- Treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older

The recommendation for approval for the treatment of active pJIA is based on an extrapolation of efficacy of CZP established in adults with RA, based on a PK-matching approach and supportive descriptive efficacy assessments observed in pediatric patients with juvenile idiopathic arthritis (JIA) with active polyarthritis from Study RA0043.

Juvenile Idiopathic Arthritis (JIA) is the term used to refer to multiple subtypes of inflammatory arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age. Polyarticular JIA (pJIA) is one form of JIA and is defined by the presence of ≥ 5 inflammatory joints with onset prior to age 16 years and a minimum duration of 6 weeks and is the form of JIA most similar to adult RA. Other forms of JIA may also have polyarticular joint involvement but are defined based on other clinical characteristics, such as psoriatic skin disease in juvenile psoriatic arthritis (JPsA). The clinical manifestations of pJIA are discussed further in Section 2.1. Study RA0043 enrolled patients with JIA with polyarticular involvement of multiple subtypes, not specifically limited to ILAR classification criteria for pJIA. Therefore, in this review, this study population of patients with polyarticular course JIA will be referred to as JIA with active polyarthritis.

The following aspects were considered for the extrapolation of efficacy approach for pediatric patients with pJIA from adults with RA:

1. Disease similarity between adult patients with RA and pediatric patients with pJIA
2. Similar PK exposure-response in adult patients with RA and pediatric patients with pJIA
3. Extrapolation of efficacy in pediatric pJIA patients from adult RA patients

Study RA0043 is an ongoing multicenter, open-label study to assess the PK, safety, and efficacy of CZP in children and adolescents with JIA with active polyarthritis. As the PK samples of adult RA participants from a completed study (Study RA0055) were destroyed and no longer available, the Applicant conducted a multicenter, open-label PK study to evaluate CZP in adults with active RA (Study RA0138). PK data from Study RA0043 and from Study RA0138 were included in the population PK analysis. The Clinical Pharmacology review team has determined that the proposed weight-tiered dosing strategy provides comparable CZP exposure in pediatric patients 2 to less than 18 years of age with JIA with active polyarthritis to that with the currently approved dosing regimen in adult RA patients, supporting the extrapolation of efficacy from adult RA patients. In addition, supportive numerical trends of improvement from baseline were observed for the descriptive efficacy endpoints in Study RA0043. No new safety signals were identified, and the observed safety of CZP in patients with JIA with active polyarthritis was consistent with the known safety profile of CZP in RA and other approved indications.

Therefore, the review team recommends Approval of S-275 for certolizumab pegol for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Polyarticular Juvenile Idiopathic Arthritis (pJIA) is a childhood-onset inflammatory arthritis affecting ≥ 5 joints during the first 6 months of disease. PJIA is the subtype of Juvenile Idiopathic Arthritis (JIA) most similar to adult RA, with articular manifestations being predominant. Extraarticular manifestations, such as uveitis, can also be present. Without appropriate treatment, pJIA can lead to significant life-long disability that starts in childhood. Although multiple therapies are approved for pJIA in the United States, there still remains an unmet need for additional therapeutic options in this population.

Certolizumab pegol (CZP, Cimzia) is a subcutaneously administered humanized fragment antigen binding prime (Fab') conjugated to polyethylene glycol (PEG) which targets tumor necrosis alpha (TNFα). CZP is approved in the United States for the treatment of adults with Crohn's disease (CD), rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), and psoriasis (PsO). It was approved for RA on May 13, 2009, with a deferred pediatric PMR study (PMR-2563-1) under Pediatric Research Equity Act (PREA) to provide an *Assessment of pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance, and immunogenicity in the pediatric population ≥ 2 years to < 17 years with polyarticular JIA.* The Applicant conducted Study RA0043 and Study RA0138, the supportive data in this submission, to address the PMR.

Study RA0043 is an ongoing, multicenter, open-label PK, safety, and efficacy study conducted in 193 patients 2 to 17 years of age with JIA with active polyarthritis with an inadequate response or intolerance to at least 1 DMARD (nonbiologic or biologic) who received a subcutaneous weight-tiered CZP dose regimen (loading and maintenance doses). Based on interval PK analyses, the CZP dose regimen was modified to better match the adult exposure; therefore, patients were treated with one of two dose regimens (described as the Original CZP Dose and the Reduced CZP Dose). A supplemental BLA was first submitted on May 27, 2016, which included an initial Week 24 interim clinical study report (CSR) with PK and anti-CZP antibody (ADAb) data generated to support the extrapolation of efficacy from RA to pJIA. However, a Complete Response Letter (CRL) was issued on March 22, 2017, due to deficiencies related to the PK and ADAb assays, as well as product quality concerns about drug stability and duration of storage. The Applicant subsequently addressed the assay deficiencies, agreed to conduct Study RA0138 to assess the PK in adult RA patients using the new assay, and to enroll additional subjects in RA0043 at the Original CZP Dose which seemed to better match the adult exposures.

The efficacy of CZP in pJIA is based on exposure matching and extrapolation of established efficacy of CZP in RA. The similarities between the clinical presentation, disease progression, and responsiveness to therapies, including TNFα inhibitors, of pJIA and RA support the extrapolation of efficacy based on PK-matching. The exposures observed in JIA patients with active polyarthritis treated with the Original CZP Dose in Study RA0043 are within the range of exposures seen in RA patients treated with CZP in Study RA0138. Based on the similarity in disease and PK between adult RA and pJIA, the PK bridge is established to support the extrapolation of the efficacy established in adults with RA to pediatric patients with pJIA. In addition, supportive numerical trends of improvement from baseline were observed for the exploratory efficacy endpoints in the open-label uncontrolled Study RA0043 in JIA with active polyarthritis.

The safety assessment of CZP for the proposed pJIA indication is primarily based on the safety data from 193 JIA patients with active polyarthritis in Study RA0043. The overall safety profile was generally consistent with the safety observed with treatment with CZP in adult RA patients, and the known safety profile of other TNFα inhibitors in JIA with active polyarthritis, including pJIA. No new safety signals were identified.

The Applicant has provided adequate data to inform the benefit-risk assessment of CZP for the treatment of active pJIA in patients 2 years of age and older. Overall, the efficacy and safety evidence provided in this submission supports a favorable benefit-risk profile of CZP for the treatment of pJIA patients at ages of 2 years of age and older at the proposed subcutaneous weight-tiered dosing regimen: *10 kg (22 lbs) to less than 20 kg (44 lbs):* 100 mg initially and at Weeks 2 and 4, followed by 50 mg every other week; *20 kg (44 lbs) to less than 40 kg (88 lbs):* 200 mg initially and at Weeks 2 and 4, followed by 100 mg every other week; *Greater than or equal to 40 kg (88 lbs):* 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week. The safety of CZP in JIA with active polyarthritis was consistent with the known safety of CZP in RA and offers an acceptable risk for the therapeutic benefits. Approval of CZP will provide an additional treatment option for pJIA in the US. Therefore, we recommend approval of CZP for active pJIA in pediatric patients 2 years of age and older. In addition, the submission of Study RA0043 and Study RA0138 provides the assessment consistent with the post-marketing requirement 2563-1; we recommend the PMR be considered fulfilled.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Juvenile Idiopathic Arthritis (JIA) refers to multiple subtypes of inflammatory arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age. • The prevalence of JIA in developed countries has been reported to be	PJIA is a serious disabling form of juvenile inflammatory arthritis with significant impact on quality of life for patients and families.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>between 16 and 150/100,000 children.
• Polyarticular juvenile idiopathic arthritis (pJIA), one subtype of juvenile idiopathic arthritis, is a serious inflammatory arthritis in children, defined by the presence of ≥ 5 inflammatory joints with onset prior to age 16 years and a minimum duration of 6 weeks.
• Extraarticular manifestations, such as uveitis, may be present.
• PJIA is the form of JIA most similar to adult rheumatoid arthritis (RA) in clinical manifestations as well as response to therapy.</td><td></td></tr>
<tr><td>Current Treatment Options</td><td>• Recommendations for treatment are based on Expert Consensus Treatment Guidelines, and treatment is determined based on active disease manifestations.
• Approved treatments include some NSAIDs; corticosteroids (oral, parenteral, and intra-articular); conventional DMARDs such as sulfasalazine and methotrexate; biologic DMARDs such as tumor necrosis factor (TNFα) inhibitors, interleukin-6 receptor inhibitors, and abatacept; and targeted synthetic DMARDs (tofacitinib and upadacitinib).</td><td>Although many patients with pJIA may respond to the current treatment options, there are patients who may have contraindications to or continued disease activity despite these available therapies. Therefore, an unmet need remains for additional therapeutic options for this population remains.</td></tr>
<tr><td>Benefit</td><td>• In Study RA0043, 193 patients with juvenile idiopathic arthritis with active polyarthritis age 2 years and older received CZP with 105 participants enrolled on the Original CZP Dose regimen and 88 participants enrolled on the Reduced CZP Dose regimen.
<table>
<tr><th>Weight Range</th><th>Original CZP Dose Regimen</th><th>Reduced CZP Dose Regimen</th></tr>
<tr><td colspan="3">Loading dose (Weeks 0, 2, 4)</td></tr>
<tr><td>10 to <20 kg</td><td>100mg Q2W</td><td>50mg Q2W</td></tr>
<tr><td>20 to <40 kg</td><td>200mg Q2W</td><td>100mg Q2W</td></tr>
<tr><td>≥40 kg</td><td>400mg Q2W</td><td>200mg Q2W</td></tr>
<tr><td colspan="3">Maintenance dose (Weeks 6 [Weeks 8 for Q4W] onwards)</td></tr>
</table></td><td>• Efficacy of CZP in patients with active pJIA ages 2 and older was based on PK-exposure matching and extrapolation of established efficacy of CZP in adults with RA.
• Because PK-matching was confirmed with the Original CZP Dose regimen, this dosage regimen is recommended for approval.
• Descriptive efficacy assessments in Study RA0043 were consistent with improvement with treatment with CZP in pediatric patients with JIA with active polyarthritis.</td></tr>
</table>

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><td>10 to <20 kg</td><td>50mg Q2W</td><td>50mg Q4W</td></tr>
<tr><td>20 to <40 kg</td><td>100mg Q2W</td><td>50mg Q2W</td></tr>
<tr><td>≥40 kg</td><td>200mg Q2W</td><td>100mg Q2W</td></tr>
</table>

The exposures observed in JIA patients with active polyarthritis treated with the Original CZP Dose in Study RA0043 were within the range of exposures seen in adult RA patients in Study RA0138, a multicenter, open-label PK study to evaluate CZP in adults with active RA.
Numerical trends of improvement from baseline were observed for exploratory efficacy endpoints (such as PedACR response) in Study RA0043, providing additional supportive evidence of efficacy.

</td><td></td></tr>
<tr><td>Risk and Risk Management</td><td>

The safety database (N=193) from Study RA0043 is sufficient to provide a risk assessment for CZP in the pJIA population.
In Study RA0043, there were 3 deaths including two due to disseminated TB.
SAEs and AEs in the Infections and Infestations SOC were the most frequently reported.

The most common serious infection was pneumonia.
Opportunistic infections included esophageal candidiasis, disseminated TB, TB, fungal pneumonia, and varicella.

The most frequently reported SAEs (other than pneumonia) included anemia, JIA, pregnancy, pyrexia, sepsis, vomiting, varicella, and inflammatory bowel disease.
AEs leading to discontinuation were singular by preferred term, except for 2 cases of Crohn's disease and 2 cases of pregnancy.
Adverse Events of Special Interest (AESI) that occurred in the study included infections, cytopenia (specifically, anemia [n=3, 1.6%]), and

</td><td>

The overall safety profile of CZP in the pJIA population was generally consistent with the safety observed with CZP in adult RA, and the known safety profile of other TNFα inhibitors in pJIA. There were no new safety signals.

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</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	injection reactions (hypersensitivity) (n=29, 15.0%). • In general, the types and numbers of adverse events were similar across both dose regimens and across weight categories. • There were no new safety signals.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		x	Observer reported outcome (ObsRO)	8.1
		x	Clinician reported outcome (ClinRO)	8.1
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	x	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

The classification system historically used to characterize arthritis in children and adolescents used the nomenclature of Juvenile Rheumatoid Arthritis (JRA), as defined by the American College of Rheumatology (ACR). This classification system distinguished categories of disease into pauciarticular, polyarticular, and systemic disease (Brewer 1997). The more detailed classification system proposed by the International League of Associations for Rheumatology (ILAR) in 1997 and revised in 2001, is the currently accepted classification system used to characterize arthritis in children and adolescents (Petty 2001). In this system, JIA is broadly defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age, where other diagnoses have been excluded. As summarized in Table 1, the ILAR classification system divides JIA into 7 different clinical subtypes based on the presence of clinical features in the first 6 months of disease.

Table 1. ILAR Classification of JIA Subtypes

Category	Diagnostic Criteria
Systemic Arthritis	Fever of at least 2 weeks duration (daily for at least 3 days) and arthritis in ≥1 joint, plus one or more of the following: 1. Erythematous rash 2. Generalized lymphadenopathy 3. Hepatomegaly and/or splenomegaly 4. Serositis Exclusions: a, b, c, d
Oligoarthritis (persistent or extended)	Arthritis affecting ≤4 joints during the first 6 months of disease There are 2 subcategories: 1. Persistent: affecting no more than 4 joints throughout the disease course 2. Extended: affecting more than 4 joints after the first 6 months of disease Exclusions: a, b, c, d, e
Polyarthritis, Rheumatoid Factor (-)	Arthritis affecting ≥5 joints during the first 6 months of disease; test for RF is negative Exclusions: a, b, c, d, e
Polyarthritis, Rheumatoid Factor (+)	Arthritis affecting ≥5 joints during the first 6 months of disease; ≥ 2 tests for RF at least 3 months apart during the first 6 months of disease is positive Exclusions: a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative Exclusions: b, c, d, e

Enthesitis related arthritis (ERA)	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain** 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative Exclusions: a, d, e
Unclassified arthritis	Arthritis that fulfills criteria in no category or in 2 or more of the above categories

Exclusions: a) Psoriasis or a history of psoriasis in the patient or first-degree relative; b) Arthritis in an HLA-B27 positive male beginning after the sixth birthday; c) Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease or acute anterior uveitis or a history of one of these disorders in a first-degree relative; d) the presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart; and e) the presence of systemic JIA in the patient.
*JIA is arthritis of unknown etiology that begins before the sixteenth birthday and persists for at least 6 weeks.
**Inflammatory lumbosacral pain is defined as lumbosacral pain at rest with morning stiffness that improves with movement.
Abbreviation: RF=rheumatoid factor
Source: Petty RE, Southwood TR, Manners P, et al., 2004, International League of Associations for Rheumatology classification of juvenile idiopathic arthritis, second revision, Edmonton, 2001, *J Rheumatol*, 31:390-2.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) is a childhood-onset inflammatory arthritis affecting ≥5 joints during the first 6 months of disease and encompasses the RF+ polyarthritis and RF- polyarthritis subtypes of the ILAR classification for JIA described in Table 1 (Petty 2001; Oberle 2014; Feger 2019). Differences in classification criteria complicate epidemiologic studies. However, the prevalence of JIA in developed countries has been reported to be between 16 and 150/100,000 children, corresponding to an estimated prevalence in the United States of approximately 300,000 children (Ravelli 2007; Espinosa 2012). Among patients with JIA, pJIA accounts for approximately 13-35% of cases (Ravelli 2007; Oberle 2014).

PJIA occurs more frequently in females than males (Ravelli 2007; Oberle 2014). There is a bimodal distribution in the age of onset with a peak between ages 2 and 5 years and a second peak between 10 and 14 years. In children under 10 years of age, the disease often begins with an oligoarthritis course, affecting one or two joints, and then progresses to involve five or more joints. Older children may have a more rapid onset. The laboratory findings are notable for the presence of antinuclear antibodies typically in younger children, whereas a rheumatoid factor is more often present in older children, particularly females. Extraarticular manifestations, such as uveitis, can also be present. Without appropriate treatment, pJIA can lead to significant life-long disability starting in childhood.

The CZP clinical development program evaluated CZP in a JIA patient population with active polyarthritis encompassing the following ILAR subgroups: rheumatoid factor (RF) positive polyarticular JIA, RF negative polyarticular JIA, extended oligoarticular JIA, juvenile psoriatic arthritis, and enthesitis-related arthritis. Because the program included JIA patients with active polyarticular involvement not limited to the polyarticular subgroup by the ILAR classification for

this program and in this review, the term "JIA with active polyarthritis" is used to refer to the study population evaluated. Polyarticular course JIA (pcJIA) has been used to identify the indicated population in recent labeling for some products (e.g., tofacitinib) that are supported by a clinical efficacy study in patients with JIA with active polyarthritis, not limited to polyarticular juvenile idiopathic arthritis subgroup, whereas polyarticular JIA (pJIA) has been used to describe the indicated population most similar to adult RA for which extrapolation of efficacy is supported.

2.2. Analysis of Current Treatment Options

The classes of therapies for treatment of JIA include non-steroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular glucocorticoids, conventional/non-biologic disease modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, and targeted synthetic DMARDs. Table 2 lists the approved biologic and non-biologic DMARDs for pJIA, polyarticular course JIA, or JRA; it also includes leflunomide and infliximab, which are not approved for these conditions but are recommended in the current treatment guidelines. Table 2 does not include nonsteroidal anti-inflammatory drugs (NSAIDs) such as celecoxib, naproxen, meloxicam, and naproxen/esomeprazole or glucocorticoids that are also approved for the treatment of JIA and JRA.

Table 2. FDA-Approved Treatments for Polyarticular Juvenile Arthritis†

Product Name	Relevant Indication	Year of Approval for First Indication/ Juvenile Arthritis Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Sulfasalazine	JRA	1950/2000	Children ≥ 6 years: Initial therapy: 40-60 mg/kg/day, divided into 3 to 6 doses Maintenance: 30 mg/kg/day in 4 divided doses	Approval based on submission of 19 published studies	• Leukopenia • Elevated liver enzymes • Gastrointestinal symptoms • Hypersensitivity reactions
Methotrexate	JRA	1953/1993	Starting dose 10 mg/m^2 once weekly; Experience with doses up to 30 mg/m^2/wk	Improvement in PhGA or patient composite over PBO	Similar to safety profile in adults with RA
Abatacept	pJIA	2005/2008	Children ≥ 2 years: IV formulation <75 kg 10 mg/kg at wks 0, 2, and 4, then q4w	RW study with fewer flares (IV); OL	Similar to safety profile in adults

			≥75 kg 750 mg at wks 0, 2, and 4, then q 4w Children ≥2 years: SC formulation 10 kg to <25 kg: 50 mg qw 25 kg to <50 kg: 87.5 mg qw ≥50 kg: 125 mg qw	PK-extrapolation (SC)	
Adalimumab	pJIA	2002/2008	Children ≥2years: 10 to <15 kg: 10 mg SC q2w 15 to <30 kg:20 mg SC q2w ≥30 kg: 40 mg SC q2w	RW study with fewer flares vs PBO	Infections, hypersensitivity, and ↑CPK
Etanercept	pJIA	1998/1999	Children ≥2 years: <63 kg: 0.8 mg/kg SC qw ≥63 kg: 50 mg SC qw	RW study with fewer flares vs PBO	Similar to safety profile in adults
IV Golimumab	pJIA	2009/2020	Children ≥2 years: IV formulation 80mg/m^2 at wks 0, 2, and 4, then q8w	OL, single-arm PK, safety, and exploratory efficacy study; PK extrapolation	Similar to safety profile in adults
Tocilizumab	pJIA	2010/2013	Children ≥2 years: IV formulation ≥2 years of age: <30 kg: 10mg/kg q2w ≥30 kg: 8 mg/kg q2w SC formulation <30kg: 162 mg q3w ≥30kg: 162 mg q2w	IV: RW study with fewer flares compared to PBO SC: PK extrapolation	Similar to safety profile in adults
Tofacitinib	Polyarticular course JIA*	2012/2020	Children ≥2 years: 10 to <20 kg: 3.2 mg (3.2 mL oral solution) BID 20 to <40 kg: 4 mg (4 mL oral solution) BID ≥40 kg: 5 mg (one 5 mg tablet or 5 mL oral solution) BID	RW study with fewer flares vs PBO	Similar to safety profile in adults

Upadacitinib	pJIA	2019/2024	Children ≥2 years: 10 to <20 kg: 3 mg (3 mL oral solution) BID 20 to <30 kg: 4 mg (4 mL oral solution) BID ≥30 kg: 6 mg (6 mL oral solution) BID or 15 mg (one 15 mg tablet) QD	OL, PK, safety, and tolerability study; PK extrapolation	Similar to safety profile in adults
Sarilumab	pJIA	2016/2024	PFS SC formulation ≥63 kg: 200 mg q2w	OL, dose-finding study with secondary PD, efficacy, safety; PK extrapolation	Similar to safety profile in adults
Other Treatments‡					
Infliximab	NA	1998/NA		Failed randomized, double-blind, efficacy study	• Infection • Infusion reactions • Immunogenicity
Leflunomide	NA	1998/NA		Failed double-blind, active-controlled study	• Abdominal pain, nausea, vomiting • Elevated liver enzymes

Abbreviations: BID=twice daily; CPK=phosphokinase; DB=double-blind; IV=intravenous; JRA=Juvenile Rheumatoid Arthritis; NA=not applicable; PBO=placebo; PC=placebo-controlled; PD=pharmacodynamic; PFS=prefilled syringe; PhGA=Physician Global Assessment; pJIA=polyarticular juvenile idiopathic arthritis; PK=pharmacokinetic; Q2W=every other week; QW=every week; Q4W=every four weeks; Q8W=every eight weeks; QD=once daily; R=randomized; RW=randomized withdrawal; SC=subcutaneous; WKs= weeks

† FDA-approved treatments for Polyarticular juvenile arthritis includes products indicated for treatment of juvenile rheumatoid arthritis (JRA), polyarticular juvenile idiopathic arthritis (pJIA), or polyarticular-course juvenile idiopathic arthritis (pcJIA).

*The efficacy information that supported approval of tofacitinib came from a RWD study in 225 JIA patients with active polyarthritis. 143 of these patients had a diagnosis in an ILAR subgroup of pJIA (i.e., rheumatoid factor (RF) positive polyarticular JIA or RF negative polyarticular JIA). The study also included patients with extended oligoarticular JIA, juvenile psoriatic arthritis, enthesitis-related arthritis of patients, and systemic JIA without systemic manifestations.

‡ Not FDA-approved for polyarticular juvenile arthritis (JRA, pJIA, pcJIA)

Source: Clinical Reviewer

Patients with pJIA are generally managed via expert, consensus-driven, treatment regimens recommended for JIA and polyarthritis that were updated in 2019 by the American College of Rheumatology/ Arthritis Foundation (Ringold 2019). Initial treatment regimens are based on level of disease activity. The treatment regimens are similar to those used to treat adults with RA. Initial therapy with a DMARD is strongly recommended over NSAID monotherapy in all patients; use of methotrexate is conditionally recommended over leflunomide or sulfasalazine as alternatives. For patients with risk factors for disease severity and potentially a more refractory disease course, initial therapy with a DMARD is conditionally recommended over a biologic, although initial biologic therapy may be considered in certain circumstances. For patients with moderate/high disease activity on DMARD monotherapy, adding a biologic to the original DMARD is conditionally recommended over changing to second DMARD or changing to triple DMARD therapy. If a patient has moderate/high disease activity while on TNFα inhibitor (TNFi +/- DMARD), switching to a non-TNFi biologic is conditionally recommended over switching to a second TNFi. Short courses of oral corticosteroids may be used during initiation or escalation of therapy in patients with high or moderate activity. NSAIDs and intra-articular corticosteroid injections may be used as adjunctive therapies. Physical therapy to maintain range of motion, to prevent deformities, and to minimize loss of function of affected joints is an integral component of the treatment and management of children with pJIA.

Although these 2019 guidelines included TNFα inhibitors, tocilizumab, abatacept, and rituximab, they did not include therapies with JAK inhibition as a mechanism of action nor sarilumab because of a lack of published studies in pediatrics at the time.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Certolizumab pegol (CZP) first became available in Switzerland on January 3, 2008, for patients with Crohn's disease (CD). The US Food and Drug Administration (FDA or the Agency) has since approved CZP for multiple indications as described in Table 3.

Table 3. FDA Approval History of Certolizumab Pegol (CZP)

Indication	Date of Approval	Approved Dose
Reducing the signs and symptoms of **Crohn's disease (CD)** and maintaining clinical response in adult patients with moderately to severely active disease with inadequate response to conventional therapy *BLA 125160*	April 22, 2008	400mg initially and at Weeks 2 and 4, followed by 400mg Q4W
Treatment of adult patients with moderately to severely active **rheumatoid arthritis (RA)** (b) (4) *BLA 125160/supplement 80*	May 13, 2009	400mg initially and at Weeks 2 and 4, followed by 200mg Q2W. For maintenance dosing, 400mg Q4W can be considered.
Treatment of adult patients with active **psoriatic arthritis (PsA)** *BLA 125160/supplement 213*	September 27, 2013	400mg initially and at Weeks 2 and 4, followed by 200mg Q2W. For maintenance dosing, 400mg Q4W can be considered.
Treatment of adults with active **ankylosing spondylitis (AS)** *BLA 125160/supplement 215*	October 17, 2013	400mg initially and at Weeks 2 and 4, followed by 200mg Q2W or 400mg Q4W
Treatment of adults with moderate-to-severe **plaque psoriasis (PsO)** who are candidates for systemic therapy or phototherapy *BLA 125160/supplement 283*	May 29, 2013	400mg Q2W. For some patients (body weight ≤ 90kg), 400mg initially and at Weeks 2 and 4, followed by 200mg Q2W may be considered.
Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation *BLA 125160/supplement 237*	March 28, 2019	400mg initially and at Weeks 2 and 4, followed by 200mg Q2W or 400mg Q4W

Abbreviations: Q2W=every other week; Q4W=every 4 weeks
Source: Clinical Reviewer

3.2. Summary of Presubmission/Submission Regulatory Activity

(b) (4). However, after CZP was approved for CD and RA, the applications were merged under BLA 125160 in June 2009 per the Agency's request. Efficacy supplement 275 (S-275) was submitted to BLA 125160 on May 27, 2016, at which time the Applicant sought the indication of treatment of (b) (4) active polyarticular (b) (4) juvenile idiopathic arthritis in pediatric patients 2 years to less than 18 years of age. The submission was intended to fulfill the Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) that was issued at the time of approval of CZP for RA. PMR 2563-1 required an "assessment of pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance, and immunogenicity in the pediatric population ≥2 years to <17 years with polyarticular JIA." The Agency agreed that a PK-matching approach to extrapolate efficacy from the adult RA population to the pJIA population was acceptable to fulfill the PMR. Thus, S-275 was supported by Study RA0043, an open-label study with the primary objective of evaluating

the PK and safety (including immunogenicity) of CZP administered subcutaneously in children and adolescents with moderately-to-severely active JIA with polyarthritis.

The original protocol for study RA0043 (submitted in October 2009) proposed a fixed dose CZP regimen based on 3 body weight categories, consisting of 3 loading doses at Weeks 0, 2, and 4, followed by a maintenance dose. This dosing regimen was referred to as the Original CZP Dose. In June 2013, an interim population PK analysis of the first 34 pediatric study participants suggested that the observed CZP plasma concentrations were at the upper end of the distribution of the adult range. The protocol was amended to reduce the loading and maintenance dose by 50% for ongoing and newly enrolled participants (referred to as the Reduced CZP Dose). At the time of original submission of S-275, 163 pediatric participants had been enrolled into Study RA0043 with 78 participants enrolled on the Original CZP Dose and 85 participants enrolled on the Reduced CZP Dose. The proposed dose for approval was the Reduced CZP Dose.

During the review, the Clinical Pharmacology team concluded that the Original CZP Dose would be the more appropriate dose for patients with pJIA as long as there was adequate safety justification. In terms of matching with adult PK exposures, the Clinical Pharmacology team noted that the 10 to <20 kg and 20 to <40 kg weight categories adequately matched the Original CZP Dose. It was the highest weight category (≥40 kg) that matched better with the Reduced CZP Dose. However, taking into account higher anti-drug antibody (ADA) formation with the Reduced CZP Dose concentration, the Clinical Pharmacology team favored the Original CZP Dose to support the efficacy extrapolation. The safety profile for both dosing regimens was consistent with the known experience with CZP in adult RA, TNFα inhibitors in general, and other bDMARDs in pJIA, although interpretation of the safety data was limited by the study design (open-label, uncontrolled) and small number of patients and different exposures on each dosing regimen.

However, all conclusions from S-275 were compromised by the inspection findings of the Office of Study Integrity and Surveillance (OSIS). Based on the findings from an on-site inspection at (b) (4) where the measurement of CZP plasma concentrations and ADA were conducted, the inspection report concluded that PK data presented in Study RA0043 should not be accepted for Agency review, and the Clinical Pharmacology team agreed with these conclusions (see details in the Clinical Pharmacology review of the original submission, DARRTS date February 22, 2017). S-275 received a Complete Response (CR) with the following issues listed in the CR letter (DARRTS submission date March 22, 2017, summarized below). Accordingly, it was also determined that the Applicant did not fulfill PREA PMR 2563-1.

1. Based upon inspection findings at (b) (4) the reliability of the submitted PK data was in question. The inspection identified issues with the following:
    a. (b) (4)

b. [redacted] (b) (4)

c.

d.

Given that the clinical development program was based upon PK extrapolation, the submitted data were inadequate to determine the efficacy, safety, and dosing of CZP for patients with pJIA.

To address these clinical pharmacology issues, the Agency advised UCB, Inc. to provide data to support the efficacy, safety, and dosing of CZP in pediatric patients with pJIA ages 2 to 17 years. The Applicant could conduct an efficacy, safety, and dose-ranging trial. Alternatively, if the Applicant proposed a program based on PK extrapolation, they would need to address the inspection issues, including, but not limited to the following measures to ensure the reliability of the PK data:

- Develop a new validated analytical method or improve the current analytical method for measurement of plasma CZP concentrations in accordance with guidance recommendations.
- Once the validated analytical method is available, address the stability issue discovered during the review cycle. Long-term stability samples should be compared to freshly made calibrators and/or freshly made quality controls.
- Re-analyze PK samples from Study RA0043 and representative adult study(ies). If data from RA0043 are not able to be utilized because of stability or unreliability, then conduct a new trial to evaluate PK parameters, dosing, and immunogenicity of CZP in pJIA.

2. The descriptions of the drug product manufacturing controls for syringe filling were not sufficient to ensure that the released syringes contain sufficient fill volume and do not include an inappropriate overfill. [redacted] (b) (4)

To address these product quality issues, the Agency advised UCB, Inc. to provide justification for the acceptable fill volume ranges based on tolerance for overfill as indicated by the clinical data. Also, appropriate controls should be implemented to ensure the release of only units filled within the approved limits and should be clearly described in the application. Lastly, the Applicant needed to submit complete batch records for lots specified in the CR letter.

A summary of interactions between the Applicant and the Agency preceding the original submission of S-275 was provided in the Clinical review of the original submission (DARRTS submission date March 2, 2017). Table 4 below details the interactions following the Complete Response, including several PREA PMR deferral extension requests.

Table 4. Overview of Regulatory Interactions for pJIA Development Program

Date	Type of Meeting/ Interaction	FDA Recommendations and Key Discussion Topics
November 15, 2017 *Meeting Minutes (DARRTS December 8, 2017)*	Type B, End-of-Review Meeting (Post-Action)	• Agency reiterated ways to address deficiencies outlined in the CR letter. • Agency provided clarification on validating a new bioanalytical method to reanalyze PK samples from children with pJIA and adults with RA. A validated ADA bioanalytical method is also preferred. • Responses were provided to several detailed questions regarding the new bioanalytical method. • Agency noted that UCB's plans to justify the syringe fill volume range were generally reasonable for the upper limit but insufficient for the lower limit. Additionally, the Agency requested more information for the review of the proposed (b) (4) (b) (4) control strategy. • Because of the lack of precedent in utilizing the PK extrapolation approach and Agency experience with failed pJIA studies (despite matching PK exposures with adults), the Agency noted that an Advisory Committee or other public discussion may be necessary.
October 9, 2018 *Meeting Minutes (DARRTS October 23, 2018)*	Type C Meeting	• Agency noted the complexities and concerns in proceeding with a PK-based extrapolation approach for CZP for the treatment of pJIA in order to fulfill PREA: o New ECL method o Adult RA study (Study RA0055) only evaluated one dosing regimen and, thus, would not provide a sufficiently wide exposure range to establish a exposure-response relationship in adults, utilizing the new bioanalytical method. o Considerations to characterize the dose-response relationship in adults by utilizing other adult studies o Delayed timeline for completion, i.e., 6 years for long-term stability data • Agency recommended that UCB, Inc. consider an efficacy, safety, and dose-ranging trial in pediatric patients with pJIA. To increase the feasibility of this trial, Bayesian approaches that borrow information from adult efficacy trials may be utilized. An active-controlled study may also address the Applicant's concerns regarding feasibility of an efficacy study with the current therapeutic landscape. o No additional dose-ranging would be necessary, as Study RA0043 could be considered the dose-ranging study.

November 5, 2019	PREA PMR Deferral Extension	• UCB, Inc. requested an extension on October 2, 2019, for submission of the final report for the study intended to fulfill the PREA PMR. UCB, Inc. planned to conduct a new study (Study JA0006) to assess the efficacy, safety, and PK of CZP in pJIA within the Bayesian framework. However, minimal details were provided in this deferral extension request, other than UCB, Inc. intends to discuss the new study in Q4 2019. • Deferral extension was **denied**, as there was insufficient information to determine whether the extension was appropriate. • The Division advised UCB, Inc. to submit additional details of the planned Study JA0006 with a new deferral extension request or as a separate meeting request prior to the deferral extension request. • On December 20, 2019, the Applicant received a Letter of Non-Compliance with PREA.
January 21, 2020 *Meeting Minutes (DARRTS February7, 2020)*	Type B, PMR/PMC Meeting	• UCB, Inc. proposed a new study (Study JA0006), a multicenter, randomized, double-blind, placebo-controlled, parallel group study to assess efficacy, safety, and PK of CZP in JIA with polyarthritis with a plan to enroll 40 pediatric patients on the Original CZP Dose. The Applicant proposed utilizing a Bayesian analysis method. • The Agency informed the Applicant that, since the time of last interaction, a workshop (with University of Maryland CERSI), entitled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis" occurred (October 2, 2019) and was a collaborative event between the Agency, academia, and industry. The workshop concluded that a PK-matching approach for pJIA programs is feasible for TNFα inhibitors. A similar drug effect in pJIA is expected if the pediatric drug systemic exposure is within the therapeutic range in adult RA patients. • Therefore, the Agency advised UCB, Inc. that the PK-matching approach is still feasible for their pJIA program based on these scientific discussions. • UCB, Inc. noted that the RA reference adult PK samples from Study RA0055 have been destroyed and are no longer available. The Applicant proposed to use adult PK samples from other indications (AS and nr-axSpA). • The Agency indicated that pediatric PK extrapolation from adults with RA to children with pJIA is preferred because of the disease similarity between RA and pJIA. The Agency suggested that the Applicant conduct a single dose study in RA adults with a well-characterized PK profile. • The Agency also encouraged the Applicant to retest ADA from pediatric and adult studies using the same new bioanalytical assay in order to interpret the PK data. • The Agency recommended that, if the Applicant proceeds with the PK-matching approach, they should enroll additional subjects at the Original CZP Dose into Study RA0043. UCB, Inc. proposed enrolling an additional 30 participants so that a total of 108 pediatric participants will be exposed to the Original CZP dose, and the Agency agreed this may be reasonable in the absence of new safety signals.

		• Lastly, the Agency confirmed that the pJIA public workshop facilitated relevant public discussion; therefore, further public discussion in the form of an AC meeting may not be needed.
March 16, 2020	PREA PMR Deferral Extension	• UCB, Inc. confirmed that they will utilize the PK-matching approach to fulfill PREA. • To accommodate for the destroyed adult RA samples, the Applicant will conduct a new study (Study RA0138) in 30 adult participants with RA. • In addition, the Applicant will enroll approximately 30 additional patients to study RA0043 at the Original CZP Dose. • In order to accommodate the above along with reanalysis of existing PK samples from RA0043 (which require additional long-term stability [approximately 1.5 years]), the Applicant requested a new timeline for protocol submission and study completion. • Deferral extension was **granted** with planned resubmission of S-275 by September 2022.
October 8, 2021	PREA PMR Deferral Extension	• Due to the COVID-19 global pandemic, the Applicant noted there was a delay in implementation of Study RA0138. • Also, delays from the pandemic, the unavailability of vaccines for children under 12 years of age, and the evolving treatment landscape in pJIA (including a treat-to-target approach and the availability of oral agents) slowed and complicated enrollment of additional participants to Study RA0043. • The Applicant requested another extension for Study RA0138 completion and for interim analysis of Study RA0043. These data would be utilized to complete the PK/PD report to support the PK-matching approach. Deferral extension was **granted** for study completion with planned resubmission of S-275 by March 2024.
February 3, 2023	Type C Meeting, Written Responses	• The Agency provided advice on the planned safety analyses, PK modeling approach and comparison of PK across pJIA and adult RA populations, and immunogenicity analyses. • The Agency agreed that the totality of data to select a dose for pJIA appeared reasonable in principle. However, the suitability of the data would be a review issue. • The Agency also provided advice on the testing strategy of the (b) (4) as well as strategy to support (b) (4) months shelf life for the (b) (4) and validation approach.
December 21, 2023 Clarification January 30, 2024	Type C Meeting, Written Responses	• The Agency generally agreed with the proposed content and format of the sBLA resubmission, noting that the adequacy of the data to support the proposed indication would be a review issue. • Additional recommendations were provided regarding the fill volume control strategy, a component of the (b) (4) (b) (4) used to ensure the achievement of sufficient (b) (4) in every PFS for the delivery of the intended dose. • The Agency reiterated safety analyses recommendations from the previous meeting. • The Agency also confirmed that any new safety data from clinical studies, off-label use, or literature should be included

		at the time of resubmission. Additional safety updates after resubmission could be submitted by Day 90. • UCB, Inc. requested further clarification of the Day 90 update. The Agency stated that the plan for the safety update (from cut-off date March 6, 2023, to December 19, 2023) appeared reasonable and should also include any literature updates. AE and ADaM datasets should also be included.
March 14, 2024	S-275 Resubmission	S-275 was resubmitted, classified as a Class 2 resubmission, and determined the resubmission constitutes a complete response that addresses all deficiencies in the Complete Response letter.
June 27, 2024	S-275 Update	• The Applicant informed the Agency that they will not (b) (4) not due to concerns over safety and efficacy. • The Applicant provided the following key considerations: ○ (b) (4) ○ • The Applicant states that the 200 mg PFS (approved for adults) will cover pediatric patients with pJIA ≥40 kg. • In response to an Agency IR dated July 9, 2024, that followed this update, the Applicant confirmed that the lyophilized vial presentation will be adequate for administration of lower doses. The PFS has no graduated markings for lower dose administration.

Abbreviations: AC=Advisory Committee; ADA=anti-drug antibody; AE=adverse event; AS=ankylosing spondylitis; CR=complete response; CZP=certolizumab pegol; ECL=electrochemiluminexcence; JIA=juvenile idiopathic arthritis; nr-AxSpA=nonradiographic axial spondyloarthritis; PFS=prefilled syringe; pJIA=polyarticular juvenile idiopathic arthritis; PK=pharmacokinetic; PMC=postmarketing commitment; PMR=postmarketing requirement; PREA=Pediatric Research Equity Act; RA=rheumatoid arthritis
Source: Clinical Reviewer

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Review of the data did not identify any data integrity issues. Therefore, an OSI audit was not requested.

Office of Study Integrity and Surveillance (OSIS) inspection was requested for Study RA0043 for this resubmission review. OSIS determined that an inspection is not able to be completed for the site. OSIS conducted a remote regulatory assessment (RRA) for the site in (b) (4). OSIS also concluded that data from the reviewed studies were reliable. Refer to the OSIS review by Dr. James Lumalcuri dated May 8, 2024, for more details.

4.2. Product Quality

Product quality-related CR deficiencies were identified during the review cycle of the original submission of S-275. See the Product Quality review of the original submission (dated March 1, 2017) and the CR letter. With this resubmission, the Applicant responded to the deficiencies noted in the CR letter with information to support the (b) (4) (b) (4) is a sufficient approach to resolve the quality-related deficiencies in the CR letter. The Office of Product Quality Assessment (OPQA) III, thus, recommends approval of S-275. See the OPQA III review, dated July 30, 2024.

See Section 6.3.2 for a discussion of the availability of the (b) (4) (b) (4) for patients with pJIA.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

There are no changes to the approved devices. The Division of Medication Error Prevention and Analysis 1 (DMEPA1) requested the Applicant submit a comprehensive use-related risk analysis (URRA) to support the [redacted] is not necessary and there are no Human Factors (HF) recommendations.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

At the time of the original submission of S-275, the pharmacology-toxicology (P/T) team reviewed the study reports for (1) a 52-week subcutaneous toxicology study with CZP in juvenile cynomolgus monkey followed by a 52-week recovery and (2) a 6-week toxicology study with a rodent surrogate pegylated anti-TNF mAb in juvenile rats followed by a 4-week recovery. See the P/T review for full details (DARRTS submission date February 16, 2017). The P/T recommended approval of S-275 from the nonclinical perspective. As no CR deficiencies were related to P/T issues, no new nonclinical data were submitted with this resubmission.

6 Clinical Pharmacology

6.1. Executive Summary

Certolizumab pegol (Cimzia, CZP) is a humanized antibody antigen-binding fragment (Fab'), with specificity for human tumor necrosis factor alpha (TNFα), which is conjugated to 2 linked 20 kDa polyethylene glycol (PEG) chains via a maleimide linker. In this application, the Applicant is seeking approval for an indication for treatment of (b) (4) active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older. This submission serves as the Complete Response/Resubmission for the supplemental Biologics License Application (BLA) 125160/275. Study RA0043 was initiated in subjects with JIA with active polyarthritis pursuant to post-marketing requirement (PMR) 2563-1 and a supplemental BLA was first submitted on May 27, 2016, which included an initial Week 24 interim clinical study report (CSR) with PK and anti-CZP antibody (ADAb) data generated to support the efficacy extrapolation concept in pJIA. A Complete Response Letter (CRL) was issued on March 22, 2017, mainly due to findings related to the PK and ADAb assays following an inspection at (b) (4) In the CRL, the following issues were identified:

- (b) (4)

Following the Type B meeting discussions held on January 21, 2020, between the Applicant and the Agency, pharmacokinetic (PK) matching between RA adults and pJIA was agreed as an acceptable path forward for the pJIA CZP program. At the meeting, agreement was reached on the following steps:

- Improved and validated PK and ADA assays would be used to address the points detailed in the CRL
- Additional clinical data would be collected through the addition of 30 study participants to RA0043 following the original dosing in the study. Where sample volumes allowed, samples from previous participants in RA0043 would be tested in the new PK and ADA assays
- Study RA0138 would be performed in adult RA study participants to provide PK and ADA samples for testing in the new assays to use as reference in support of the extrapolation.

The development program in this pJIA resubmission consists of 2 clinical studies: an ongoing, open-label study to assess the PK, immunogenicity, safety, and efficacy of CZP in pediatric study participants with moderately-to-severely active JIA with active polyarthritis (Study RA0043); and a completed, 24-week, open-label study to assess the PK, safety, and tolerability of CZP in adults with active RA receiving the approved dose (Study RA0138).

The PK and anti-CZP antibody (ADAb) data in Studies RA0043 and RA0138 were analyzed with newly developed electrochemiluminescence immunoassay (ECLIA) methods that align with current regulatory guidances. The collective PK data from Studies RA0043 and RA0138 formed the basis of the population PK analysis and the PK analysis of observed data to support the PK-bridging approach for extrapolation of efficacy in pJIA subjects in this resubmission.

The Clinical Pharmacology review team has determined that the proposed weight-tiered dosing strategy provides comparable CZP exposure in pediatric patients 2 to less than 18 years of age with JIA with active polyarthritis to that with the currently approved dosing regimen in adult RA patients, supporting the extrapolation of efficacy from adult RA patients.

Recommendations

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of BLA 125160/S-275 and finds the application acceptable to support approval from a clinical pharmacology perspective. The Division Signatory agrees with this assessment and recommendations.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

An original supplemental BLA (BLA 125160/S-275) was submitted in May 2016, and a CRL was issued by the Agency in March 2017. This submission serves as the resubmission of the sBLA 125160/S-275 using newly generated data. Two studies have been conducted to support an approach of PK-matching and efficacy extrapolation in the pJIA indication:

- Study RA0043: an open-label study to assess the PK, safety, and efficacy of CZP in children and adolescents with moderately-to-severely active JIA with active polyarthritis
- Study RA0138: an open-label study to evaluate the PK of CZP in adults with active rheumatoid arthritis (RA) to provide PK data from a reference adult population with RA using the same bioanalytical assay that is in line with current regulatory guidelines

The collective PK data from Studies RA0043 and RA0138 formed the basis of the population PK analysis and the PK analysis of observed data to support the PK-bridging approach for extrapolation of efficacy in pJIA subjects in this resubmission. The major findings for this Clinical Pharmacology review are as follows:

- The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all dosage levels tested for the adult populations, which is in line with the $t_{1/2}$ estimated for the pediatric population in Study RA0043 based on the population PK analysis.
- With the proposed weight tiered dosing regimen, the observed pre-dose (trough) concentrations are generally comparable between adults with RA and pediatric patients with JIA with active polyarthritis. In pediatric patients with JIA with active polyarthritis,

the mean trough plasma concentrations at Week 12 (steady-state) were 31.8 µg/mL, 27.9 µg/mL, and 36.8 µg/mL for patients weighing 10 to <20 kg, 20 to <40 kg, and ≥40 kg, respectively (**Table 6**).

- In pediatric patients with JIA with active polyarthritis, mean peak plasma concentrations, measured 1 week following loading dose and maintenance dose were 58.8 µg/ml and 41.8 µg/ml, respectively. Similar peak plasma concentrations were observed across the different body weight groups (10 kg to less than 20 kg, 20 kg to less than 40 kg, and greater than or equal to 40 kg).
- Population pharmacokinetic analyses showed that plasma concentrations in pediatric patients with JIA with active polyarthritis following original CZP dose are in the same range as observed in adult patients with RA receiving a 200 mg Q2W maintenance dose.
- Similar to the adult indications, body weight and anti-certolizumab antibodies titers affected certolizumab pegol pharmacokinetics, where higher body weights and presence of anti-certolizumab antibodies was associated with lower exposures. There was no observed impact from the use of concomitant methotrexate on certolizumab pegol plasma concentrations.

Overall, for PK-matching and efficacy extrapolation, the clinical pharmacology results support the selection of the Original CZP Dose for the pJIA population as follows:

- *Body weight group 10kg to <20kg:* loading doses of CZP 100mg at Weeks 0, 2, and 4, followed by CZP 50mg Q2W Week 6 onwards.
- *Body weight group 20kg to <40kg:* loading doses of CZP 200mg at Weeks 0, 2, and 4, followed by CZP 100mg Q2W Week 6 onwards.
- *Body weight group ≥40kg:* loading doses of CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg Q2W Week 6 onwards.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing for patients with pJIA is as follows:

- *10 kg (22 lbs) to less than 20 kg (44 lbs):* 100 mg initially and at Weeks 2 and 4, followed by 50 mg every other week
- *20 kg (44 lbs) to less than 40 kg (88 lbs):* 200 mg initially and at Weeks 2 and 4, followed by 100 mg every other week
- *Greater than or equal to 40 kg (88 lbs):* 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week

Therapeutic Individualization

Population PK analyses showed that body weight was a significant covariate impacting the apparent clearance and volume of distribution of CZP. Therefore, the recommended dosing in patients with pJIA is based on body weight categories as shown above.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Two studies have been conducted to support an approach of PK-matching and efficacy extrapolation in the pJIA indication:

- **Study RA0043:** an open-label study to assess the PK, safety, and efficacy of CZP in children and adolescents with moderately-to-severely active JIA with active polyarthritis
- **Study RA0138:** an open-label study to evaluate the PK of CZP in adults with active rheumatoid arthritis (RA) to provide PK data from a reference adult population with RA using the same bioanalytical assay that is in line with current regulatory guidelines

Study RA0043: Study RA0043 has been conducted to fulfill the pediatric PMR requirement 2563-1 issued by FDA following the approval of CZP in adult RA, to "assess the pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance and immunogenicity in the pediatric population ≥2 years to 17 years with polyarticular JIA". A PK-matching approach to extrapolate efficacy from the adult RA population to the pJIA population was previously agreed with FDA to fulfill the PMR. Study RA0043 was designed as an open-label study with the primary objective of evaluating the PK and safety, including the immunogenicity, of CZP administered subcutaneously in children and adolescents with moderately-to-severely active pJIA. Study RA0043 was initiated in 2012 and an initial sBLA was submitted on May 27, 2016, with PK and ADAb data generated with legacy enzyme-linked immunosorbent assay methods, to support the efficacy extrapolation concept in pJIA. A CRL was issued by FDA on March 22, 2017, due to issues identified at the PK testing facility (b) (4) and outstanding product quality issues. In this resubmission, the Applicant has generated new PK and ADAb data from previously and newly enrolled study participants in RA0043, using electrochemiluminescence immunoassay (ECLIA) methods that meet current regulatory guidances.

The primary objective of Study RA0043 was to assess PK and safety, including immunogenicity, of CZP in the pJIA population. PK data from Studies RA0043 and RA0138 allowed a PK matching approach to support the extrapolation of efficacy from the adult RA population to the pJIA population. There were several major changes to the study design for Study RA0043 in terms of dosing regimens. At the onset, study participants were to receive a fixed-dose CZP regimen based on body weight categories (10 to <20kg, 20kg to <40kg, or ≥40kg), consisting of 3 loading doses at Weeks 0, 2, and 4 followed by a maintenance dose (**Table 5**), referred to as Original CZP Dose. An interim population PK analysis of the first 34 pediatric study participants suggested that while observed CZP plasma concentrations remained in the adult range, they were at the upper end of the distribution. The Applicant reduced the loading and maintenance doses by 50% for ongoing and newly enrolled participants (referred to as the Reduced CZP Dose, **Table 5**). The CZP dose was not reduced due to any safety findings during the study. Following the CRL of March 2017,

and further interaction with the Agency in January 2020, it was agreed to enroll an additional 30 study participants on the Original CZP Dose.

Table 5. Dosing Regimens in Study RA0043

Body Weight Category	Original CZP Dose	Reduced CZP Dose
RA0043		
Loading dose (Weeks 0, 2, 4)		
10kg to <20kg	100mg Q2W	50mg Q2W
≥20kg to <40kg	200mg Q2W	100mg Q2W
≥40kg	400mg Q2W	200mg Q2W
Maintenance dose (starting at Week 6)		
10kg to <20kg	50mg Q2W	50mg Q4W
≥20kg to <40kg	100mg Q2W	50mg Q2W
≥40kg	200mg Q2W	100mg Q2W

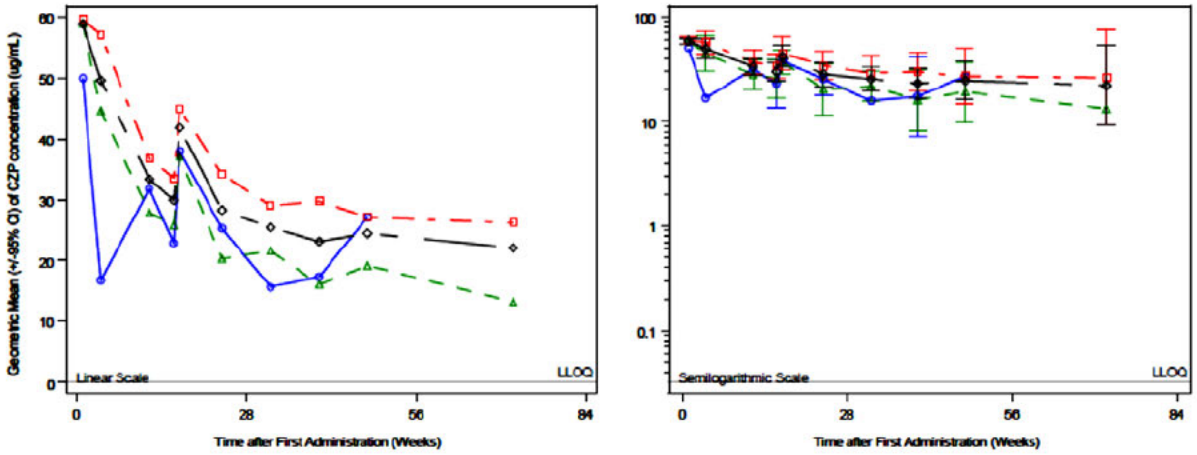
CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks

Source: Clinical overview, Table 1-2.

PK Results: Peak CZP plasma concentrations after the first loading dose of CZP at Week 0 and after the maintenance dose at Week 16 were sampled at 1 week post-dose (i.e., Week 1 and Week 17). Geometric mean CZP plasma concentrations (95% confidence interval [CI]) of 58.8268 (55.6579, 62.1762) µg/mL at Week 1 and 41.7981 (33.1584, 52.6889) µg/mL at Week 17 were observed for the Original CZP Dose. The plasma concentrations of CZP appeared to have reached steady state at Week 12 in both the Original CZP Dose and the Reduced CZP Dose and were overall sustained after Week 24. For the Original CZP Dose, a geometric mean trough CZP plasma concentrations (95% CI) of 33.3820 (27.3627, 40.7255) µg/mL and 28.2614 (21.7867, 36.6603) ug/mL were observed at Week 12 and Week 24, respectively.

PK results by Baseline weight group:
Geometric mean CZP plasma concentrations were lower for the Reduced CZP Dose compared with the Original CZP Dose for all Baseline weight groups, as expected. For the Original CZP Dose, the CZP plasma concentrations were generally numerically higher for the ≥40 kg Baseline weight group compared with the 2 lower Baseline weight groups (10 kg to <20 kg and 20 kg to <40 kg), which had similarly observed CZP plasma concentrations (**Figure 1.** and **Table 6**). The overlapping 95% CIs of the concentrations for the baseline weight groups do not appear to indicate any meaningful differences across baseline weight groups in the Original CZP Dose.

Figure 1. Geometric Mean (95% CI) CZP Plasma Concentrations (µg/mL) in RA0043 for Entire Treatment Period by Baseline Weight – Original CZP Dose



Baseline Weight Group: 10 - < 20 kg (N=7), Week/n: 0/1, 1/4, 4/4, 12/4, 16/5, 17/4, 24/5, 32/3, 40/5, 48/2
Baseline Weight Group: 20 - < 40 kg (N=34), Week/n: 0/5, 1/31, 4/28, 12/26, 16/29, 17/23, 24/21, 32/17, 40/18, 48/11, 72/4
Baseline Weight Group: ≥ 40 kg (N=64), Week/n: 0/22, 1/54, 4/52, 12/50, 16/49, 17/43, 24/40, 32/32, 40/32, 48/24, 72/12
Total (N=105), Week/n: 0/28, 1/89, 4/84, 12/80, 16/83, 17/70, 24/66, 32/52, 40/55, 48/37, 72/16

Source: Summary of Clinical Pharmacology Studies, Figure 2-2.

Table 6. CZP Plasma Concentration (µg/mL) for Entire Treatment Period by Baseline Weight Group and Visit - Original CZP Dose

Baseline Weight Group: 10 - <20kg (N=7)

Visit	n	Geometric Mean	95% CI	Geometric CV (%)	Median	Minimum	Maximum
Visit 2 (Week 0)	1					0.160	0.160
Visit 3 (Week 1)	4	49.9450		17.7	49.8000	41.000	61.500
Visit 5 (Week 4)	4	16.7678		479.4	36.3000	1.170	51.300
Visit 7 (Week 12)	4	31.7912		34.3	34.5500	20.600	42.600
Visit 8 (Week 16)	5	22.9060	(13.3380, 39.3374)	45.7	21.5000	15.300	42.500
Visit 8 (Week 17)	4	37.9904		39.6	31.6500	30.900	67.300
Visit 10 (Week 24)	5	25.2239	(17.6543, 36.0390)	29.3	24.3000	19.100	39.600
Visit 11 (Week 32)	3	15.6828		39.6	19.0000	10.100	20.100
Visit 12 (Week 40)	5	17.3215	(7.1598, 41.9053)	81.2	23.1000	4.870	25.800
Visit 13 (Week 48)	2	27.1474		35.3	27.9500	21.300	34.600
Early Disc/EOT	1	42.6000			42.6000	42.600	42.600

Baseline Weight Group: 20 - <40kg (N=34)

Visit	n	Geometric Mean	95% CI	Geometric CV (%)	Median	Minimum	Maximum
Visit 2 (Week 0)	5					0.160	0.160
Visit 3 (Week 1)	31	58.8550	(53.9885, 64.1601)	23.9	59.3000	36.800	91.100
Visit 5 (Week 4)	28	44.5679	(30.0821, 66.0292)	134.0	54.8500	0.371	100.000
Visit 7 (Week 12)	26	27.8839	(20.0466, 38.7852)	97.4	34.2500	0.960	64.100
Visit 8 (Week 16)	29	25.7752	(16.9024, 39.3058)	155.7	34.3000	0.160	73.200
Visit 8 (Week 17)	23	37.0800	(28.0085, 49.0896)	72.3	43.5000	3.510	78.500
Visit 10 (Week 24)	21	20.2888	(11.5774, 35.5550)	188.9	28.1000	0.160	59.900
Visit 11 (Week 32)	17	21.6235	(15.6217, 29.9310)	70.1	25.9000	4.070	59.300
Visit 12 (Week 40)	18	16.0733	(8.1707, 31.6191)	231.7	24.2000	0.160	57.300
Visit 13 (Week 48)	11	19.1703	(9.9319, 37.0019)	126.8	23.2000	1.390	60.000
Visit 16 (Week 72)	4	13.2224		498.8	23.2500	0.960	59.100
Early Disc/EOT	2	9.5898		90.9	11.0700	5.540	16.600
Final (12-Week SFU)	1					0.160	0.160

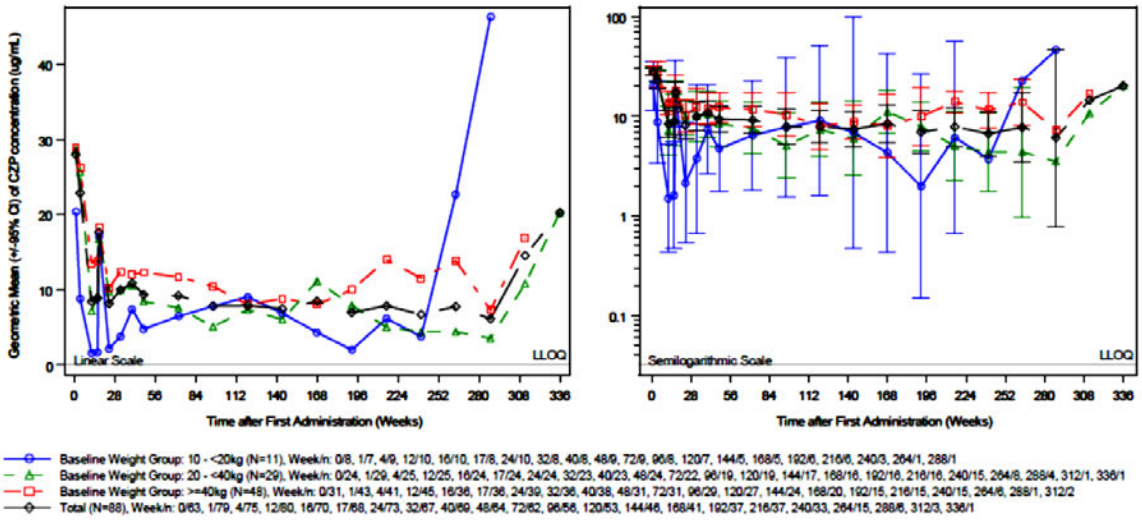
Baseline Weight Group: >=40kg (N=64)

Visit	n	Geometric Mean	95% CI	Geometric CV (%)	Median	Minimum	Maximum
Visit 2 (Week 0)	22					0.160	0.960
Visit 3 (Week 1)	54	59.5280	(55.1188, 64.2899)	28.8	57.7000	21.200	115.000
Visit 5 (Week 4)	52	57.0651	(44.3973, 73.3475)	112.0	63.6500	0.160	123.000
Visit 7 (Week 12)	50	36.8003	(28.0505, 48.2795)	122.1	44.9000	0.160	266.000
Visit 8 (Week 16)	49	33.5680	(25.7883, 43.6945)	115.0	44.4000	0.160	70.400
Visit 8 (Week 17)	43	44.9613	(31.6372, 63.8968)	163.9	64.3000	0.160	119.000
Visit 10 (Week 24)	40	34.1142	(24.8459, 46.8397)	129.3	40.8000	0.160	73.700
Visit 11 (Week 32)	32	29.0049	(19.7619, 42.5711)	145.0	35.9000	0.160	65.500
Visit 12 (Week 40)	32	29.7161	(19.6167, 45.0151)	166.4	42.5000	0.160	105.000
Visit 13 (Week 48)	24	27.1180	(14.9512, 49.1859)	251.0	41.2500	0.160	91.400
Visit 16 (Week 72)	12	26.1765	(9.2393, 74.1620)	369.9	42.3000	0.160	68.800
Early Disc/EOT	7	26.2831	(14.9955, 46.0673)	66.7	31.8000	9.470	51.300
Final (12-Week SFU)	4					0.160	17.100

Source: Study RA0043 Clinical Study Report, Table 4.1.2.

For the Reduced CZP Dose, in general, the CZP plasma concentrations were numerically higher for the ≥40 kg Baseline weight group compared with the 2 lower Baseline weight groups (10 kg to <20 kg and 20 kg to <40 kg) (**Figure 2**). There was less consistency across the 2 lower weight groups based on the 95% CIs, which may have been due to the Q4W dosing in the 10 kg to <20 kg baseline weight group vs the Q2W dosing in the 20 kg to <40 kg baseline weight group.

Figure 2. Geometric Mean (95% CI) CZP Plasma Concentrations (µg/mL) in RA0043 for Entire Treatment Period by Baseline Weight – Reduced CZP Dose

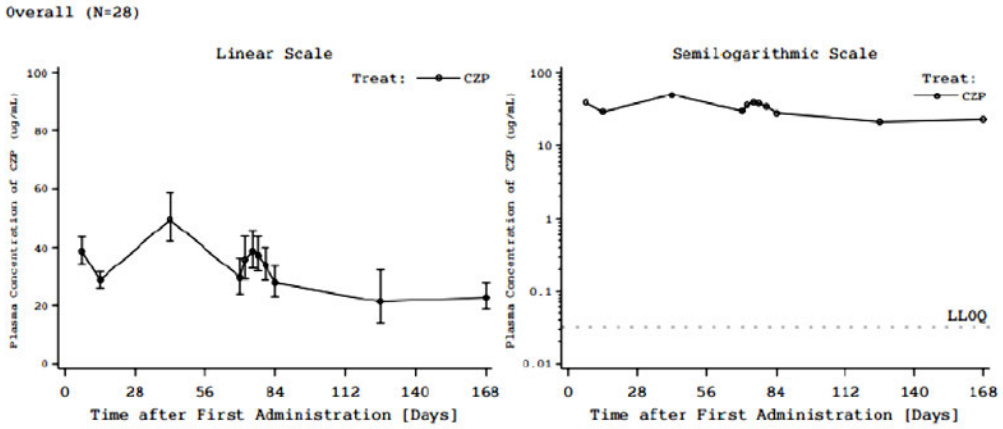


Source: Summary of Clinical Pharmacology Studies, Figure 2-3.

Study RA0138: Central to the application of the PK matching approach is the existence of a reference systemic exposure (PK) range which is associated with therapeutic benefit of the drug in the adult RA population. A separate adult study (Study RA0138) was conducted to generate ECLIA-based PK data in adults with RA, in agreement with FDA. Study RA0138 provides a supporting adult reference PK dataset for PK matching in the pJIA program. Study RA0138 was a multicenter, open-label, phase 1B study to assess the PK, safety, and tolerability of CZP in adults with active RA. In this 24-week study, study participants who were naïve to CZP, had an inadequate response or intolerance to at least 1 DMARD, and had not previously failed to respond to any TNFi, received CZP in subcutaneous loading doses of 400mg at Weeks 0, 2, and 4, followed by treatment with 200mg Q2W (approved adult RA dosing regimen), and the final dose taking place at Week 24. As agreed with FDA in the Type B meeting of January 2020, this study was conducted to generate ECLIA-based PK data in adults with RA to provide a supporting adult reference PK dataset for PK-matching in the pJIA program. A total of 33 study participants were enrolled and received CZP.

PK Results: A plot of the geometric mean CZP plasma concentrations is shown in **Figure 3**. At Week 10, geometric mean CZP concentration (95% CI) was 29.6138 (24.0687, 36.4364) µg/mL and at Week 12 and Week 24, geometric mean CZP concentration (95% CI) was 27.9509 (23.2353, 33.6235) µg/mL and 22.9050 (18.8160, 27.8826) µg/mL, respectively. From Week 10 onwards, plasma concentrations remained stable throughout the study (**Figure 3**). When comparing the summary PK profile by visit for study participants with and without methotrexate (MTX) use, no clear differences were observed and overlapping CIs were observed. The PK profile of CZP in adult study participants with active RA receiving the approved dose was consistent with previous adult RA studies.

Figure 3. Geometric Mean CZP Plasma Concentrations (µg/mL) in Study RA0138



Source: Summary of Clinical Pharmacology Studies, Figure 2-6.

Population PK modeling analysis and simulations:

To support the PK-matching approach for extrapolation of efficacy in pJIA for the proposed dosing regimen, the Applicant conducted a population PK analysis integrating data available from Studies RA0043 and RA0138. For the population PK analysis, the PK and ADAb data measured with the ECLIA PK and ADAb assays, together with the RA0138 PK and ADAb data measured with the same ECLIA PK and ADAb assays, was used to guide the simulations for the dose selection for pJIA that most closely matches the adult exposure range. A population PK analysis by means of a nonlinear mixed-effect modeling (NONMEM) approach was performed for the pediatric pJIA population based on Study RA0043 data alone (i.e., pediatric CZP PK model), the adult RA population based on Study RA0138 data alone (i.e., adult CZP PK model), and then a combined model including both adult CZP PK and pediatric CZP PK data. All 3 final population PK models were able to characterize the PK of CZP in the populations of interest with precise parameter estimates. The combined CZP PK model was used to support the PK-matching approach for extrapolation of efficacy in pJIA for the proposed dosing regimen by means of simulations.

The final combined CZP PK model was a 1-compartment model with first-order absorption and first-order elimination. Inter-individual variability was included on CL/F and V/F. The effect of body weight on CL/F and V/F, ADAb titer on CL/F, and age on patients <18 years on V/F was included in the final model following the covariate analysis. The 3 covariates were included as time varying covariates. CL/F and V/F increased with increasing body weight, leading to lower exposure in heavier patients. However, since body weight-based dosing was used, the difference in exposure between the different body weight groups was small. Apparent clearance increased and CZP exposure decreased with increasing ADAb titer, but ADAb titer values up to the observed median value had a minor impact on CZP exposure. Body weight demonstrated the largest impact on CZP exposure, with a 1.40-fold decrease in median $AUC_{\tau,ss}$ and a 1.33-fold decrease in median $C_{max,ss}$ predicted in a typical patient who is 3 years of age with a body weight of 12 kg, receiving CZP 50mg Q2W, compared with a typical patient who is 3

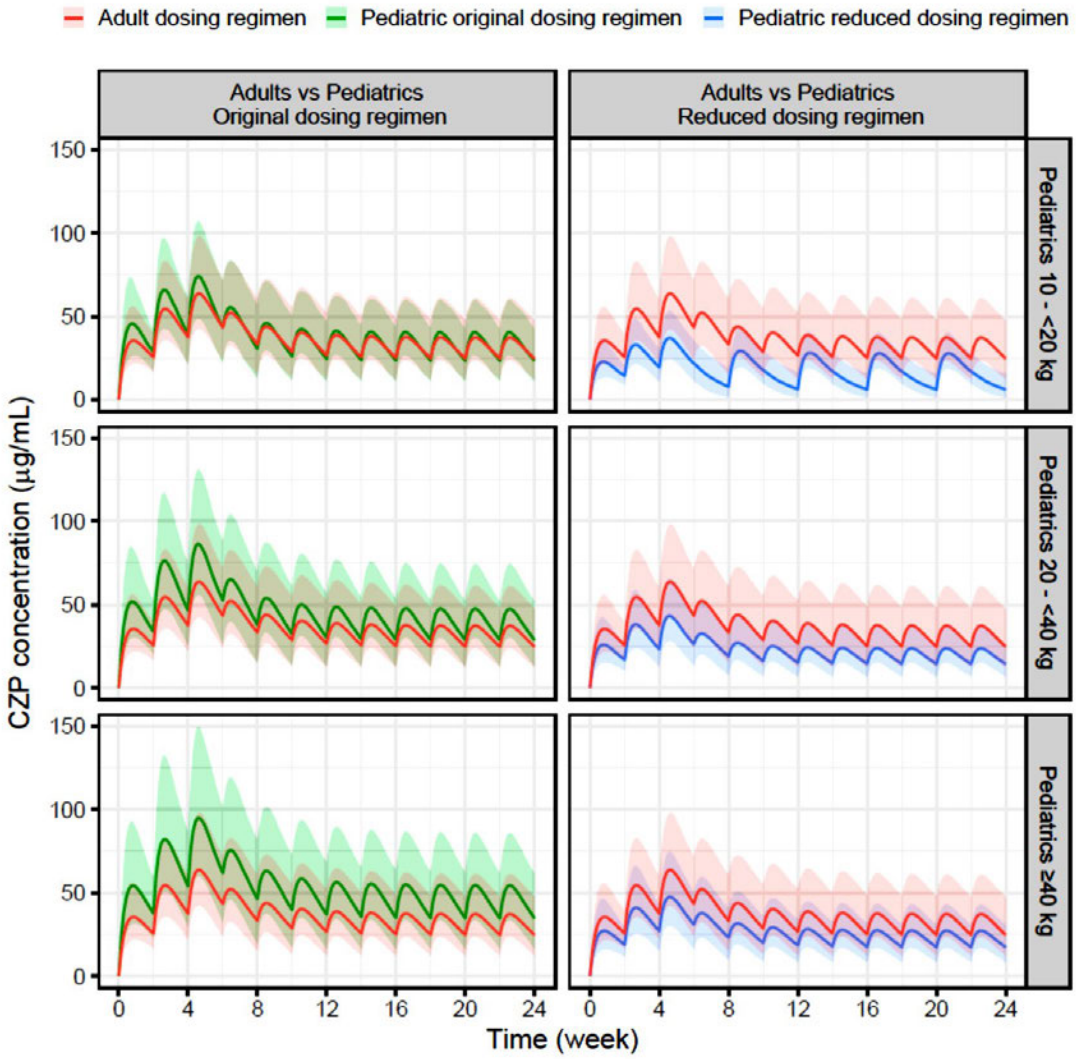
years of age with a body weight of 17 kg, also receiving CZP 50mg Q2W. Similarly, a 1.70-fold decrease in median $AUC_{\tau,ss}$ and a 1.63-fold decrease in median $C_{max,ss}$ were predicted in a typical patient who is 17 years of age with a body weight of 48 kg, receiving CZP 200mg Q2W, compared with a typical patient who is 17 years of age with a body weight of 84 kg, also receiving CZP 200mg Q2W.

PK Simulations: Simulations were performed to compare the CZP exposure in pediatric patients with pJIA with the CZP exposure in adult patients with RA (24 weeks were simulated). The PK profiles of predicted CZP concentrations vs time, using the final combined adult and pediatric CZP PK model, stratified by dosing regimen and pediatric body weight and dosing regimen and pediatric age are shown in

Figure 4 and **Figure 6**, respectively. Boxplots of predicted CZP $AUC_{\tau,ss}$, $C_{av,ss}$, $C_{max,ss}$, and $C_{min,ss}$, using the final combined adult and pediatric CZP PK model, stratified by population and body weight and population and age are presented in **Figure 5** and **Figure 7**, respectively. A summary of predicted percentage of pediatric patients with CZP exposure parameters falling within the 5^{th} and 95^{th} percentiles of the adult exposure metrics, using the final combined adult and pediatric CZP PK model, stratified by dosing regimen and population is presented in **Table 7**.

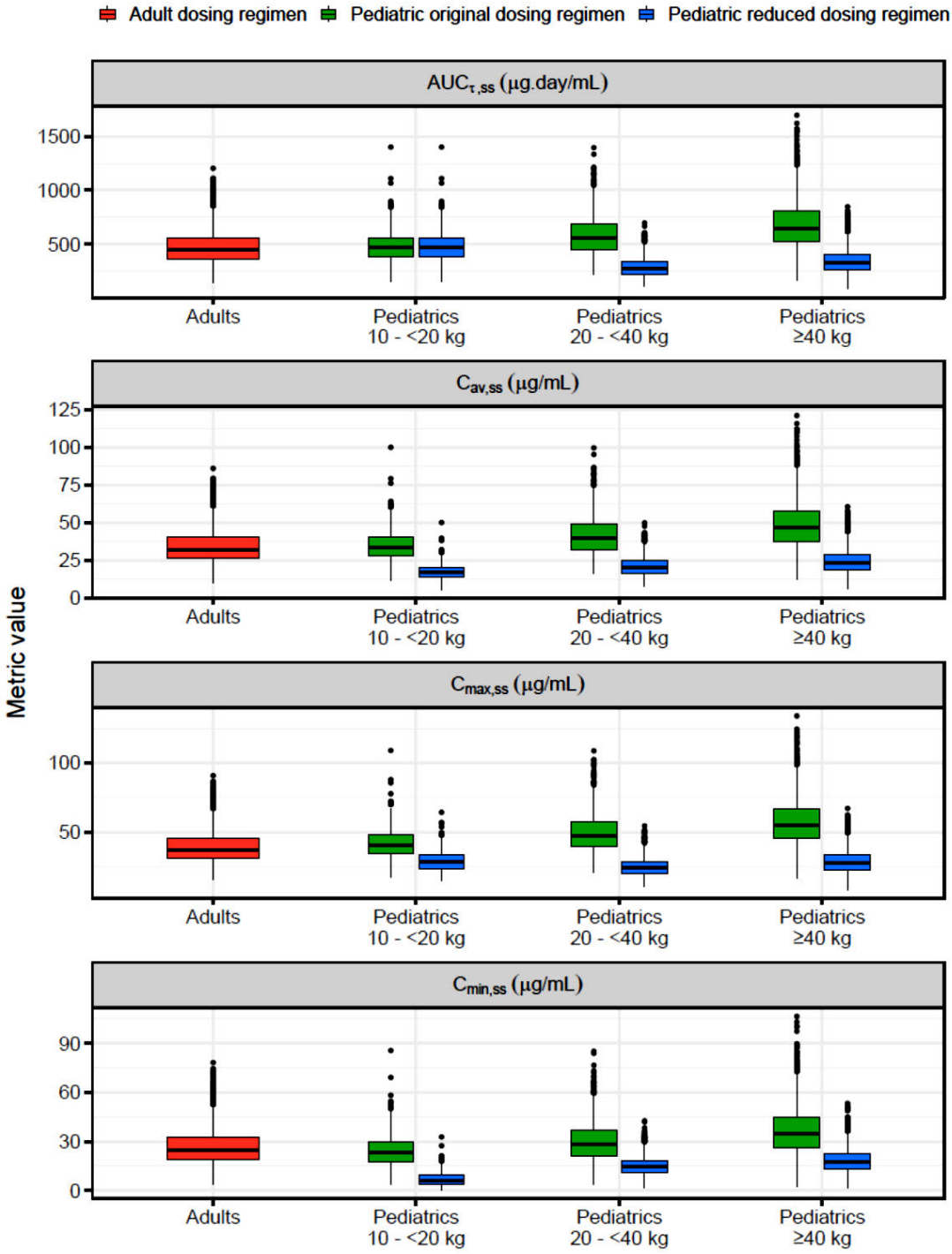
The simulations demonstrated that the Original CZP Dose provided similar exposure between adults and pediatric patients 10 kg to <20 kg and 20 kg to <40 kg, while pediatric patients ≥40 kg showed higher exposures with the Original CZP Dose when compared with the adult reference population, although a substantial overlap was observed. For the Original CZP Dose, the ≥40kg pediatric patients received the same doses as adults. The slightly higher exposure in ≥40kg pediatric patients compared with adults may be explained by lower body weight observed in the pediatric ≥40kg group, compared with the adults. The simulations also showed that the Reduced CZP Dose provided lower exposure compared with adults for all pediatric groups, primarily in the 10 kg to <20 kg and 20 kg to <40 kg groups, and to a lesser extent in the ≥40 kg group, where an overlap in CZP concentrations was observed compared with adults.

Figure 4. Predicted CZP Concentration vs Time, Using the Final Combined Adult and Pediatric CZP PK Model, Stratified by Dosing Regimen and Pediatric Body Weight



Source: Summary of Clinical Pharmacology Studies, Figure 3-5.

Figure 5. Boxplots of Predicted CZP AUCτ,ss, Cav,ss, Cmax,ss, and Cmin,ss, Using the Final Combined Adult and Pediatric CZP PK Model, Stratified by Population and Body Weight

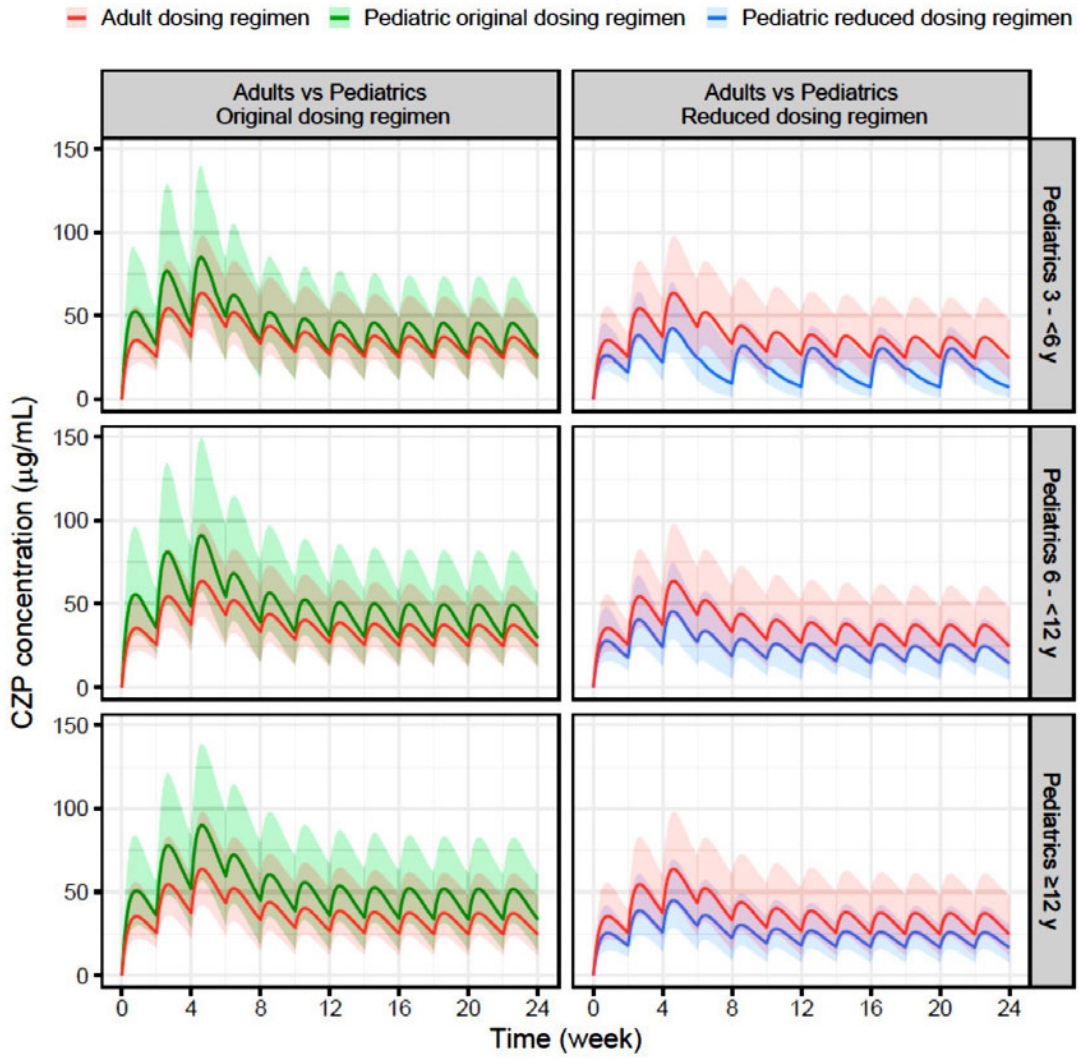


Source: Summary of Clinical Pharmacology Studies, Figure 3-6.

When stratified by dosing regimen and pediatric age (**Figure 6** and **Figure 7**), similar trends to those observed by pediatric body weight when compared with adults were observed, as pediatric age is highly correlated with pediatric body weight. Overall, a substantial overlap in

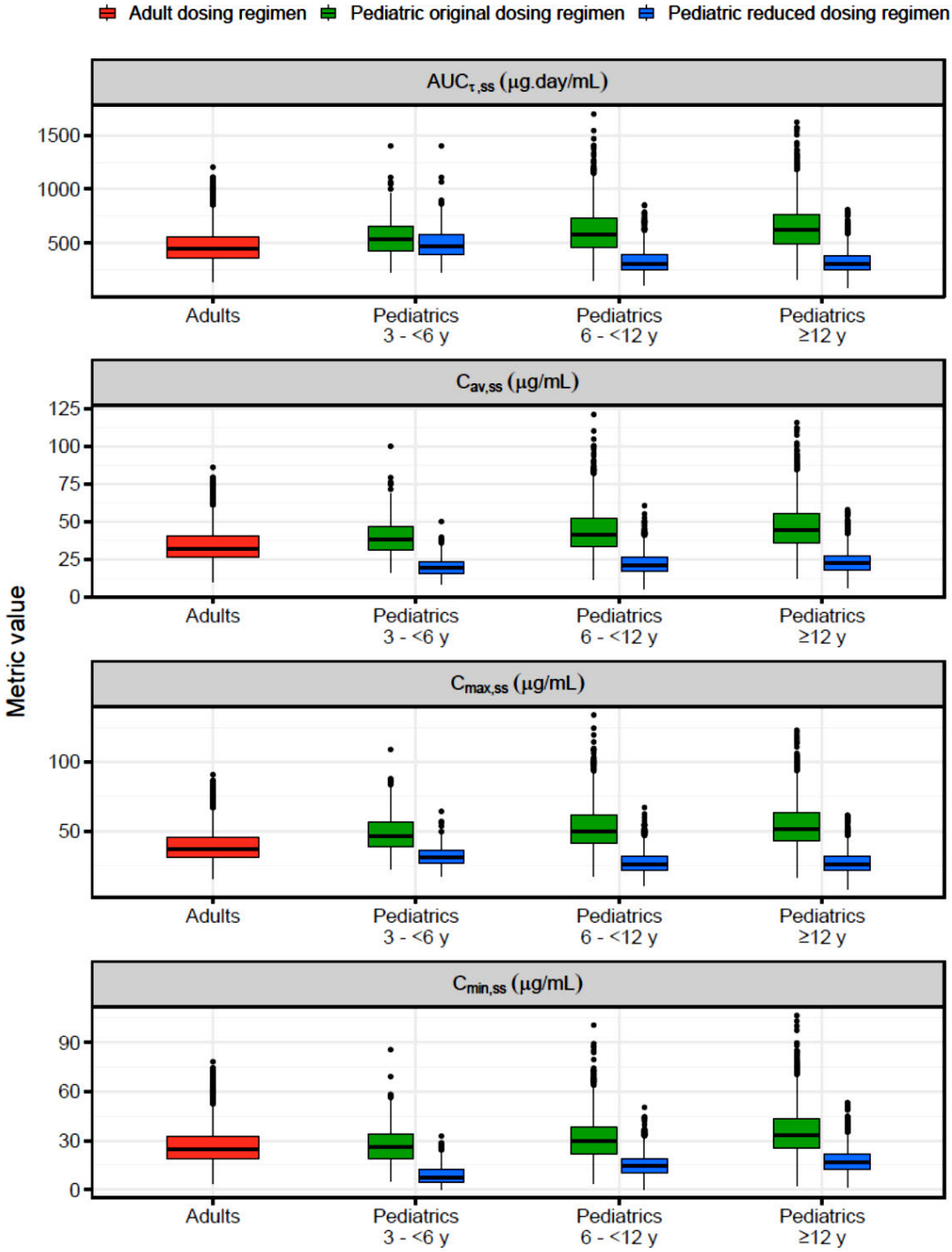
CZP concentrations was observed for the Original CZP Dose with respect to the adult PK profiles. The ≥12 years of age group for pediatric patients showing a trend towards higher exposure compared with adults, which may be explained by the body weight distribution.

Figure 6. Predicted CZP Concentration vs Time, Using the Final Combined Adult and Pediatric CZP PK Model, Stratified by Dosing Regimen and Pediatric Age



Source: Summary of Clinical Pharmacology Studies, Figure 3-7.

Figure 7. Boxplots of Predicted CZP AUCτ,ss, Cav,ss, Cmax,ss, and Cmin,ss, Using the Final Combined Adult and Pediatric CZP PK Model, Stratified by Population and Age



Source: Summary of Clinical Pharmacology Studies, Figure 3-8.

Table 7. Predicted Percentage of Pediatric Patients with CZP $AUC_{T,ss}$, $C_{av,ss}$, $C_{max,ss}$, and $C_{min,ss}$ Falling within 5th to 95th Percentiles of the Adult Exposure Metrics, Using the Final Combined Adult and Pediatric CZP PK Model, Stratified by CZP Dose Group and Population

CZP dose group Population	N	Patients within 5th to 95th percentiles of adult exposure (%)			
		$AUC_{T,ss}$	$C_{av,ss}$	$C_{max,ss}$	$C_{min,ss}$
Original CZP Dose					
Pediatric patients 10kg to <20kg	360	92.8	92.8	94.2	89.7
Pediatric patients 20kg to <40kg	1256	84.5	84.5	79.9	86.9
Pediatric patients ≥40kg	2384	69.5	69.5	64.4	77.0
Pediatric patients 3 years to <6 years	224	85.3	85.3	83.9	87.1
Pediatric patients 6 years to <12 years	1504	78.1	78.1	72.5	82.9
Pediatric patients ≥12 years	2272	74.3	74.3	70.4	79.6
All pediatric patients	4000	76.3	76.3	72.0	81.3
Reduced CZP Dose					
Pediatric patients 10kg to <20kg	360	92.8	30.6	74.4	11.1
Pediatric patients 20kg to <40kg	1256	54.1	54.1	50.6	63.2
Pediatric patients ≥40kg	2384	72.2	72.2	69.8	78.8
Pediatric patients 3 years to <6 years	224	89.7	46.9	88.4	24.1
Pediatric patients 6 years to <12 years	1504	67.4	58.9	61.9	62.0
Pediatric patients ≥12 years	2272	66.9	66.9	63.3	76.0
All pediatric patients	4000	68.4	62.8	64.2	67.8

Source: Summary of Clinical Pharmacology Studies, Table 3-3.

Overall, the simulations demonstrated that the Original CZP Dose yields a substantial overlap in CZP concentrations when compared with the adult RA population, whereas the Reduced CZP Dose demonstrated lower CZP concentration distributions, especially in pediatric patients with a body weight of <40 kg. These results provide support that the PK exposure for the Original CZP Dose in the pediatric pJIA population is more closely aligned with the PK exposure for the adult CZP dose approved in RA and, therefore, support the use of Original CZP Dose for patients with pJIA.

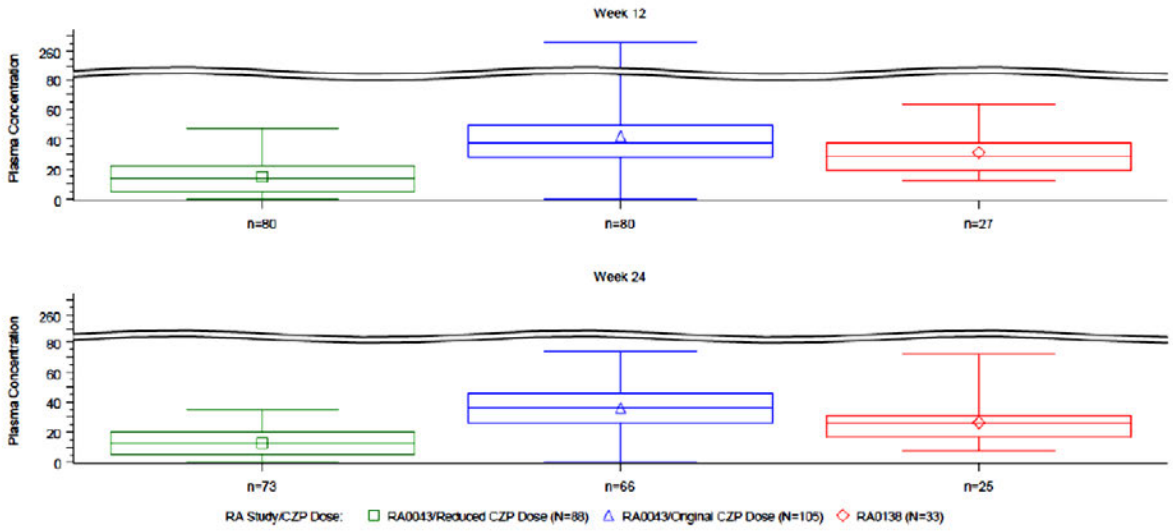
Observed PK data comparison

In addition to the population PK analyses, a comparison of observed data from both studies RA0043 and RA0138 was also performed. Comparisons between RA0043 and RA0138 data for this analysis focused on common time points at the anticipated steady state (Week 12 and Week 24). The dose groups compared were the Original CZP Dose and the Reduced CZP Dose from Study RA0043 and the adult dose from Study RA0138.

Boxplots of the CZP plasma concentrations at Week 12 and Week 24 for RA0043 by CZP dose group and for RA0138 are presented in **Figure 8**. Even though the median CZP plasma concentrations in the adult RA population (red) at Week 12 and Week 24 were between the medians of the Reduced CZP Dose (green) and the Original CZP dose (blue), the median and

quartile CZP plasma concentrations observed in the adult RA population were generally more closely aligned with the RA0043 Original CZP Dose compared with the Reduced CZP Dose.

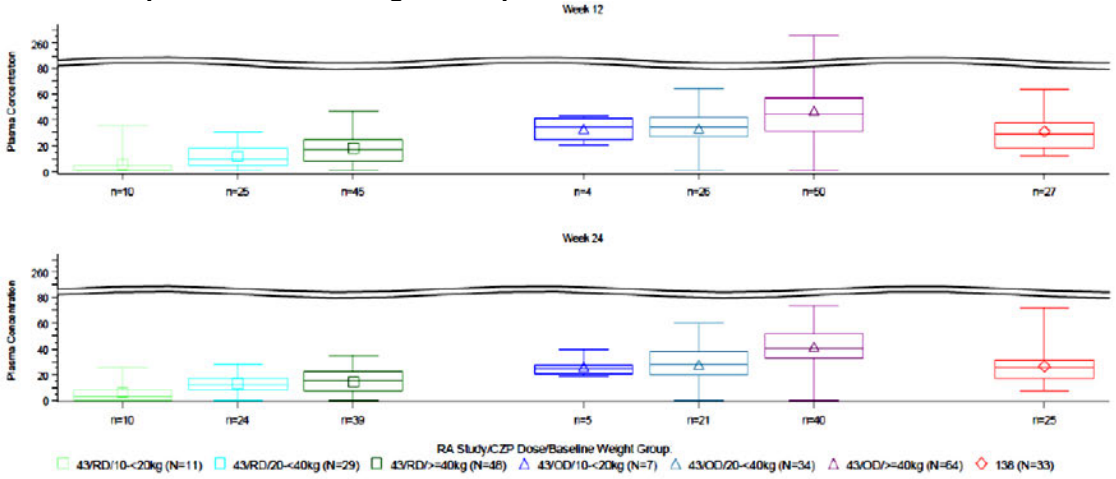
Figure 8. Boxplots of CZP Plasma Concentration (µg/mL) at Week 12 and Week 24 for RA0043 by CZP Dose Group and for RA0138



Source: Summary of Clinical Pharmacology Studies, Figure 3-10.

Boxplots of the CZP plasma concentrations at Week 12 and Week 24 for RA0043 by CZP dose group and Baseline weight group and for RA0138 are presented in **Figure 9**. At Week 12 and Week 24, for the RA0043 Original CZP Dose, median and quartile CZP plasma concentrations for the 2 Baseline weight groups <40 kg were more closely aligned with the adult RA population, compared with the Reduced CZP Dose for which plasma concentrations for the 2 Baseline weight groups <40 kg were noticeably lower than those observed in the adult RA population. For the RA0043 Original CZP Dose, higher plasma concentrations were observed in the ≥40 kg Baseline weight group compared with the adult RA population, with median and quartile CZP plasma concentrations from the Reduced CZP Dose for this weight group more closely aligned with the adult RA population.

Figure 9. Boxplots of CZP Plasma Concentration (µg/mL) at Week 12 and Week 24 for RA0043 by CZP Dose Group and Baseline Weight Group and for RA0138



Source: Summary of Clinical Pharmacology Studies, Figure 3-11.

Overall, the data demonstrated that the observed PK values after use of the Original CZP Dose in the pediatric pJIA population were more closely aligned with the observed PK values for the adult CZP dose approved for RA. Results from the descriptive comparison in the PK analysis of observed data are consistent with the modeling and simulation conclusions and serve as further support for the proposed dosing regimen for the pJIA population.

Immunogenicity

Study RA0043: The prevalence and incidence of ADAb categories by Baseline weight group of the Original CZP Dose and the Reduced CZP Dose up to Week 24 and for the entire Treatment Period are shown in **Table 8**.

For the Original CZP Dose, the prevalence of pretreatment ADAb positivity was 3.3% (3/105 study participants). The incidence of treatment-emergent ADAb positivity (combination of treatment-induced and treatment-boosted ADAb categories) was 88.6% (93/105 study participants) up to Week 24 and was 92.4% (97/105 study participants) for the entire Treatment Period.

For the Reduced CZP Dose, the prevalence of pretreatment ADAb positivity was 2.4% (2/88 study participants). The incidence of treatment-emergent ADAb positivity (combination of treatment-induced and treatment-boosted ADAb categories) was 93.2% (82/88 study participants) up to Week 24 and was 94.3% (83/88 study participants) for the entire Treatment Period.

For the entire Treatment Period, the incidences of treatment-emergent ADAb positivity (combination of treatment-induced and treatment-boosted ADAb categories) ranged from 90.6% to 100% for the Original Dose CZP group and from 90.9% to 96.6% for the Reduced CZP Dose across the 3 Baseline weight groups and thus were considered to be similar; however,

interpretation of these results is limited due to the low numbers of study participants in the 10 to <20kg group (n=7 and n=11 for the Original CZP Dose and the Reduced CZP Dose, respectively).

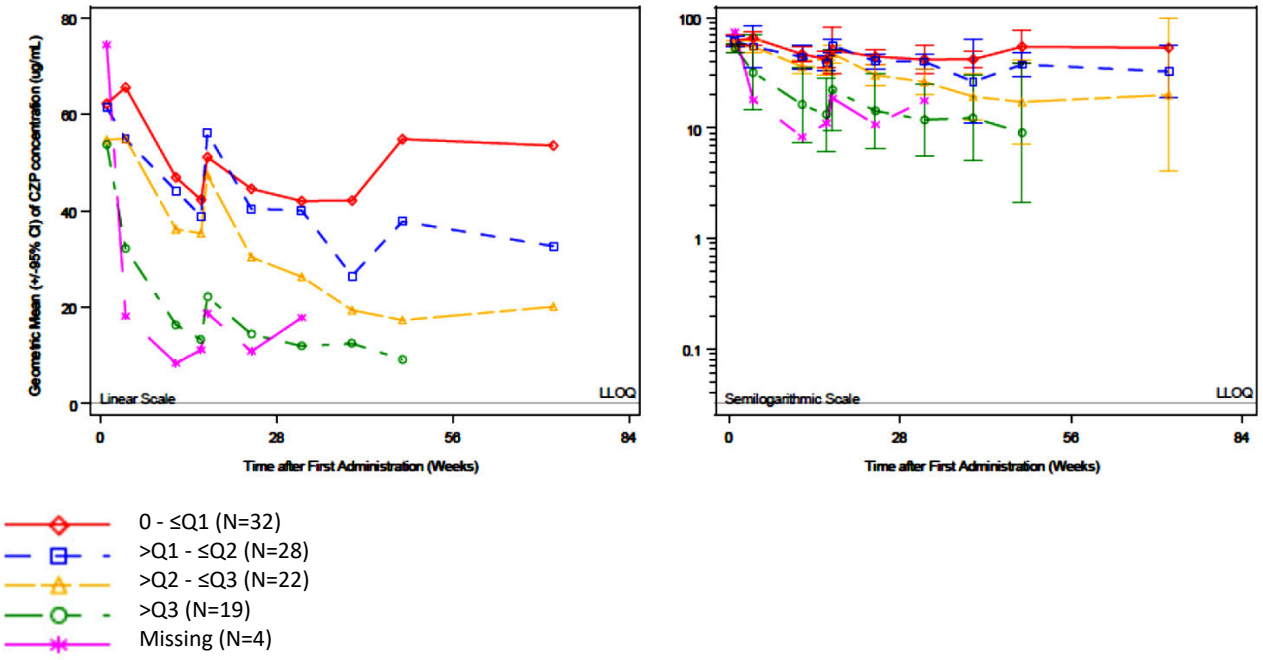
Table 8. Prevalence and Incidence of ADAb Categories by Baseline Weight Group (SS)

	Original CZP Dose				Reduced CZP Dose			
ADAb category	10 to <20kg N=7 n (%)	20 to <40kg N=34 n (%)	≥40kg N=64 n (%)	Total N=105 n (%)	10 to <20kg N=11 n (%)	20 to <40kg N=29 n (%)	≥40kg N=48 n (%)	Total N=88 n (%)
Up to Week 24								
Prevalence of pretreatment ADAb+	0	1 (3.1)	2 (3.7)	3 (3.3)	0	0	2 (4.4)	2 (2.4)
Incidence of treatment-induced ADAb+	7 (100)	31 (91.2)	53 (82.8)	91 (86.7)	10 (90.9)	28 (96.6)	43 (89.6)	81 (92.0)
Incidence of treatment-boosted ADAb+	0	0	2 (3.1)	2 (1.9)	0	0	1 (2.1)	1 (1.1)
Incidence of combined treatment-induced and treatment-boosted ADAb+	7 (100)	31 (91.2)	55 (85.9)	93 (88.6)	10 (90.9)	28 (96.6)	44 (91.7)	82 (93.2)
For entire treatment period								
Prevalence of pretreatment ADAb+	0	1 (3.1)	2 (3.7)	3 (3.3)	0	0	2 (4.4)	2 (2.4)
Incidence of treatment-induced ADAb+	7 (100)	32 (94.1)	56 (87.5)	95 (90.5)	10 (90.9)	28 (96.6)	44 (91.7)	82 (93.2)
Incidence of treatment-boosted ADAb+	0	0	2 (3.1)	2 (1.9)	0	0	1 (2.1)	1 (1.1)
Incidence of combined treatment-induced and treatment-boosted ADAb+	7 (100)	32 (94.1)	58 (90.6)	97 (92.4)	10 (90.9)	28 (96.6)	45 (93.8)	83 (94.3)

Source: Integrated Summary of Immunogenicity, Table 5-6.

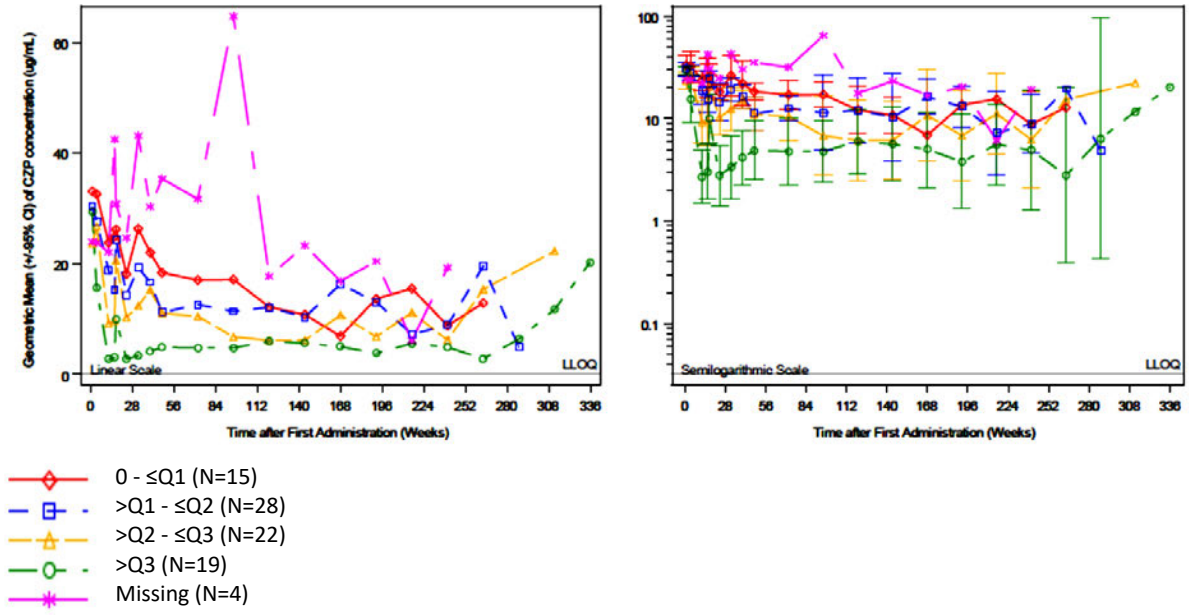
Impact of ADA on PK: For the Original CZP Dose and the Reduced CZP Dose, CZP plasma concentrations appeared to be lower in the pretreatment ADAb negative and treatment emergent-induced ADAb positive group compared with the pretreatment ADAb negative and treatment-emergent ADAb negative group, although the number of study participants in this group is small in both Dose groups (n≤8). Anti-CZP antibody titer classification did appear to impact CZP plasma concentrations. Plots of geometric mean CZP plasma concentrations by ADAb titer classification for the Entire Treatment Period for the Original CZP Dose and the Reduced CZP Dose are shown in **Figure 10** and **Figure 11**, respectively.

Figure 10. Geometric Mean (95% CI) CZP Plasma Concentration (µg/mL) in RA0043 for Entire Treatment Period by ADAb Titer Classification – Original CZP Dose



Source: Summary of Clinical Pharmacology Studies, Figure 4-1.

Figure 11. Geometric Mean (95% CI) CZP Plasma Concentration (µg /mL) in RA0043 for Entire Treatment Period by ADAb Titer Classification – Reduced CZP Dose



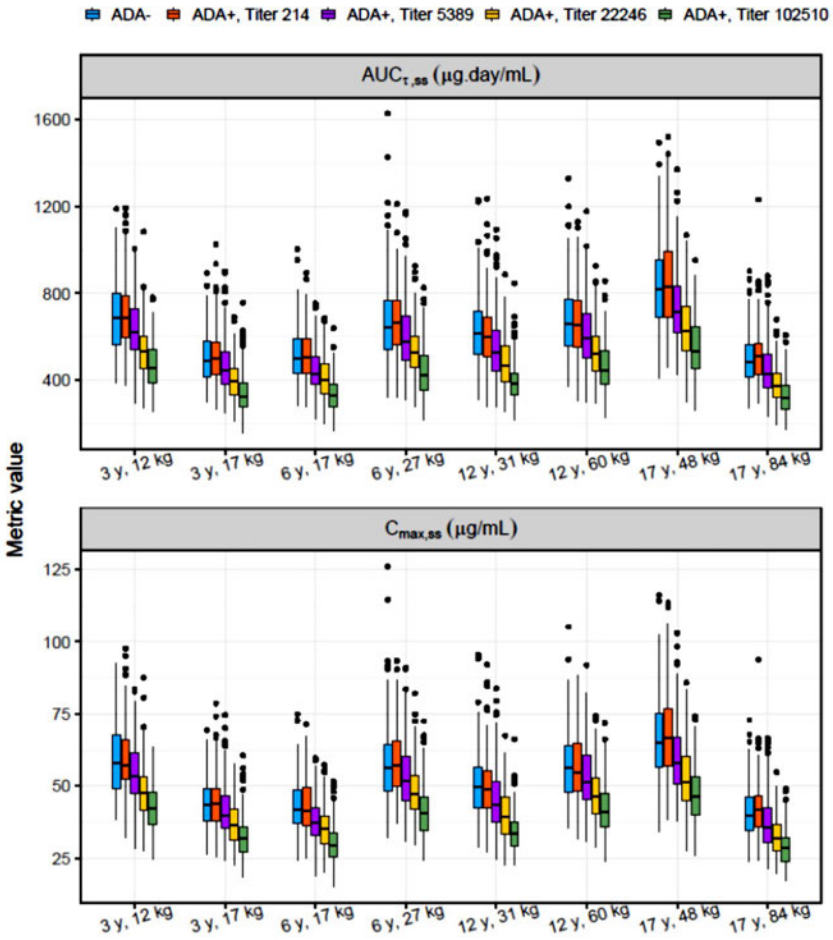
Source: Summary of Clinical Pharmacology Studies, Figure 4-2.

Overall, for the Original CZP Dose and the Reduced CZP Dose, CZP plasma concentrations appear to decrease with increase in ADAb titer quartile. For the Original CZP Dose, the geometric mean trough CZP plasma concentrations were numerically lower across most time points in the >Quartile 3 ADAb titer classification group compared with the other ADAb titer classifications (0 to ≤Quartile 1, >Quartile 1 to ≤Quartile 2, and >Quartile 2 to ≤Quartile 3), which were generally similar.

For the Reduced CZP Dose, the CZP plasma concentrations followed a similar trend from Week 12 onwards as the Original CZP Dose, with numerically lower geometric mean trough CZP plasma concentrations in the >Quartile 3 titer classification compared with the other ADAb titer classifications (0 to ≤Quartile 1, >Quartile 1 to ≤Quartile 2, and >Quartile 2 to ≤Quartile 3). Across all time points, the >Quartile 2 to ≤Quartile 3 ADAb titer classification appeared to have lower geometric mean trough CZP plasma concentrations compared with the 0 to ≤Quartile 1 and >Quartile 1 to ≤Quartile 2 ADAb titer classifications.

Based on the population PK analyses, certolizumab pegol exposure decreased with increasing ADAb titer, but ADAb titer values up to the observed median value had a minor impact on CZP exposure (**Figure 12**). For the 2 extremes of typical patients, a patient 3 years of age and a patient 17 years of age with the corresponding 5th and 95th percentile anticipated body weights, median $AUC_{\tau,ss}$ and $C_{max,ss}$ would decrease up to approximately 1.5-fold, with the higher ADAb titers of >100,000 as compared with ADAb negative.

Figure 12. Predicted CZP AUCτ,ss and Cmax,ss vs age and body weight, using the final combined adult and pediatric CZP PK model, colored by ADAb



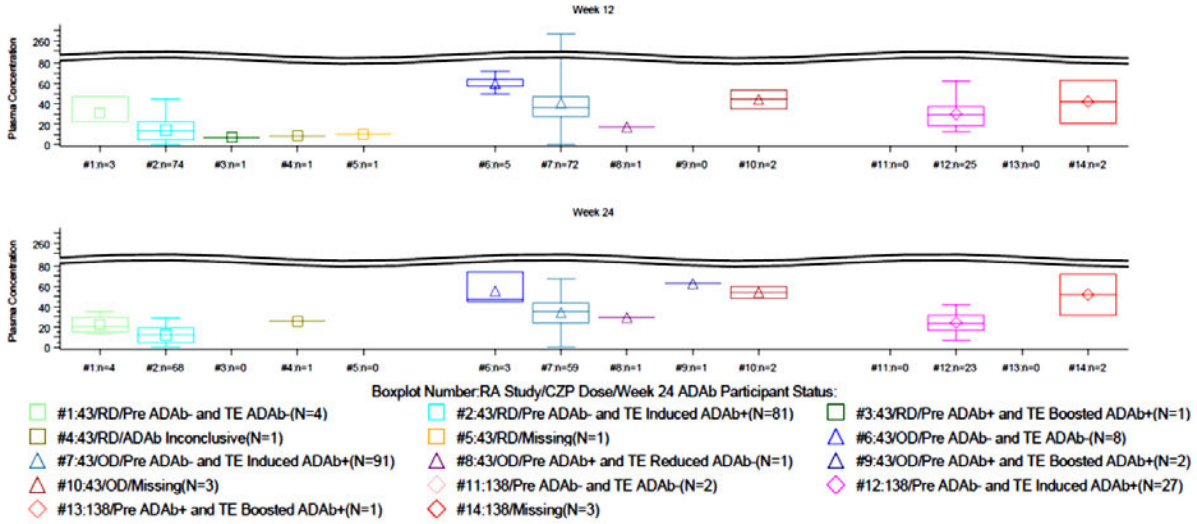
Source: Summary of Clinical Pharmacology Studies, Figure 4-3.

Study RA0138: The overall incidence of treatment-emergent ADAb positivity (combination of treatment-induced and treatment-boosted ADAb categories) was 93.3% (28/30 study participants). The median time to treatment-emergent ADAb positivity was 12 weeks; once study participants became ADAb positive, they remained so through the end of the study. No clear impact of ADAb on PK concentrations could be concluded. Given the high incidence of treatment-emergent ADAb positivity, it is difficult to compare the overall PK profiles between negative and positive study participants to elucidate any potential ADAb impact on PK.

Boxplots of the CZP plasma concentrations at Week 12 and Week 24 for RA0043 by CZP dose group and ADAb participant status classification and for RA0138 by ADAb participant status classification are shown in **Figure 13**. For the adult RA population from RA0138, at Week 24, among those with a pre-ADAb negative and TE induced positive status, the median plasma concentration of CZP was 23.600µg/mL, with Q1 and Q3 values of 16.700µg/mL and 31.400µg/mL, respectively. These values for the adult RA population at Week 24 were more

closely aligned with the median (Q1, Q3) plasma concentration of the RA0043 Original CZP Dose (35.200µg/mL [Q1=24.100µg/mL, Q3=43.500µg/mL]) compared with the Reduced CZP Dose (11.950µg/mL [Q1=4.695µg/mL, Q3=19.200µg/mL]). This trend was also observed at Week 12.

Figure 13. Boxplots of CZP Plasma Concentration (µg/mL) at Week 12 and Week 24 for RA0043 by CZP Dose Group and ADAb Participant Status Classification and for RA0138 by ADAb Participant Status Classification



Source: Summary of Clinical Pharmacology Studies, Figure 4-5.

Overall, at Week 12 and Week 24, among those with a pre-ADAb negative and TE induced positive status, median and quartile CZP plasma concentration in the adult RA population were more closely aligned with median and quartiles of the RA0043 Original CZP Dose compared with the Reduced CZP Dose.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The PK bridge is established to support the extrapolation of the efficacy established in adults with RA to pediatric patients with pJIA. Overall, based on (1) the disease similarity of pJIA and adult RA and (2) the similarity in PK of CZP between adults with RA and pediatric subjects with pJIA, the PK bridge would support the extrapolation of established efficacy of CZP in adult RA population to pJIA population.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed CZP dosing regimen for the treatment of pJIA is loading doses of CZP 100 mg at Weeks 0, 2, and 4, followed by CZP 50 mg Q2W Week 6 onwards for body weight group 10 kg to <20kg, loading doses of CZP 200 mg at Weeks 0, 2, and 4, followed by CZP 100 mg Q2W Week 6 onwards for body weight group 20 kg to <40 kg, and loading doses of CZP 400 mg at

Weeks 0, 2, and 4, followed by CZP 200 mg Q2W Week 6 onwards for body weight group ≥40 kg, administered SC. This dose recommendation is based on the use of exposure matching for PK to support extrapolation of efficacy from adult RA to pJIA. Population PK simulations showed that Original CZP Dose (same as the proposed dosing regimen in pJIA) provided similar exposure between adults and pediatric patients 10 kg to <20 kg and 20 kg to <40 kg, while pediatric patients ≥40 kg showed higher exposures with the Original CZP Dose when compared with the adult reference population, although a substantial overlap was observed in CZP concentrations between adults and pediatrics of different body weight categories. For the proposed dosing regimen, the ≥40kg pediatric patients received the same doses as adults. The simulations demonstrated that the Reduced CZP Dose provided lower exposure compared with adults for all pediatric groups, primarily in the 10 kg to <20 kg and 20 kg to <40 kg groups, and to a lesser extent in the ≥ 40kg group, where an overlap in CZP concentrations was observed compared with adults. Overall, the population PK analysis and simulations showed that the PK exposure for the proposed dosing regimen (Original CZP Dose) in the pediatric pJIA population is more closely aligned with the PK exposure for the adult CZP dose approved in RA. This was also supported by the PK analysis of observed data, which demonstrated that the observed PK values after use of the Original CZP Dose in the pediatric pJIA population were more closely aligned with the observed PK values for the adult CZP dose approved for RA.

Based on the similarity in disease and PK between adult RA and pJIA, the PK bridge is established to support the extrapolation of the efficacy established in adults with RA to pediatric patients with pJIA. Therefore, the dosing regimen proposed by the Applicant for pJIA appears reasonable from a Clinical Pharmacology perspective.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Population PK analyses showed that body weight was a significant covariate impacting the apparent clearance and volume of distribution of CZP. In Study RA0043, since dosing was based on body weight categories (same as the proposed dosing regimen in pJIA), the difference in exposure between the different body weight groups was small with overlapping concentrations across different body weight groups. Therefore, the recommended dosing in patients with pJIA based on body weight categories is appropriate.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Certolizumab pegol is a recombinant, humanized, monoclonal fragment antigen-binding antibody (Fab') with specificity for human tumor necrosis factor alpha (TNFα), conjugated to a polyethylene glycol (PEG) moiety and therefore food-drug or drug-drug interactions are not expected.

Is the to-be-marketed formulation the same as the clinical trial formulation?

The PFS presentations used in Study RA0043 were 200 mg/mL solution in a single-dose prefilled syringe (PFS), 100 mg/ 0.5 mL solution in a single-use PFS, and 50 mg/0.25 mL solution in a single-use PFS. The 200 mg/mL solution in a single-dose prefilled syringe is currently approved and marketed. Cimzia (certolizumab pegol) for injection is also supplied as a sterile white, lyophilized powder in a single-dose vial for subcutaneous use containing 200 mg of certolizumab pegol. After reconstitution of the lyophilized powder with 1 mL Sterile Water for Injection, USP, the final concentration is 200 mg/mL with a deliverable volume of 1 mL (200 mg), from which the appropriate amount is to be given by subcutaneous injection. Solutions in PFS and the reconstituted solution in vial have the same concentration. (b) (4)

Therefore, for patients who need 100 mg and 50 mg dose, the vial would be used for administration by a healthcare professional. Analytical comparability has been shown previously between the vial and PFS presentations (b) (4) BLA 125160 as part of S-080). Results from a PK-bridging study (Study CDP870-038) performed in healthy volunteers showed comparable PK between the vial and PFS presentations (b) (4) BLA 125160/S-080). In addition, the efficacy and safety were comparable between the vial and PFS presentations from phase 3 studies in adult RA (Study CDP870-027 [vial presentation] and Study CDP870-050 [PFS presentation]) (b) (4) BLA 125160/S-080). Overall, these data provide support for the use of the vial presentation for the administration of Cimzia in the pJIA population, in addition to the 200 mg/mL solution in a single-dose PFS presentation.

(b) (4)

(b) (4)

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 9. Clinical Trials Supporting BLA 125160 Supplement 275

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	Study Population/ No. of patients enrolled	No. of Centers and Countries
RA0043 PASCAL (Pediatric Arthritis Study of CertolizumAb pegoL) *Ongoing* *Database Cutoff Date for Resubmission: March 6, 2023*	Phase 3, multicenter, open-label study to assess the PK, immunogenicity safety, and efficacy of CZP in children and adolescents with moderately to severely active JIA with polyarthritis	Original CZP Dose • 10 to <20 kg: 100 mg Q2W x 3, then 50 mg Q2W • 20 to <40 kg: 200 mg Q2W x 3, then 100 mg Q2W • ≥40 kg: 400 mg Q2W x3, then 200 mg Q2W Reduced CZP Dose • 10 to <20 kg: 50 mg Q2W x 3, then 50 mg Q4W • 20 to <40 kg: 100 mg Q2W x 3, then 50 mg Q2W • ≥40 kg: 200 mg Q2W x 3, then 100 mg Q2W	• PK and Immunogenicity - CZP plasma concentration and ADAb levels at Wks 16 and 48 and other timepoints • Safety • Efficacy - PedACR30/50/70/90 at Wk 16 and other timepoints - Change from baseline: o # of joints with active arthritis o # of joints with limited ROM o Physician's Global Assessment of Disease Activity (VAS) o CHAQ o Parent's Assessment of Arthritis Pain (VAS) o Parent's Global Assessment of	24 weeks or longer (ongoing "until approval") Week 24 interim CSR: database cutoff date (March 6, 2023) 90-day safety update: June 3, 2024	Pediatric patients (2 to 17 years of age) with active JIA with polyarthritis N=193	36 sites in North America, Latin America, Russia *21 active sites at Database Cutoff Date*

			Overall Well-Being (VAS) ○ CRP ○ JADAS-71			
RA0138 *Complete*	Phase 1B, multicenter, open-label study evaluate the PK, safety, and tolerability of CZP in adults with active RA using an ECLIA	CZP 400 mg Q2W x 3, then 200 mg Q2W	• PK and Immunogenicity - PK parameters (Cmin and AUC) following 10 weeks of CZP dosing - CZP plasma concentrations - ADAb • Safety • Efficacy - Change from baseline in RAPID3 at Week 12	24 weeks with 70 days follow-up Max: up to 38 weeks	Adults with active RA N=33	9 sites in the United States

Abbreviations: ADAb=anti-drug antibody; CHAQ=Childhood Health Assessment Questionnaire; CRP=C-reactive protein; CSR=clinical study report; CZP=certolizumab pegol; ECLIA=electrochemiluminescent Immuno-Assay; JADAS-71=Juvenile Arthritis Disease Activity Score; JIA=juvenile idiopathic arthritis; PK=pharmacokinetics; Q2W=every 2 weeks; Q4W=every 4 weeks; RA=rheumatoid arthritis; RAPID3=Routine Assessment of Patient Index Data 3; ROM=range of motion; VAS=visual analog scale
Source: Clinical Reviewer

7.2. Review Strategy

The Applicant conducted a single clinical study in pediatric subjects with JIA with active polyarthritis. Study RA0043 is an ongoing, multicenter, open-label study to assess the PK, immunogenicity, safety, and efficacy of CZP in children and adolescents with moderately-to-severely active JIA with polyarthritis. All subjects received a subcutaneous weight-tiered CZP dose regimen (loading and maintenance doses). Based on interval PK analyses, the CZP dose regimen changed; therefore, data from two dose regimens (described as the Original CZP Dose and the Reduced CZP Dose) were analyzed. The primary objectives were to evaluate the PK and safety including immunogenicity of CZP in children and adolescents with JIA with active polyarthritis. The secondary objective was to evaluate the descriptive efficacy of CZP in JIA with active polyarthritis. See Section 8.1.1 for a description of the study protocol.

The proposed basis of approval is the extrapolation of efficacy from RA patients to pJIA patients based on PK exposure matching. As discussed in Section 6, review of the PK data from Study RA0043 demonstrated a similar range of observed exposures for the Original CZP Dose in pediatric subjects to the exposures for the approved CZP dose in adult RA subjects in Study RA0138 (protocol and brief results summarized in Section 8.1.3 and 8.1.4). In addition, Study RA0043 provided open-label, uncontrolled descriptive efficacy data to support the efficacy of CZP in JIA with active polyarthritis. Descriptive efficacy analyses were performed using data from 193 participants who received any dose of CZP (105 participants enrolled on the Original CZP Dose and 88 participants enrolled on the Reduced CZP Dose) through the data cutoff date of March 6, 2023. This additional descriptive efficacy is presented in Section 8.1.2.

The safety assessment of CZP in JIA with active polyarthritis is based on the safety data from all participants who received at least one administration of any CZP dose in Study RA0043. The safety database from the same subjects as described above (105 participants enrolled on the Original CZP Dose group and 88 on the Reduced CZP Dose) through the data cutoff for the 90-day safety update report (SUR) (December 19, 2023) were included for safety analyses. As the study is ongoing, the study duration was approximately 12 years from the time of the first study participant's first visit with 54 participants with at least 96 months of CZP exposure. The review of safety is detailed in Section 8.2.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

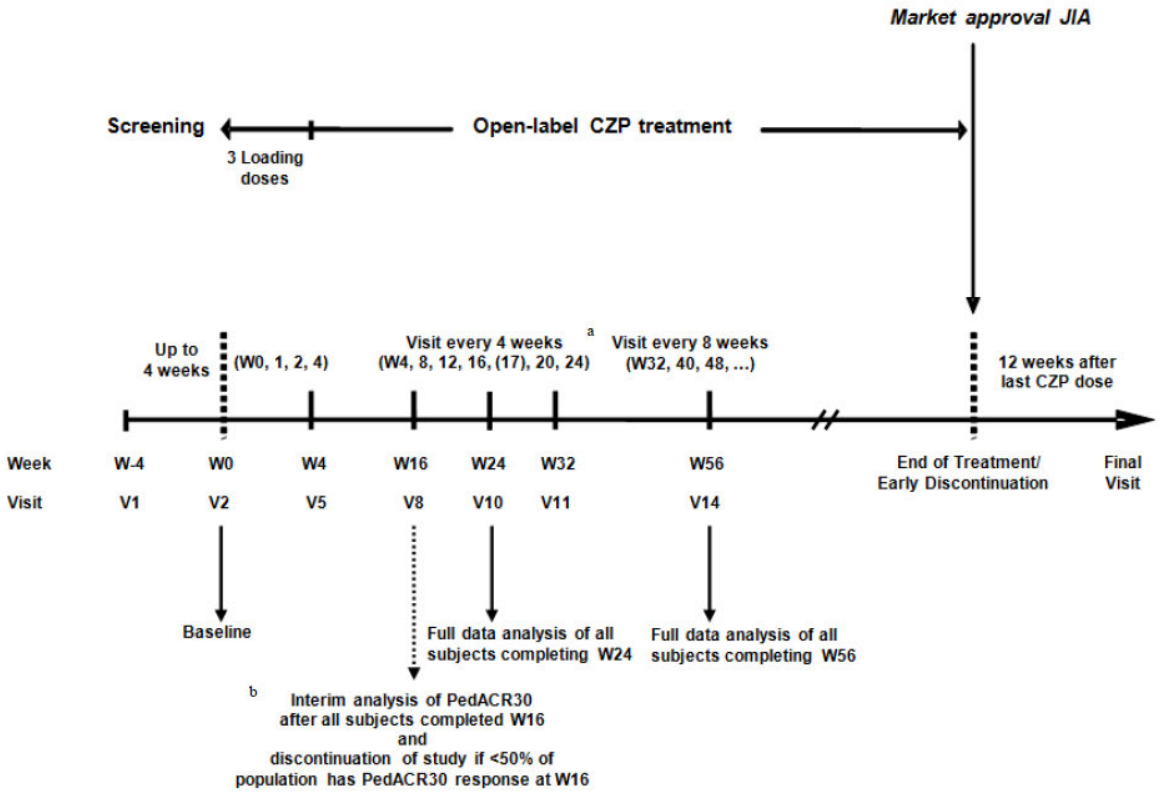
8.1.1. Study RA0043

Trial Design

The trial design for Study RA0043 and its revisions through Protocol Amendment 6 were described in detail in the Clinical review of the original submission (DARRTS submission date March 2, 2017). Key aspects of the study design are described in this review, alongside subsequent protocol amendments.

Study RA0043 is an ongoing, multicenter, open-label study to assess the PK, immunogenicity, safety, and efficacy of CZP in children and adolescents with moderately-to-severely active JIA with polyarthritis. Following a screening period (up to 4 weeks), subjects received open-label CZP. Figure 14 shows the study schematic for Study RA0043.

Figure 14. Study RA0043 Schematic



Source: UCB Clinical Study Protocol Amendment 9, dated April 27, 2020, Figure 5.3, page 29.

The original protocol has had 9 global protocol amendments and 10 country-specific (Russia)

amendments. These amendments (described below) led to changes in the conduct of the study. Aspects of these changes are described throughout the review of the trial design. Many of the major changes were attributed to results from pre-specified interim analyses that were planned for futility as well as PK, immunogenicity, safety, and efficacy.

- The first interim analysis of PK data demonstrated that the geometric mean and median concentrations were between the adult fifth percentile and the ninety-fifth percentile. Therefore, at the time of Protocol Amendment 3, no changes were made to the dosing algorithm.
- A subsequent analysis of the PK data was planned when 6 study participants in one of the age groups completed Week 12. 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 fifth and ninety-fifth percentile and minimum and maximum observed values. Based on results of the interim population PK (PopPK) analysis, the dosing regimen was reduced by 50% for all weight groups with Protocol Amendments 4 and 5.
- A futility analysis of the PedACR30 response rate was performed after all active study participants enrolled globally on the Reduced CZP Dose level had completed the Week 16 assessments. This analysis confirmed that ≥50% of the study population enrolled on the Reduced CZP Dose regimen achieved a PedACR30 response at Week 16. A further futility analysis was not performed using additional study participants that were enrolled on the Original CZP Dose regimen.
- An interim analysis of PK, immunogenicity, safety, and efficacy endpoints was performed after all active study participants that were enrolled globally, were treated, and completed Week 24 assessments (database cutoff date January 11, 2016). These results comprised the original submission that was submitted on May 27, 2016.
- Following Protocol Amendment 9.1 (which implemented the enrollment of 30 additional participants at the Original CZP Dose regimen based on interim results and Agency/Applicant review, see regulatory history in Section 3.2), another interim analysis of PK, immunogenicity, safety, and efficacy was performed. Analysis was conducted on data after Week 24 assessments from all enrolled participants, including those enrolled after Protocol Amendment 9. This interim analysis is the basis of the current submission with a database cutoff of March 6, 2023.

<u>Key Inclusion Criteria</u>

1. Study participant was 2 to 17 years of age (inclusive) at Baseline. The minimum age at Baseline for study participants enrolled in Russia was 6 years of age.
2. Study participants must have weighed ≥10 kg at Baseline. The minimum weight at Baseline for study participants enrolled in Russia was 15 kg.
3. Study participants had onset of signs and symptoms consistent with diagnosis of JIA (according to the ILAR classification of JIA). Eligible JIA categories included polyarthritis RF-positive, polyarthritis RF-negative, juvenile PsA, and ERA.
4. Study participants had active polyarticular disease, defined as ≥5 joints with active arthritis at Screening and at Baseline.

5. Study participants had an inadequate response to, or intolerance to, at least 1 DMARD (nonbiologic or biologic).
6. Prior therapies
    a. Methotrexate (MTX): If the study participant was using MTX, then the participant needed to be on MTX for a minimum of 3 months at Screening and at a stable dose between 10 to 15 mg/m^2 per week at least 1 month before Screening. If the participant was not on MTX, then there should be documentation that the participant had intolerability or inadequate response to MTX or another DMARD.
    b. Corticosteroids (CS): If the study participant was using CS, the dose of oral CS should have been stable at a maximum dose of prednisone 10 mg or 0.2 mg/kg (or equivalent) per day for at least 7 days prior to assessment of arthritis at Baseline.

Key Exclusion Criteria

1. Study participant was previously exposed to >2 biologic agents.
2. Study participant previously failed to response to treatment with >1 TNFα inhibitors. Lack of response to treatment was defined as no clinical disease improvement within the first 12 weeks of treatment. (Study participants who demonstrate clinical response within 12 weeks of treatment but subsequently lost response after 12 weeks were eligible.)
3. Study participant was currently receiving or had received an experimental (biologic or nonbiologic) therapy in the 3 months or 5 half-lives prior to Baseline.
4. Study participant was previously treated with a biologic therapy for JIA that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.
5. Previous treatment with CZP
6. Other prohibited medications
    a. Oral CS: prednisone at doses >10 mg or 0.2 mg/kg (or equivalent) per day, any change in dose in 7 days prior to Baseline
    b. IM/IV/IA CS: any use within 28 days prior to Baseline
    c. Nonbiologic DMARDs: any dose of cyclosporine within 7 days prior to Baseline; any dose of leflunomide within 6 months prior to Baseline; any change in MTX dose in the one month prior to Screening or any dose of MTX <10 or >10 mg/m^2 per week; any dose of other nonbiologic DMARDs (e.g., sulfasalazine or hydroxychloroquine) within 28 days prior to Baseline
    d. Biologic DMARDs: prior or current exposure to >2 biologic DMARDs; specific timeframes for last use prior to Baseline for each biologic DMARD (provided in the protocol); all biologic DMARDs prohibited during the study
7. History of systemic JIA with or without systemic features
8. Secondary, noninflammatory type of rheumatic disease or joint pains (e.g., fibromyalgia) that was symptomatic enough to interfere with evaluation of the effect of the investigational medical product (IMP), in the Investigator's opinion
9. Other inflammatory arthritis (e.g., systemic lupus erythematosus, inflammatory bowel disease-related, etc.)
10. Active uveitis or history of active uveitis within the preceding 6 months
11. No current or past history of infection, as follows:

a. Tuberculosis (TB) history: known active TB, history of active TB involving any organ system, history of or current latent tuberculosis infection (LTBI), high risk of exposure to TB infection, current nontuberculous mycobacterial (NTMB) infection or history of NTMB infection
b. Current signs or symptoms which may have indicated infection, history of chronic or recurrent infections within the same organ system (>3 episodes requiring antibiotics/antivirals during 12 months prior to Screening), recent serious or life-threatening infection (within 6 months prior to Screening), high risk of infections in the Investigator's opinion
c. History of or current HBV or HCV or HIV 1/2
d. History of or active systemic/respiratory infection due fungal, parasitic, or mycotic pathogens (e.g., histoplasmosis, coccidiosis, paracoccidiosis, pneumocystis, blastomyces, and aspergillus)

12. Any live (including attenuated) vaccination within 8 weeks prior to Baseline or scheduled for live vaccination during the course of study participation
13. History of chronic alcohol or drug abuse based on the Investigator's clinical judgment within the last year
14. Breastfeeding, pregnant, or planned to become pregnant during the study or within 12 weeks following the dose of IMP. If female was of childbearing potential, participant had to have negative pregnancy tests at Screening and Baseline.
15. Sexually active female participants of childbearing potential who did not agree to practice effective methods of birth control
16. History of adverse reaction to PEG
17. History of a lymphoproliferative disorder including lymphoma or signs and symptoms suggestive of lymphoproliferative disease
18. Concurrent or history of any malignancy
19. Current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease including blood dyscrasia and demyelinating disease
20. Any other medical or psychiatric condition that could have jeopardized or compromised the study participant's ability to participate in the study or which made the participant unsuitable for inclusion in the study, in the opinion of the Investigator or Sponsor
21. Any clinically significant laboratory abnormalities which would have made the participant unsuitable for inclusion in the study with specific exclusion of the following: liver function tests >2x upper limit of normal (ULN), serum creatinine >1.5x ULN, white blood cells (WBC) $<3.0 \times 10^9$/L or 3000/mm^3
22. Wheelchair-bound at the time of enrollment

<u>Concomitant and Rescue Medication</u>

Permitted concomitant medications included the following:

- Methotrexate (MTX)
    - Stable dose for at least 1 month before Screening at ≥10 to ≤15 mg/m^2 per week
    - An increase was allowed only after Week 16 to a maximum dose of 15 mg/m^2 per

week.
    - MTX dose could be decreased at any time during the study. Discontinuation was allowed only for documented reasons of intolerance or toxicity or for clinical remission (as defined as clinically inactive disease over a period of 6 months) or for CZP discontinuation.
    - A change in the route of administration was allowed after Week 16.
- NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, acetaminophen, and other analgesics scheduled or as needed
- Folic acid or folinic acid
- Topical anesthetic creams (e.g., lidocaine or NSAID creams)
- Corticosteroids (CS)
    - Stable dose for at least 7 days prior to Baseline at a maximum dose of prednisone 10 mg or 0.2 mg/kg (or equivalent) per day (whichever dose was smaller)
    - During the study, oral CS was not allowed to be initiated or increased above prednisone 10 mg or 0.2 mg/kg (or equivalent) per day. Oral CS could also be decreased. The dose needed to be stable in the 7 days prior to any joint exam.
    - Topical CS may be administered for treatment of uveitis at any time during the course of the study.
    - Intra-articular (IA) CS may be administered no more than every 4 months or no more than 3 times in 1 year. Participants could receive IA CS in only up to 2 joints at single timepoint.
- Hormonal contraceptives (oral, parenteral, implantable)
- Nonlive vaccinations

Prohibited concomitant medications included the following:
- Nonbiologic DMARDs (other than MTX) and biologic DMARDs
- Any experimental (nonbiologic or biologic) therapy
- Live/live attenuated vaccinations

Concomitant use of any of the above would lead to the participant's immediate discontinuation of CZP dosing and withdrawal from the study.

Rescue medications were defined as the initiation of treatment or an increase in dose of a concomitant medication to treat JIA with polyarthritis (in addition to the CZP) that could impact the efficacy analyses. Use of rescue medications was to be avoided during the first 4 months of treatment, if possible. Any participant requiring rescue medication was considered a treatment failure for the purpose of efficacy analyses. A participant initiating a rescue medication after Week 52 was not considered a treatment failure, as the efficacy data was to be analyzed as observed without imputation. Participants receiving rescue medications could remain on CZP if the benefit/risk assessment of continued participation was deemed favorable based on Investigator's assessment.
- Rescue medications in the first 16 weeks
    - Initiation of MTX or increase of MTX above baseline

  - Initiation of oral CS or increase above baseline
- Rescue medications after Week 16
  - Initiation of MTX or increase of MTX above 15 mg/m^2 per week at any time
  - Initiation of oral CS or increase to prednisone >10 mg or 0.2 mg/kg (or equivalent) per day
- Rescue medication at any time
  - Injection of IA CS
    - Into more than 2 joints at a single timepoint
    - Into the same joint more frequently than 3 times in a 12-month period
  - IV CS (any dose) unless used for stress dosing
  - IM CS
- Concomitant medications that result in efficacy data at the next scheduled visit being classified as missing/nonresponse
  - NSAIDs or COX-2 inhibitors use higher than baseline
  - Analgesic or opioid use higher than baseline
  - Increase in oral CS dose within 7 days prior to scheduled study visit

Dose Selection

RA0043 utilized a PK-matching approach with respect to CZP PK in adults with RA to support efficacy extrapolation to the pJIA population. The study was not originally intended to assess 2 doses; therefore, the 2 CZP dosing regimens studied were not allocated in parallel. The original loading and maintenance doses (referred to as the Original CZP Dose and described in Table 10) were proposed in the original protocol. Results of an interim PopPK analysis of 34 pediatric study participants enrolled on the Original CZP Dose (conducted in June 2013) suggested that, while observed CZP plasma concentrations remained in the adult range, they were at the upper end of the distribution. To achieve plasma concentrations that were similar to the effective concentrations observed in previous studies in adults with RA, the loading and maintenance doses were reduced (referred to as the Reduced CZP Dose and described in Table 10).

Table 10. CZP Dose Regimens in Study RA0043

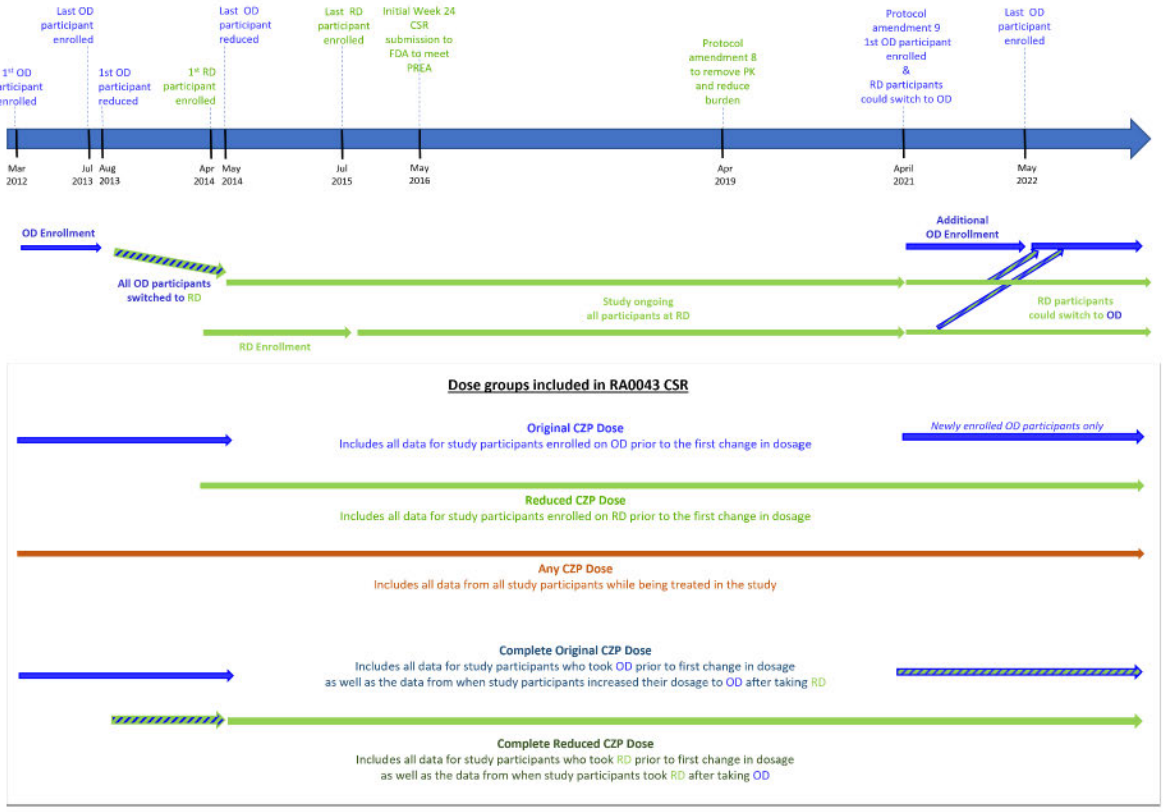
Weight Range	Original CZP Dose Regimen	Reduced CZP Dose Regimen
Loading dose (Weeks 0, 2, 4)		
10 to <20 kg	100mg Q2W	50mg Q2W
20 to <40 kg	200mg Q2W	100mg Q2W
≥40 kg	400mg Q2W	200mg Q2W
Maintenance dose (Weeks 6 [Weeks 8 for Q4W] onwards)		
10 to <20 kg	50mg Q2W	50mg Q4W
20 to <40 kg	100mg Q2W	50mg Q2W
≥40 kg	200mg Q2W	100mg Q2W

Source: UCB Updated Interim Clinical Study Report, dated December 12, 2023, Table 3-3, page 44.

As previously described, at the time of the original submission, the Applicant proposed the Reduced CZP Dose regimen for approval. However, the review team concluded that the Original CZP Dose regimen may be more appropriate, as the PK data of patients on this regimen more closely matched that of the adult RA patients. Due to inspection findings and the subsequent

Complete Response of the original submission, the Agency ultimately advised the Applicant to re-analyze and ensure the reliability of the PK data. After interactions following the Complete Response (detailed in Section 3.2), in order to adequately assess the exposure levels and clinical experience of CZP in JIA with polyarthritis at both the Original CZP Dose and the Reduced CZP Dose and also adequately support the safety assessment of the Original CZP Dose (as most of the safety data had been collected on the Reduced CZP Dose), the Applicant planned to enroll an additional 30 participants on the Original CZP Dose after Protocol Amendment 9. Figure 15 presents a study timeline with details regarding the changes in dose regimens. Additionally, this figure illustrates how the different dose groups were defined in the clinical study report (CSR) for both efficacy and safety analyses. These dose groups are further detailed below under the Statistical Analysis Plan section of this review.

Figure 15. RA0043 Dose Groups and Study Timeline



CZP=certolizumab pegol; OD=Original CZP Dose; PK=pharmacokinetic(s) [samples]; RD=Reduced CZP Dose
Source: UCB Updated Interim Clinical Study Report, dated December 12, 2023, Figure 3-2, page 58.

Study Treatments and Assignment to Treatment

CZP 200 mg/mL solution was provided as a single subcutaneous injection via pre-filled syringe (PFS) at volumes of 0.25 mL (50 mg), 0.5 mL (100 mg), and 1 mL (200 mg).

Study participants received open-label treatment of CZP based on weight at the dosing regimens described above. After Week 4, study participants or a parent/caregiver were permitted to administer CZP at home between scheduled study visits. A study participant's

dosing category only changed after confirmation of a weight change by the Investigator at a scheduled clinical visit.

Trial Location

A total of 36 sites screened study participants, and 21 sites had active study participants at the time of the database cutoff (March 6, 2023). These sites were located in North and Latin America and Russia.

Administrative Structure

The following were key personnel in preparing the updated Week 24 interim CSR:

- Principal/Coordinating Investigator: Hermine Brunner, MD, MSc
- Clinical Program Director: (b) (6)
- Study Physician: (b) (6)
- Clinical Project Manager: (b) (6)
- Statistician: (b) (6)
- Clinical Monitoring Contract Research Organization: (b) (4)
- Central laboratory facilities
  - Safety analysis and distribution of PK and anti-CZP ADAb samples to (b) (4) (b) (4)
  - PK and anti-CZP ADAb analysis: (b) (4) (b) (4);
- The Data Safety and Monitoring Board (DSMB) included (b) (6); (b) (6) (b) (6) and (b) (6) (b) (6)

Procedures and Schedule

The study consisted of a Screening Period (up to 4 weeks) and an open-label Treatment Period, which would continue until the approval of the marketing application for the pJIA indication in the study participant's region/country or until UCB notification. A Final Visit occurred 12 weeks after the last dose of CZP. The Schedule of Assessments, including visit-specific procedures, is presented in Table 28 in the Appendices of this review.

Treatment Compliance

A drug accountability form was used to record CZP dispensing and return information on a by-participant basis and at each visit after IMP was dispensed. Details of any IMP lost, not used, disposed of at the study site, or returned to the Applicant was recorded in the appropriate forms. Study participants also must return documentation on home dosing. Drug accountability was done in the study participant's presence in order to obtain explanations regarding discrepancies in compliance with the dose. If a study participant was found to be persistently noncompliant (missing ≥2 consecutive scheduled CZP doses or missing ≥3 doses over a 12-month period), UCB and the Investigator evaluated whether the participant should be withdrawn from the study. This rule did not apply if a study participant achieved clinical remission or temporarily discontinued CZP due to an AE. These participants continued

scheduled study visits even if not dosed. With temporary discontinuation due to an AE, UCB and the Investigator also needed to decide whether the participant should be withdrawn from the study.

Subject Completion, Discontinuation, or Withdrawal

A study participant who completed the whole study was defined as a study participant who completed the last scheduled safety follow-up (SFU) visit (i.e., 70 days after last IMP through SFU visit).

Discontinuation of study treatment for potential drug induced liver injury was outlined in the protocol.

Study participants were free to withdraw from the study at any time. A participant may also be withdrawn at any time at the discretion of the Investigator for safety, behavioral compliance, or administrative reasons.

Participants were to be withdrawn for any of the following:

- Study participant or legal representative withdrew his/her consent.
- UCB or regulatory agency requested withdrawal of the study participant.

Participants were to be permanently discontinued from IMP for any of the following:

- Participant/caregiver was noncompliant with the study procedures or medications in the opinion of the Investigator.
- Participant was considered to have new LTBI, TB, or NTMB infection during the study.
- Participant developed an illness that would have interfered with his/her continued participation.
- Study participant took prohibited concomitant medications as defined in the protocol.
- Study participant may have withdrawn at any time due to lack of efficacy.
- Study participant had confirmation of a pregnancy.

Investigators should attempt to obtain information on study participants in the case of withdrawal or discontinuation; the information should include a narrative description of the reason for participant removal. The Schedule of Assessments (Table 28) show the data collected at the time of study discontinuation and follow-up for any further evaluation. The protocol also provided instruction on actions to be taken if a participant was lost to follow up (e.g., at least 1 phone call and 1 written message with documentation of efforts).

Study Endpoints

The primary endpoints were assessments of PK and safety. The PK assessments are discussed in Section 6. Safety assessments will be reviewed in Section 8.2.

Secondary Efficacy Endpoints

- PedACR30, PedACR50, PedACR70, and PedACR90 at Week 16 compared to Baseline
    - PedACR (American College of Rheumatology Pediatric) is comprised of 6 core set measures:
        - Number of joints with active arthritis (joints with swelling not due to deformity or inactive synovitis or joints with limitation of motion with pain/tenderness)
        - Numbers of joints with limitation of ranges of motion
            - The Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology Collaborative Study Group (PRINTO/PRCSG) standard joint exam includes the assessment of swelling, pain on motion, and tenderness of 75 joints.
            - The assessment of limitation of motion is made by examining 69 of these 75 joints.
        - Physician's Global Assessment of Disease Activity (Visual Analog Scale [VAS])
            - The Investigator assess the overall status of the study participant with respect to their JIA signs and symptoms and functional capacity using a 0 to 100 mm VAS where 0 is "very good, asymptomatic, no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities."
        - Childhood Health Assessment Questionnaire (CHAQ) completed by parent or caregiver
            - CHAQ is an adaptation of the Health Assessment Questionnaire-Disability Index (HAQ-DI), which is a questionnaire developed to assess physical function in adults. The CHAQ is a parent/caregiver-reported questionnaire, and the recall period is the "past week."
            - The CHAQ uses 30 questions (5-point Likert scare) to assess 8 domains of daily living, use of aids/devices, and activities in which assistance of another person is required. The question with the highest score determines the score for that domain, and the scores for each of the 8 functional domains are averaged to calculate the Disability Index yielding a score of 0 (no disability) to 3 (very severe disability).
        - Parent's Global Assessment of Overall Well-Being (VAS)
            - For this assessment, 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 100 mm horizontal line ranges from 0 (very well) to 100 (very poor."
        - Acute phase reactant (CRP)
    - PedACR30, PedACR50, PedACR70, and PedACR90 are based on 30%, 50%, 70%, and

90% or greater improvement, respectively, in at least 3 of the 6 core set measures without worsening of >1 remaining measure by >30%.

Other efficacy and health outcome assessments were conducted and included in the CSR. However, other than PedACR30/50/70/90, these are not further discussed in this review. As noted, efficacy in pJIA is based on a PK-matching approach with adult RA. All of these efficacy assessments, including PedACR, are supportive.

- PedACR30, PedACR50, PedACR70, and PedACR90 at every study visit (except Week 16) compared to Baseline
- Change from baseline at every visit in the following:
    - Number of joints with active arthritis
    - Number of joints with limited range of motion
    - Physician's Global Assessment of Disease Activity (VAS)
    - CHAQ
    - Parent's Global Assessment of Overall Well-Being (VAS)
    - Juvenile Arthritis Disease Activity Score-71 joint (JADAS-71)
- Ratio to Baseline in CRP at every visit

Additional efficacy endpoints assessed in the study but not presented in the CSR included the Parent's Assessment of Arthritis Pain (VAS), Clinically Inactive Disease (defined in the protocol), Clinical Remission on Medication (defined in the protocol), duration of morning stiffness, Faces Pain Scale-Revised, JIA Pain VAS, Fatigue Assessment Scale, and Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey. These endpoints and results will not be discussed in this review.

Statistical Analysis Plan

SAS® Version 9.4 performed all summaries and analyses. As Study RA0043 is an open-label study, all efficacy and safety summaries and analyses were descriptive. Data were organized by CZP dose groups. In Figure 15 above, the Applicant illustrated how these dose groups corresponded with changes in the CZP Dose regimens along the study timeline.

- Original CZP Dose group: data for all participants receiving the Original CZP Dose at study entry until any change in dosage. Only data obtained prior to the first change in dosage were included.
- Reduced CZP Dose group: data for all participants receiving the Reduced CZP Dose at study entry until any change in dosage. Only data obtained prior to the first change in dosage were included.
- Any CZP Dose group: data for all participants who received Any CZP dose regardless of dose switching

The Applicant stated that the above groupings allowed for a pure PK comparison of the Original CZP Dose and Reduced CZP Dose between pediatrics and adults without the potential of confounding differences in CZP plasma concentrations due to dose switching. Additionally,

these dose groups allowed for the continuity of safety, immunogenicity, and open-label efficacy analyses for each dose regimen.

Additional safety analyses and exposures were conducted on the following dose groupings after Agency recommendations:

- Complete Original CZP Dose group: data for all study participants while receiving the Original CZP Dose
    - For study participants who began treatment with the Original CZP Dose, the time prior to first change in dosage as well as time after returning to the Original CZP Dose after previous dose reduction
    - For study participants who began treatment with the Reduced CZP Dose, the time after dose escalation to the Original CZP Dose
- Complete Reduced CZP Dose group: data for all study participants while receiving the Reduced CZP Dose
    - For study participants who began treatment with the Reduced CZP Dose, the time prior to first change in dosage
    - For study participants who began treatment with the Original CZP Dose, the time after dose reduction to the Reduced CZP Dose and prior to any potential later dose escalation back to the Original CZP Dose

This review will use the same definitions for these different dose groups for presentation of efficacy and safety data.

Protocol Amendments

Protocol Amendments 1 through 6 were described in the Clinical review of the original submission (DARRTS submission date March 2, 2017). Table 11 highlights the more clinically significant amendments in regards to dosing from the original submission and then describe the amendments following Protocol Amendment 6. Three country-specific amendments were implemented in Russia.

Table 11. Study RA0043 Global Protocol Amendments

Global Amendments	Date	Major Modifications
Amendment 4	August 1, 2013	• A total of 78 study participants had entered the study at the time of this amendment. • The primary purpose of this amendment was to change the dosing algorithm based on the results of the interim PopPK analysis conducted in June 2013 with data from 34 study participants. • New enrollment was suspended on July 17, 2013. • The maintenance dose of participants already in Study RA0043 was reduced by 50% with this amendment.
Amendment 5	January 20, 2014	• The primary purpose of this amendment was to reopen enrollment under the new Reduced CZP Dose.

		• To allow for a comparison with the 78 participants already enrolled on the Original CZP Dose, enrollment of another 78 study participants on the Reduced CZP Dose was planned. Therefore, the overall number of participants was increased from 125 to at least 156. • A minimum of 10 participants in each weight category needed to enter the study on the Reduced CZP Dose. • The Week 16 futility analysis would be conducted on participants enrolled on the Reduced CZP Dose after Amendment 5.
Amendment 7	September 22, 2016	• The primary purpose of this amendment was to update the protocol in accordance with current UCB TB detection procedures including the introduction of yearly TB testing and the extension of prophylactic TB treatment duration from 4 to 8 weeks. • Long-term efficacy data from study participants who withdrew or started rescue medication after Week 56 would be analyzed "as observed," instead of imputed as nonresponse.
Amendment 8	June 24, 2019	• The primary purpose of this amendment was to reduce the study participants' burden by limiting the frequency of on-site visits, safety sampling, and efficacy assessments. • At the time of Amendment 8, all ongoing study participants had completed the Week 180 visit. • The frequency of on-site visits was reduced from every 8 weeks to every 16 weeks. • UCB also determined there was limited value in collecting ADAb and CZP plasma concentration data after >4 years of CZP exposure.
Amendment 9	April 27, 2020	• The primary purpose of this amendment was to enroll an additional 30 study participants on the Original CZP Dose in order to adequately assess the exposure levels and clinical experience of CZP in JIA with polyarthritis at both the Reduced CZP Dose and the Original CZP Dose. This would also allow for a better safety assessment of the Original CZP Dose. • Study participants on the Reduced CZP Dose were able to switch to the Original CZP Dose at the discretion of the Investigator. • Sampling for CZP plasma concentrations and ADAb was reinitiated for study participants enrolled following Amendment 9. • ECLIA assays were validated to meet the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics. CZP plasma concentrations and ADAb for participants enrolled following Amendment 9 were analyzed using the ECLIA methods. In addition, previously collected PK and ADAb samples, for which sufficient volume and stability data were available, were reanalyzed with the ECLIA methods. • Exclusion criteria related to TB, HBV, HCV, and HIV were updated to align with current clinical guidelines.

Source: UCB Updated Interim Clinical Study Report, dated December 12, 2023.

8.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the current version of the applicable regulatory and International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) requirements and the local laws of the countries involved. UCB (or designee) monitored the study to ensure the study met Standard Operating Procedures, ICH-GCP guidelines, and applicable regulatory requirements.

Financial Disclosure

Appendix Section 15.2 presents the financial disclosure review for Study RA0043. The Applicant adequately disclosed financial interests and arrangements. The financial disclosures do not raise concerns. Two investigators received a significant payment, and, to mitigate the possibility of bias for these investigators, UCB ensured consistent protocol implementation across all sites with measures for handling protocol deviations.

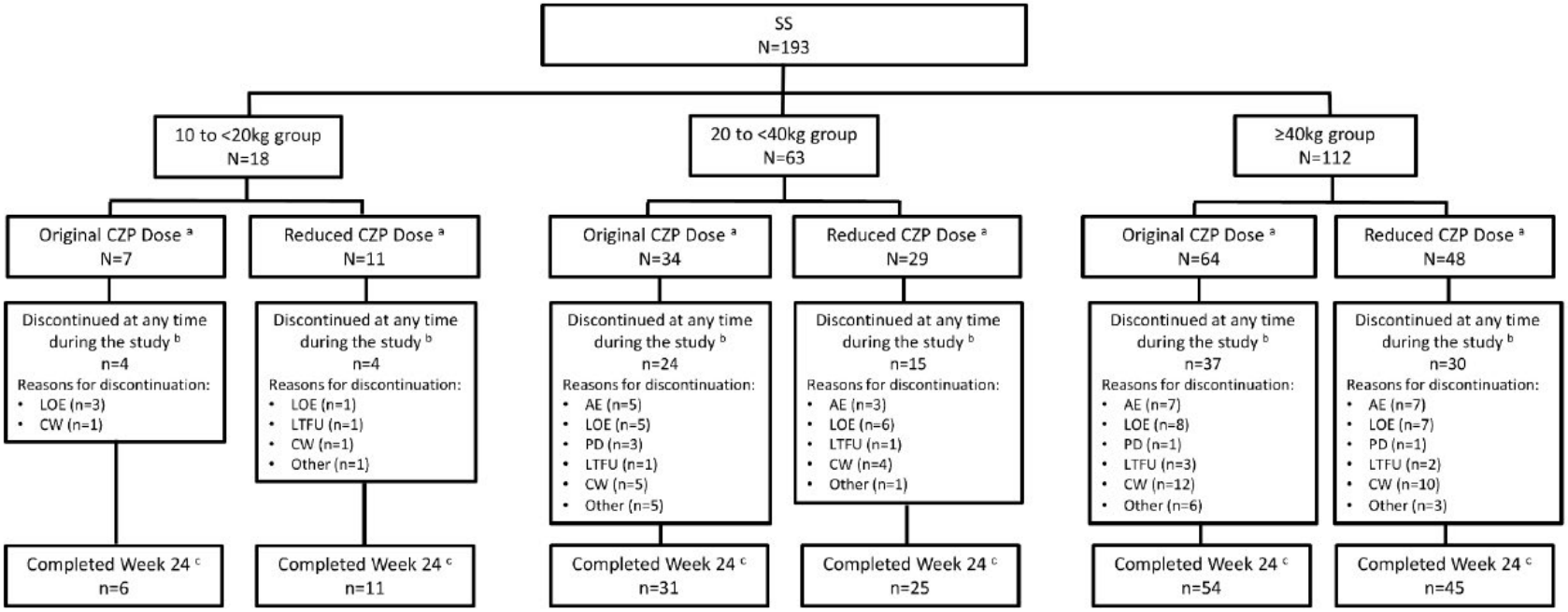
Patient Disposition

A total of 193 study participants were enrolled in the study and received at least 1 dose of CZP. These 193 participants were included in the safety set, full analysis set, and PK-per protocol set. Of the 193 participants in the study, 18, 63, and 112 study participants were enrolled in the 10 to <20 kg, 20 to <40 kg, and ≥40 kg weight groups, respectively. Therefore, at least 10 participants were enrolled at each weight group.

Of the 193 participant who enrolled in the study, 172 participants (89.1%) completed at least Week 24. At the time of database cutoff (March 6, 2023), 114 study participants had discontinued from the study. Figure 16 presents the disposition by weight group and by CZP dose at the time of enrollment. The proportion of participants who discontinued study drug was 61.9% in the Original CZP Dose Group and 55.7% in the Reduced CZP Dose Group. The most common reasons for discontinuation were also similar for both dose groups:

- Withdrawal of consent: 17.1% in the Original CZP Dose group vs. 17.0% in the Reduced CZP Dose group
- Lack of efficacy: 15.2% in the Original CZP Dose group vs. 15.9% in the Reduced CZP Dose group
- Adverse event: 11.4% in both CZP Dose groups

Figure 16. Study RA0043 Participant Disposition



AE=adverse event; CW=consent withdrawn; CZP=certolizumab pegol; LOE=lack of efficacy; LTFU=lost to follow up; PD=protocol deviation; SS=Safety Set
[a] Dose that the study participant enrolled on. The study participant may have changed dose prior to discontinuation.
[b] Discontinued as of the database cutoff date of 06 Mar 2023 (included study participants who discontinued after Week 24 [Visit 10]).
[c] Completed at least Week 24 (Visit 10) as of the database cutoff date of 06 Mar 2023 (may have subsequently discontinued).
Data sources: Table 1.3 and Table 1.4.1

Source: UCB Study RA0043 Interim Clinical Study Report, dated December 12, 2023; Figure 7-1, page 126.

The majority of patients completed the study in all weight groups. The reasons for discontinuation were also similar across weight groups. Notably, no discontinuations due to adverse events occurred in the lowest weight group, but the number of patients in this group was small.

Protocol Violations/Deviations

After implementation of Protocol Amendment 9, 30 study participants were planned to be enrolled on the Original CZP Dose. However, because of a delay in updating the Interactive Voice/Web Response System at one site, 3 study participants were incorrectly enrolled at the Reduced CZP Dose. The other 27 additional participants after Protocol Amendment 9 were enrolled at the Original CZP Dose.

As of the database cutoff of March 6, 2023, 173 study participants on Any CZP Dose (89.6%) had at least 1 important protocol deviation. The proportion of participants with at least 1 protocol deviation was similar across baseline weight groups on Any CZP Dose (100% in the 10 to <20 kg group, 93.1% in the 20 to <40 kg group, 89.6% in the ≥40 kg group) and on each dose group at any weight (87.5% in the Original CZP Dose group and 92.0% in the Reduced CZP Dose group). The most common reason for protocol deviation fell in the category of incorrect treatment or dose, which included dosing deviations, PK sampling deviations, and site CZP temperature exclusions; of these, the majority of subjects had PK sampling deviations.

Table of Demographic Characteristics

Table 12 presents the demographics of the participants in Study RA0043. The mean age of participants who received Any CZP Dose was 11.9 years at baseline. The majority of participants enrolled on either the Original CZP Dose or the Reduced CZP Dose were older than 6 years of age, female, and white.

Table 12. Participant Demographics in Study RA0043

	Original CZP Dose N=105	Reduced CZP Dose N=88	Any CZP Dose N=193
Age, n (%)			
2 to <6 years	6 (5.7)	5 (5.7)	11 (5.7)
6 to <12 years	33 (31.4)	42 (47.7)	75 (38.9)
12 to 17 years	66 (62.9)	41 (46.6)	107 (55.4)
Weight (kg),			
Mean (SD) Min, max	44.7 (16.7) 14.7, 89.7	43.0 (20.5) 12.3, 122.6	44.0 (18.5) 12.3, 122.6
BMI (kg/m^2)			
Mean (SD) Min, max	19.1 (3.6) 13.4, 32.7	19.6 (4.9) 11.4, 38.2	19.3 (4.3) 11.4, 38.2
Gender, n (%)			
Male	39 (37.1)	24 (27.3)	63 (32.6)
Female	66 (62.9)	64 (72.7)	130 (67.4)
Race, n (%)			
American Indian/Alaskan Native	2 (1.9)	3 (3.4)	5 (2.6)
Asian	3 (2.9)	2 (2.3)	5 (2.6)
Black or African American	4 (3.8)	2 (2.3)	6 (3.1)
Native Hawaiian or other Pacific Islander	0	0	0
White	80 (76.2)	75 (85.2)	155 (80.3)
Other/Mixed	16 (15.2)	6 (6.8)	22 (11.4)

BMI=body mass index; SD=standard deviation
Source: UCB Study RA0043 Interim Clinical Study Report, dated December 12, 2023; Tables 7-4 and 7-5, pages 131-132, 134-136.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 13 presents the baseline disease characteristics for the study participants. Most participants were diagnosed with JIA for approximately 3 years (mean 3.5 years in the Any CZP Dose group). Fiver ILAR subtypes were represented amongst the participants with the majority having RF-negative polyarthritis. For participants enrolled on Any CZP Dose, 19.2% had RF-positive polyarthritis; 51.3% had RF-negative polyarthritis; 14.0% had extended oligoarthritis; 3.6% had juvenile PsA; and 15.0% had enthesitis-related arthritis. The proportion of participants with each subtype were similar for both the Original CZP Dose group and the Reduced CZP Dose group. The mean number of joints with active arthritis was similar in the Original CZP Dose and Reduced CZP Dose groups (16.8 and 14.1, respectively) with a similar mean baseline JADAS-71 score. Additionally, 72.0% of participants took MTX (Any CZP Dose group) at baseline with 72.4% of participants in the Original CZP Dose group and 81.8% of participants in the Reduced CZP Dose group receiving it concurrently during the study.

Table 13. Baseline Disease Characteristics in Study RA0043

	Original CZP Dose N=105	Reduced CZP Dose N=88	Any CZP Dose N=193
Time since first diagnosis of JIA (years)			
Mean (SD) Min, Max	3.7 (3.6) 0.3, 16.1	3.2 (3.2) 0.5, 14.7	3.5 (3.4) 0.3, 16.1
ILAR JIA Subtype			
Polyarthritis – RF positive	21 (20.0)	16 (18.2)	37 (19.2)
Polyarthritis – RF negative	47 (44.8)	52 (59.1)	99 (51.3)
Extended oligoarthritis	14 (13.3)	13 (14.8)	27 (14.0)
Juvenile psoriatic arthritis	5 (4.8)	2 (2.3)	7 (3.6)
Enthesitis-related arthritis*	20 (19.0)	9 (10.2)	29 (15.0)
Number of joints with active arthritis at Baseline			
Mean (SD) Min, max	16.8 (11.1) 3, 57	14.1 (10.9) 2, 57	15.6 (11.1) 2, 57
JADAS-71 at Baseline†			
N Mean (SD) Min, max	103 28.3 (13.0) 8.8, 78.6	86 24.7 (13.0) 7.5, 76.3	189 26.7 (13.1) 7.5, 78.6
Baseline MTX use, n (%)	70 (66.7)	69 (78.4)	139 (72.0)
Concomitant MTX use, n (%)	76 (72.4)	72 (81.8)	148 (76.7)

ILAR=International league of Associations for Rheumatology; JADAS-71=Juvenile Arthritis Disease Activity Score 71 joints; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; SD=standard deviation
* Protocol specified that at least 10 study participants with enthesitis-related arthritis be enrolled in Study RA0043.
† JADAS-71is a composite disease activity score based on a 71-joint count and includes the following measures: Physician's Global Disease Assessment of Disease Activity, Parent's Global Assessment of Overall Well-Being, active joint count, and CRP. JADAS-71 score is calculated as the linear sum of scores of the 4 components with total score range of 0 to 101 with higher scores indicating higher disease activity.
Source: UCB Study RA0043 Interim Clinical Study Report, dated December 12, 2023; Tables 7-6 and 7-7, pages 137-138, 139-140.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The majority of participants on both dose regimens (92.4% of participants in the Original CZP Dose group and 70.5% in the Reduced CZP Dose group) received CZP in compliance with the study protocol (i.e., ≥80% and ≤100% compliance). In the Reduced CZP Dose group, the lower proportion can be attributed to 9 participants in the 10 to <20 kg weight category who received a greater number of CZP administration than expected. Although the Applicant did not provide reasons for these greater than expected administrations, no AEs were reported secondary to higher doses of CZP.

As described above, after Protocol Amendment 9, three participants were enrolled on the Reduced CZP instead of the Original CZP Dose. One participant (10 to <20 kg) was switched to the Original CZP Dose after Week 16, and two participants (≥40 kg) switched to the Original CZP Dose after Week 18.

Efficacy Results – Primary Endpoint

The primary endpoint for this study was CZP plasma concentrations and ADAb levels at Week 16 and 48, as well as safety assessments. These levels were analyzed using ECLIA methods that met current regulatory guidelines. Refer to Section 6 Clinical Pharmacology for discussion of the PK results. The efficacy of CZP in pJIA is based on these PK results, allowing for PK-matching and the extrapolation of efficacy from adults with RA.

Data Quality and Integrity

There are no potential issues concerning the submitted data quality or integrity about the study results. No OSI or OSIS inspections were conducted (Section 4.1).

Efficacy Results – Secondary and other relevant endpoints

The descriptive assessment of the efficacy endpoints in Study RA0043 are supportive of the efficacy extrapolation based on PK-matching. The secondary endpoints of PedACR30, PedACR50, PedACR70, and PedACR90 at Week 16 compared to baseline are presented in this review.

The majority of participants were PedACR30 responders at Week 16 (Table 14). Similar responses were seen at Week 24 (73.8% in the Original CZP Dose group and 77.3% in the Reduced CZP Dose group).

Table 14. PedACR30 Response at Week 16 Compared to Baseline

	Original CZP Dose N=105	Reduced CZP Dose N=88	Any CZP Dose N=193
n	104	88	193
Frequency of response (%)†	83 (79.8)	68 (77.3)	152 (78.8)
95% CI for percentage response*	70.8, 87.0	67.1, 85.5	72.3, 84.3

CI=confidence interval; FAS=Full Analysis Set; NRI=nonresponder imputation; PedACR=Pediatric American College of Rheumatology
† Response rates incorporated NRI for study participants who discontinued or used prohibited or rescue medication, and NRI was applied up to Week 56 for study participants who discontinued from the study.
* 95% CI was calculated using Clopper-Pearson method.
Source: UCB Study RA0043 Interim Clinical Study Report, dated December 12, 2023; Tables 11-1, pages 271.

Table 15 shows that the majority of participants in each weight group (numerically greater in the ≥40 kg weight group) were PedACR30 responders in the Original CZP Dose group. Similarly, in the Reduced CZP Dose group, the majority of participants in each weight group (numerically greater in the 10 to <20 kg weight group) were PedACR30 responders.

Table 15. PedACR30 Response at Week 16 by Weight Category

	Original CZP Dose		
	10 to <20 kg N=7	20 to <40 kg N=34	≥40 kg N=64
n	7	34	63
Frequency of response (%)†	5 (71.4)	27 (79.4)	51 (81.0)
95% CI for percentage response*	29.0, 96.3	62.1, 91.3	69.1, 89.8
	Reduced CZP Dose		
	10 to <20 kg N=11	20 to <40 kg N=29	≥40 kg N=48
n	11	29	48
Frequency of response (%)†	10 (90.9)	22 (75.9)	36 (75.0)
95% CI for percentage response*	58.7, 99.8	56.5, 89.7	60.4, 86.4

CI=confidence interval; FAS=Full Analysis Set; NRI=nonresponder imputation; PedACR=Pediatric American College of Rheumatology
† Response rates incorporated NRI for study participants who discontinued or used prohibited or rescue medication, and NRI was applied up to Week 56 for study participants who discontinued from the study.
* 95% CI was calculated using Clopper-Pearson method.
Source: UCB Study RA0043 Interim Clinical Study Report, dated December 12, 2023; Tables 11-2, page 273.

For participants enrolled at Any CZP Dose, the proportion of PedACR50, PedACR70, and PedACR90 responders were 72.0%, 54.4%, 27.5%, respectively. Similar responses were seen for the Original CZP Dose and Reduced CZP Dose groups. PedACR response was also generally similar by demographic subgroups.

Other efficacy assessments are not discussed in this review.

Although two dose regimens were assessed in Study RA0043, the study was not designed to assess a dose response. However, the efficacy endpoints generally showed similar response in both regimens. The study was not designed to evaluate durability of response or persistence of effect.

Overall, open-label efficacy assessment showed consistent improvement with treatment of JIA patients with active polyarthritis with CZP.

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted on this trial.

Integrated Review of Effectiveness

Not applicable since only a single clinical study in JIA was conducted to assess efficacy.

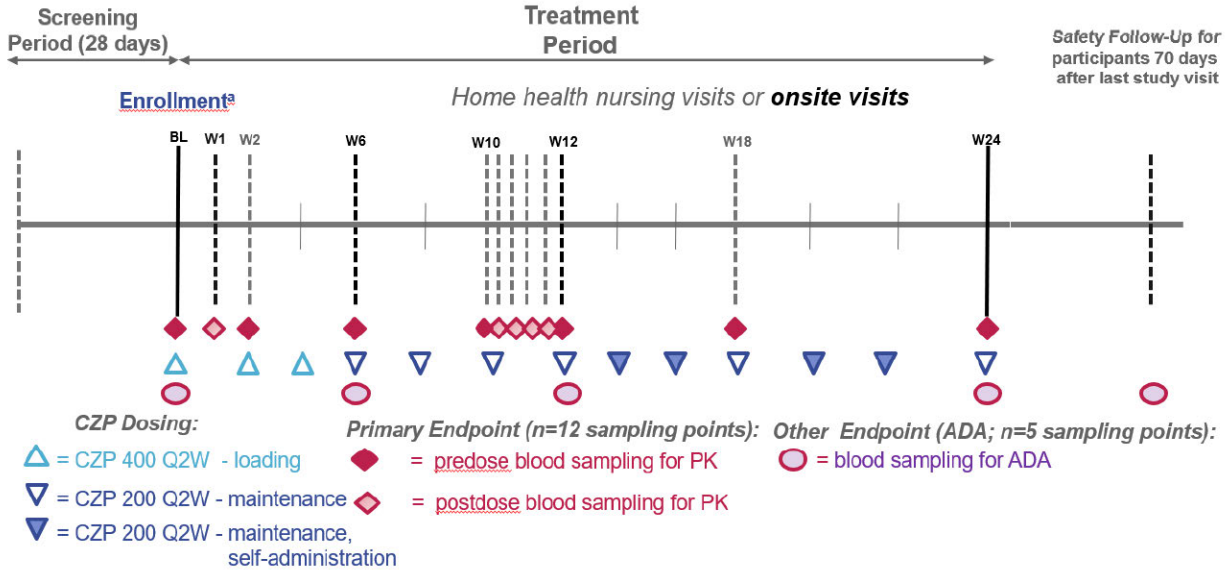
8.1.3. Study RA0138

Trial Design

Study RA0138 was a multicenter, open-label phase 1B study to evaluate the PK, safety, and tolerability of CZP in adults with active RA using an ECLIA. The purpose of this study was to provide the supporting adult reference PK dataset for PK matching in the pJIA program for this resubmission. The trial design and efficacy results will be summarized briefly in this review (Sections 8.1.3 and 8.1.4). The PK results are detailed in Section 6. The safety from Study RA0138 is not presented in this review.

The protocol planned to enroll a total of 30 study participants who were naïve to CZP and had not previously failed to respond to treatment with ≥1 TNFα inhibitor. Participants received CZP at the currently approved dose for RA, i.e., 400 mg SC at Week 0, 2, and 4, followed by treatment with 200 mg SC every 2 weeks. A minimum of 8 study participants were not to be receiving concurrent MTX. Participants received the final dose of CZP at Week 24. Figure 17 presents the study schematic for Study RA0138. The figure also annotates CZP dosing and timing of blood sampling for PK and ADAb.

Figure 17. Study RA0138 Schematic



ADAb=antidrug antibody; BL=Baseline; CZP=certolizumab pegol; PK=pharmacokinetic; Q2W=every 2 weeks; W=week
[a] CZP naïve at enrollment.
Source: UCB RA0138 Clinical Study Report, dated January 24, 2023; Figure 3-1, page 27.

Key Inclusion/Exclusion Criteria

- Age 18 to 69 years inclusive
- Diagnosis of moderately-to-severely active RA
- Inadequate response or intolerance to at least 1 DMARD (nonbiologic or biologic)
- Negative interferon-gamma release assay (IGRA) at Screening

Participants could not have previous exposure to CZP or be a primary failure to at least 1 TNFα inhibitor.

Participants were excluded for medical conditions (infections including TB or LTBI, neoplastic disease, other inflammatory conditions) and for laboratory abnormality at Screening.

Concomitant Medications
Methotrexate was permitted during the study. Other conventional DMARDs other than MTX, targeted synthetic DMARDs (i.e., JAK inhibitors), biologic DMARDs other than CZP, and experimental therapy were prohibited during the study.

Rescue medications (excluding the prohibited medications described above) could be used when needed. If a participant required a prohibited medication for control of their RA, they were removed from the study.

Study Endpoints

The primary and secondary endpoints were PK parameters and safety.

One efficacy endpoint was assessed as a change in baseline at Week 12. RAPID3 (Routine Assessment of Patient Index Data) is a Multi-dimensional Health Assessment Questionnaire (MDHAQ). The MDHAQ is composed of 3 assessments of physical function (10 activities, scale from 0 to 10), pain (scale from 0 to 10, assessed in 0.5 increments), and the patient's global status (scale from 0 to 10, assessed in 0.5 increments). The RAPID3 is calculated as a sum from 0 to 30 with a higher score indicating higher disease activity.

8.1.4. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the current version of the applicable regulatory and ICH-GCP requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved.

Financial Disclosure

Appendix Section 15.2 presents the financial disclosure review for Study RA0138. The Applicant adequately disclosed financial interests and arrangements. The financial disclosures do not raise concerns. Two investigators received a significant payment. To mitigate the possibility of bias for these investigators, UCB ensured consistent site monitoring and/or audits for investigators who report financial interests above the allowed limits, consistent protocol implementation across all sites with measures for handling protocol deviations, and review/analysis for "outlier" points.

Patient Disposition

Forty-four participants were screened, and 11 participants were screen failures. Therefore, 33 participants started the study. Of these, 23 participants (69.7%) completed the study. The reasons for study discontinuation included AE (9.1%), withdrawal of consent not due to an AE (9.1%), and protocol violation (6.1%).

Demographic Characteristics

The majority of participants (81.8%) were in the age range of 18 to <65 years with a mean age of 55.9 years. The mean weight was 82.5 kg, and the mean BMI was 29.2 kg/m^2. Most participants were female (66.7%), and the represented races included Black (21.2%) and White (75.8%).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The participants of Study RA0138 had a mean RA duration of 8.27 years with a median of 5.74 years. Two participants had extra-articular manifestations of RA.

Prior immunomodulating therapies included MTX (n=30, 90.9%), hydroxychloroquine (n=6, 18.2%), leflunomide (n=1, 3.0%), adalimumab (n=1, 3.0%), and etanercept (n=1, 3.0%). At Screening, 69.7% of participants were using MTX. Clinically significant concomitant medications used during the study included MTX (n=23, 69.7%), hydroxychloroquine (n=3, 9.1%), leflunomide (n=1, 3.0%), and sulfasalazine (n=1, 3.0%). Participants also used corticosteroids (n=12, 36.4%), NSAIDs (n=17, 51.5%), opioids (n=5, 15.2%), and other analgesics (e.g., paracetamol, n=13, 39.4%) although the reasons for use for these medications may not have been RA.

Efficacy Results – Primary Endpoint

The primary objective of Study RA0138 was to provide the PK data for adult participants with RA on the approved dose of CZP. Therefore, the primary endpoints are PK parameters (Cmin and AUC) following 10 weeks of dosing. Secondary endpoints included CZP plasma concentrations throughout the study and safety. See Section 6 Clinical Pharmacology for details regarding the PK assessments.

Efficacy Results – Secondary and other relevant endpoints

The study did include an efficacy assessment of change in RAPID3 score from baseline at Week 12. Twenty-six participants had RAPID3 scores at Baseline and at Week 12.

- 2/26 participants had an increase of 2.
- 3/26 participants had an unchanged score.
- 21/26 participants had a decrease of 1 to 13.

These efficacy results in this open-label PK study are generally consistent with the known treatment benefit of CZP in adult RA at the approved dose, as administered in this study.

8.1.5. Assessment of Efficacy Across Trials

Not applicable since only a single clinical study was conducted to assess efficacy of CZP in JIA with active polyarthritis.

8.1.6. Integrated Assessment of Effectiveness

The efficacy of CZP in pJIA is based on matching systemic exposure and extrapolation of established efficacy of CZP in adult RA. As discussed in Section 6, the Clinical Pharmacology team has determined that the exposures in patients with JIA with active polyarthritis treated with the Original CZP Dose in Study RA0043 were within the range of exposures seen in Study RA0138 in adult RA patients treated with CZP. Therefore, the Applicant has provided an adequate PK bridge for CZP to support the extrapolation of efficacy in the adult RA population to the pJIA population.

In addition, supportive numerical trends of improvement from baseline were observed for the descriptive efficacy endpoints in Study RA0043 in participants with JIA with active polyarthritis for both dose regimens, providing additional support of the efficacy of CZP in pJIA.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary safety assessment of CZP for JIA with active polyarthritis relies on data from a single clinical study, Study RA0043, conducted as an ongoing open-label study in pediatric participants with JIA with active polyarthritis ages 2 to 17 years of age who received CZP. The assessment presented in this review is based on all available safety data from the CSR and 90-day SUR and their supporting datasets. Data were submitted and reviewed from a total of 193 participants with JIA with active polyarthritis.

As the dose regimen was changed during the study conduct, participants received two dose regimens (Original CZP Dose and Reduced CZP Dose). Definitions of the dose groups used for safety analysis are described in detail under the Statistical Analysis Plan in Section 8.1.1 and illustrated in Figure 15 and presented briefly here.

- Original CZP Dose: all study participants who began treatment in accordance with the Original CZP Dose regimen. Only data obtained prior to their first change in dosage were included.

- Reduced CZP Dose: all study participants who began treatment in accordance with the Reduced CZP Dose regimen. Only data obtained prior to their first change in dosage were included.
- Any CZP Dose: data from all study participants while being treated with the Original CZP Dose or Reduced CZP Dose at any time in the study, regardless of dose switching.
- Complete Original CZP Dose: all study participants who began treatment with the Original CZP Dose, as well as study participants who began treatment with the Reduced CZP Dose but escalated to the Original CZP Dose. Only data obtained while the study participant was receiving the Original CZP Dose were included.
- Complete Reduced CZP Dose: all study participants who began treatment with the Reduced CZP Dose, as well as study participants who began treatment with the Original CZP Dose and later dose reduced to the Reduced CZP Dose. Only data obtained while the participant was receiving the Reduced CZP Dose were included.

The majority of the safety analysis in this review will be summarized for all 193 participants on Any CZP Dose with a focus on the Original CZP Dose which is the proposed dose for approval.

The safety of CZP in children and adolescents with JIA with active polyarthritis as observed in Study RA0043 was also compared to the established safety profile of CZP in adult RA patients. However, direct comparisons of safety of treatment with CZP in participants with JIA with active polyarthritis as compared to other indications are limited by differences in study designs, differences in frequencies of some types of events between the JIA with active polyarthritis and RA populations, and the limitations of cross-study comparisons.

8.2.2. Review of the Safety Database

Overall Exposure

Table 16 presents CZP exposures for the different dose groups at the time of the 90-day safety update (December 19, 2023).

Duration of exposure was calculated using the following general formula:

- Date of last dose of CZP - date of first dose of CZP + 14 days (if administration of CZP is Q2W) or + 28 days (if administration of CZP is Q4W).

Participant time at risk represented the time a study participant was at risk for having an AE. Participant time (in days) at risk was calculated using the formula:

- Date of last dose of CZP – date of first dose of CZP + 70 days (5 CZP half-lives)
- Participant years at risk was calculated as the above time at risk in days divided by 365.25.

Table 16. Extent of Exposure in Study RA0043

	Original CZP Dose N=105	Reduced CZP Dose N=88	Complete Original CZP Dose N=113	Complete Reduced CZP Dose N=150	Any CZP Dose N=193
Total CZP received (mg)	4897.6	10330.9	5406.2	10389.2	11239.8
Mean (SD)	(3418.3)	(7462.0)	(3876.3)	(7560.5)	(8436.9)
Min, max	200, 13800	100, 23100	200, 17600	50, 25550	100, 36710
Exposure duration (days)	412.2	1796.0	451.1	1798.6	1662.1
Mean (SD)	(257.2)	(1222.3)	(286.6)	(1233.4)	(1293.8)
Min, max	14, 987	14, 3528	14, 1385	14, 3716	14, 4207
Exposure duration (years)					
Mean (SD)	1.13 (0.70)	4.92 (3.35)	1.24 (0.79)	4.92 (3.38)	4.55 (3.54)
Min, max	0.04, 2.70	0.04, 9.66	0.04, 3.79	0.04, 10.17	0.04, 11.52
Participant time at risk (days)	423.2	1828.8	462.9	1834.7	1697.1
Mean (SD)	(249.5)	(1202.6)	(279.8)	(1214.4)	(1280.4)
Min, max	70, 987	70, 3528	70, 1385	70, 3716	70, 4207
Total time at risk Participant-years	121.7	440.6	143.2	753.5	896.7

SD=standard deviation
Source: UCB Summary of Clinical Safety 90-day Safety Update, dated June 3, 2024; Table 1-2, pages 12-13.

The majority of study RA0043 participants had >1 year of exposure. At the time of the 90-day safety update, 159 participants (82.4%) on Any CZP Dose (comprised of 50 participants [47.6%] in the Original CZP Dose group and 71 participants [80.7%] in the Reduced CZP Dose group) had >52 weeks of CZP exposure.

Adequacy of the safety database:

The safety database for this application relies primarily on the observed safety in Study RA0043 as reported in the CSR (data cutoff date March 6, 2023) and the 90-day SUR (data cutoff date December 19, 2023). The safety data from Study RA0043 include 193 participants with JIA with active polyarthritis ages 2 to 17 years who received treatment with CZP (N=105 enrolled on the Original CZP Dose; N=88 enrolled on the Reduced CZP Dose). Through the 90-day SUR, the maximum duration of exposure was 11.5 years in the Any CZP Dose group. Fifty participants in the Original CZP Dose group (proposed dose for approval) and 71 participants in the Reduced CZP Dose group had >52 weeks of exposure. The demographic and disease characteristics of the participants in Study RA0043 are described in Section 8.1.2. In general, the participants in Study RA0043 appear to adequately represent the U.S. population of patients with JIA with active polyarthritis. Overall, the safety data provided from Study RA0043 (size and baseline demographics/disease characteristics) are adequate to inform the safety assessment of CZP in patients with JIA with active polyarthritis, including pJIA, in the context of the established safety profile in adult RA.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There are no important issues regarding data quality or quality of the overall submission that had an effect on the safety review.

Categorization of Adverse Events

UCB utilized standard definitions for adverse events (AEs) and serious adverse events (SAEs). A treatment-emergent adverse event (TEAE) was defined as an AE that occurred after first study drug administration until last study drug administration + 70 days. UCB's definitions of TEAE was appropriate.

Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA) version 23.1. All medications were coded or recoded using the World Health Organization Drug Dictionary version Sep 2020.

UCB determined the adverse events of special interest (AESIs) based on the known safety of TNFα inhibitors and safety of drugs administered via the SC route. UCB utilized different queries in order to identify and summarize the AESIs, described under Section 8.2.5.

Routine Clinical Tests

The schedule of assessments (outlined in Table 28) specify the laboratory tests and the time points when they were assessed. In general, the safety assessment methods and time points were reasonable and adequate for a pediatric population and JIA with active polyarthritis and for CZP (a TNFα inhibitor that is already marketed for other indications). Measures to minimize distress and pain were considered for this study in line with the FDA "guidance for industry – *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (2000)."

Definitions of markedly abnormal laboratory values were adopted from the UCB Therapeutic Area: Central Nervous System: Clinical and Laboratory Markedly Abnormal Values (Table 17 and Table 18).

Table 17. Definitions of Markedly Abnormal Hematology Values

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

LLN=lower limit of normal; ULN=upper limit of normal
Source: UCB SAP Amendment 5, dated June 21, 2023; Table 9-3, page 61-62.

Table 18. Definitions of Markedly Abnormal Biochemistry Values

Parameter (Unit)	Age Range	Abnormal Definition	
		Low	High
AST (SGOT) (U/L)	<14 years	NA	>180
	≥14 years	NA	>144
ALT (SGPT) (U/L)	1 to < 18 years	NA	>90
	≥18 years	NA	>123
Alkaline Phosphatase (U/L)	<4 years	NA	>690
	4 to <10 years	NA	>834
	10 to <17 years	NA	>1174
	≥18 years	NA	>432 (F) >933 (M)
GGT(U/L)	<6 months	NA	>522
	6 months to <1 year	NA	>279
	1 to <13 years	NA	>66
	13 to <18 years	NA	>126
	≥18 years	NA	>255
Total Bilirubin (umol/L)	>1 month	NA	≥25.6565
Total Protein (g/L)	2 months to <1 year	<30	>100
	≥1 year	<43	>100
Albumin (g/L)	<1 year	<16	>60
	≥1 year	<24	>70
Urea (mmol/L)	<1 year	NA	>7.014
	≥1 year	NA	>10.02
Creatinine (umol/L)	1 to <10 years	NA	>79.56
	10 to <16 years	NA	>123.76
	≥16 years	NA	>141.44
Calcium (mmol/L)	<1 year	<1.725	>3.05
	1 to <18 years	<1.85	>2.925
	≥18 years	≤1.975	≥2.775
Lactate dehydrogenase (LDH) (IU/L)	2 to 17 years		>1300
Phosphorus (mmol/L)	<1 year	<0.5814	>2.6586
	≥1 year	<0.5814	>2.3902
Potassium (mmol/L)	<1 year	<3.0	>6.5
	≥1 year	<3.0	>5.8
Sodium (mmol/L)	>1 month	≤130	≥150
Glucose (mmol/L)	>1 month	<2.775	>9.99
Total Cholesterol (mmol/L)	1 to <18 years	NA	>6.475
	≥18 years	NA	>7.77
Uric acid (umol/L)	<1 year	NA	>457.996
	1 to <13 years	NA	>386.62
	13 to <18 years	NA	>511.528
	≥18 years	NA	>404.464 (F) >571.008 (M)
Creatine Kinase (CPK) (IU/L)	2 to 17 years		>600

LLN=lower limit of normal; ULN=upper limit of normal
Source: UCB SAP Amendment 5, dated June 21, 2023; Table 9-4, page 61-62.

Growth (height and weight) was evaluated with height measurements at Screening, Baseline, and every 24 weeks and with weight measurements at Screening, Baseline, and at every visit. Tanner stages were also assessed at Baseline and every 24 weeks.

The safety assessment methods and time points in the protocol for Study RA0043 were adequate for pediatric participants with JIA with active polyarthritis.

8.2.4. Safety Results

Table 19 presents a summary of safety in Study RA0043. For Any CZP Dose, 94.8% of participants experienced a TEAE. These proportions were generally similar for both dose regimens (82.9% in the Original CZP Dose group and 95.5% in the Reduced CZP Dose group). Using the Complete Original CZP Dose and Complete Reduced CZP Dose groups yielded similar proportions of AEs, 82.3% and 93.3%, respectively. With the different exposures, the difference between dose regimens is difficult to interpret. The exposure-adjusted incidence rates appear to show a higher incidence rate in the Original CZP Dose (269.80 per 100 patient-years for the Original CZP Dose group and 146.11 per 100 patient-years for the Reduced CZP Dose group), but, because these doses were not administered concurrently, the study was not designed to evaluated differences in safety between the 2 doses. The types and frequencies of AEs are discussed in detail below.

Table 19. Overview of Safety in Study RA0043 (90-Day Safety Update)

	Original CZP Dose N=105 n (%) [#]	Reduced CZP Dose N=88 n (%) [#]	Any CZP Dose N=193 n (%) [#]
Any TEAEs	87 (82.9) [507]	84 (95.5) [946]	183 (94.8) [2350]
Serious TEAEs	9 (8.6) [14]	21 (23.9) [25]	45 (23.3) [64]
Study Participant Discontinuation due to TEAEs	9 (8.6) [18]	10 (11.4) [11]	24 (12.4) [35]
Permanent Withdrawal of CZP due to TEAEs	9 (8.6) [21]	10 (11.4) [11]	25 (13.0) [39]
Severe TEAEs	7 (6.7) [13]	4 (4.5) [8]	25 (13.0) [42]
Deaths (TEAEs leading to death)	0	2 (2.3) [3]	2 (1.0) [3]

n=number of participants reporting at least 1 TEAE in that category; (%)=percentage of participants among total N, [#]=number of occurrences of the TEAE in that category
Date of 90-day Safety Update data cutoff: December 19, 2023
Source: UCB Summary of Clinical Safety 90-day Safety Update, dated June 3, 2024; Table 2-1, page 16.

Generally, the proportion of participants with AEs was similar between body weight categories in the Any CZP Dose group. A smaller proportion of participants had AEs and AEs leading to discontinuation in the lowest weight category, whereas the proportion of participants with SAEs was lower in the highest weight category. These differences may be attributed to much smaller number of participants enrolled at the lower weights and the longer exposure at higher weights. Similar trends were seen for each dose regimen.

Table 20. Overview of Safety (Any CZP Dose, by Body Weight Category, 90-Day Safety Update)

	Any CZP Dose		
	10 to <20 kg N=18 n (%)	20 to <40 kg N=63 n (%)	≥40 kg N=112 n (%)
Any TEAEs	16 (88.9)	60 (95.2)	107 (95.5)
Serious TEAEs	5 (27.8)	20 (31.7)	20 (17.9)
Study Participant Discontinuation due to TEAEs	0	8 (12.7)	16 (14.3)
Permanent Withdrawal of CZP due to TEAEs	0	9 (14.3)	16 (14.3)
Severe TEAEs	1 (5.6)	12 (19.0)	12 (0.7)
Deaths (TEAEs leading to death)	0	0	2 (1.8)

n=number of participants reporting at least 1 TEAE in that category; (%)=percentage of participants among total N
Date of 90-day Safety Update data cutoff: December 19, 2023
Source: UCB Summary of Clinical Safety 90-day Safety Update, dated June 3, 2024; Table 2-2, page 18-19.

In the Any CZP Dose group at the time of the data cutoff date for the 90-day SUR, there were 2 deaths, 45 participants with SAEs, 24 participants discontinued from the study due to an AE, and 25 participants with severe AEs. SAEs, AEs leading to discontinuation, and deaths are reviewed in more detail below. Overall, the number of participants with these events is small.

Deaths

Two deaths occurred in Study RA0043 through the 90-day SUR. Both deaths occurred in the Reduced Dose Regimen group, and both were due to AEs.

- A 17-year-old American Indian/Alaska Native female (≥40 kg weight category) from Mexico entered the study on the Reduced CZP Dose with baseline MTX [(b) (6)]. The participant was vaccinated against TB at birth and had a negative Quantiferon test at Screening. On [(b) (6)] (334 days after her first dose of CZP), she was hospitalized with adrenal suppression (SAE). CZP was discontinued. While hospitalized, she underwent a liver biopsy and was diagnosed with hepatic tuberculosis (TB) on [(b) (6)] [(b) (6)] She was treated with ethambutol, isoniazid, pyrazinamide, and rifampin. She was re-hospitalized on [(b) (6)] after a decline in her general condition and was in septic shock. She suffered cardiopulmonary arrest and died on [(b) (6)] at the age of 18 years-old.
    - SAEs reported for this case: adrenal suppression, hepatic tuberculosis, septic shock

- A 16-year-old White male (≥40 kg weight category) from the US entered the study on the Reduced CZP Dose without baseline MTX [(b) (6)] The participant was involved in a motor vehicle accident (MVA) on [(b) (6)] (182 days after his first dose of CZP). He died at the age of 16 years.

Following the data cutoff date for the 90-day SUR, another death occurred in a participant who was enrolled on the Original CZP Dose.

- A 17-year-old male (≥40 kg weight category) from Mexico entered the study on the Original CZP Dose with concomitant MTX [redacted]. The participant's interferon gamma release assay (IGRA) test was negative at screening and was positive on [redacted] but he was asymptomatic. CZP was temporarily withdrawn. On [redacted] a repeat Quantiferon test was negative; chest x-ray was normal; CZP was restarted on [redacted] On [redacted] the participant was noted to have cervical and inguinal adenopathy without further evaluation. On [redacted] (503 days after his first dose of CZP; also date of his last dose of CZP), the participant was diagnosed with anemia and an SAE of esophageal candidiasis. He was hospitalized on [redacted]. During this hospitalization, he underwent EGD which confirmed esophageal candidiasis and worsening anemia for which he received a blood transfusion. He was discharged on [redacted] but was re-admitted on [redacted], with severe abdominal pain and fever. A CT scan was normal at that time. However, on [redacted] due to dysphagia, a repeat CT scan was performed and showed mediastinal lymphadenopathy, micronodules in both lungs, hepatomegaly, diffuse thickening of the distal ileum. The participant was diagnosed with disseminated TB and treated with ethambutol, isoniazid, pyrazinamide, and rifampin. He was hospitalized again on [redacted], after 20 vomiting episodes and shock. His hospital course was significant for the need for vasopressors, antibiotics, multiple transfusions (platelets, RBCs, FF), hemodialysis, mechanical ventilation, and exploratory laparotomy. He died on [redacted], at the age of 18 years.
    - SAEs reported for this case: anemia, esophageal candidiasis, abdominal pain, disseminated TB, hypovolemic/septic shock

In total, three deaths occurred in Study RA0043. The MVA was unlikely related and is the leading cause of death in teenage white males in the US. The other 2 cases of active TB are known and labeled risks of CZP and the TNFα inhibitor class.

Serious Adverse Events

For Any CZP Dose, 23.5% of participants (n=45) experienced an SAE. The most common System Organ Class (SOC) was Infections and infestations (n=21, 10.9%) and Gastrointestinal disorders (n=7, 3.6%). The most frequently reported SAEs (by PT) were pneumonia (n=6) and anemia (n=3). JIA, pregnancy on contraceptive, pyrexia, sepsis, vomiting, varicella zoster infection, and inflammatory bowel disease (IBD, comprising IBD and Crohn's disease) (n=2 for each PT) were also reported. No other PTs were reported for more than 2 participants.

- For the Original CZP Dose group, 8.6% of participants (n=9) experienced an SAE. The most frequently reported SAEs (by PT) were JIA and anemia (each with 2 participants). Other SAEs included leukocytosis, Crohn's disease, abdominal pain, vomiting, pyrexia, esophageal candidiasis, disseminated TB, increased transaminases, idiopathic generalized epilepsy, and nephrolithiasis.

- For the Reduced CZP Dose group, 23.9% of participants (n=21) experienced an SAE. The

most frequently reported SAEs (by PT) were pneumonia (n-3), sepsis (n=2), pregnancy on contraceptive (n=2), and varicella zoster infection (n=2). Other SAEs included anemia, adrenal suppression, IBD, gastrointestinal motility disorder, drug hypersensitivity, appendicitis, gastroenteritis, sepsis, septic shock, pilonidal cyst, liver TB, forearm fracture, MVA, jaw fracture, foot deformity, and substance use.

Overall, the number of SAEs was low. The types of SAEs reported are consistent with the known risks of CZP in adult RA, as well as other TNFα inhibitors for approved indications including pJIA.

Dropouts and/or Discontinuations Due to Adverse Effects

For Any CZP Dose, 13.0% of participants (n=25) experienced an AE that led to discontinuation of CZP. The most frequently reported AEs leading to discontinuation were Crohn's disease (n=2) and pregnancy (n=2).

- The Applicant reported that 9 participants (8.6%) discontinued CZP while taking the Original CZP Dose and 10 participants (11.4%) discontinued CZP while taking the Reduced CZP Dose.
- Original CZP Dose at time of discontinuation
    - Enrolled on the Original CZP Dose:
        - SAEs (n=3): anemia, leukocytosis, increased transaminases, disseminated TB
        - Non-serious AEs (n=4): anxiety, diarrhea, fatigue, flank pain, headache, muscle spasms, peripheral edema, vomiting, pyrexia, pharyngotonsillitis, allergic dermatitis, allergic rhinitis, JIA, ulcerative colitis, staphylococcal infection
- Reduced CZP Dose at time of discontinuation
    - Enrolled on the Reduced CZP Dose:
        - SAEs (n=7): drug hypersensitivity, inflammatory bowel disease (IBD), pneumonia, pregnancy, MVA, substance use, liver TB
        - Non-serious AEs (n=4): anal fistula, Crohn's disease, increased blood CPK, arthritis, condition aggravated, hepatic enzyme increased, pregnancy, dermatitis psoriaform
    - Enrolled on the Original CZP Dose and dose reduced:
        - SAE (n=2): spontaneous abortion, tuberculosis

The number of participants experiencing AEs leading to discontinuation was low and similar for both dose regimens. The types of AEs were generally consistent with the known risks of CZP.

Common Adverse Events

For Any CZP Dose, the most common SOCs were Gastrointestinal disorders (n=72, 37.3%) and Infections and infestations (n=154, 79.8%). The five most common PTs were nasopharyngitis (n=54, 28.0%), upper respiratory tract infection (n=48, 24.9%), headache (n=39, 20.2%), JIA (n=37, 19.2%), and pyrexia (n=27, 14.0%). By weight category, the most common AEs were

generally similar across different weights. Of note, in the lowest weight group (10 to <20 kg), the second most common AE was varicella (n=5, 27.8%).

- For the Original CZP Dose group, the three most frequently reported PTs were nasopharyngitis (n=21, 20.0%), headache (n=13, 12.4%), and pyrexia (n=11, 10.5%).
- For the Reduced CZP Dose group, the three most frequently reported PTs were upper respiratory tract infection (n=23, 26.1%), nasopharyngitis (n=22, 25.0%), and headache (n=18, 20.5%).

The common adverse events for CZP in JIA with polyarthritis were generally consistent with the known risks of CZP and other TNFα inhibitors. The common AEs were also similar for both dose regimens. No new safety signals were identified.

Laboratory Findings

Hematology

The AEs related to hematology were identified using the High Level Terms (HLTs) of neutropenia, anemias not elsewhere classified (NEC), and leukopenias NEC. For Any CZP Dose, 4.1% of participants had neutropenia, 3.6% anemia NEC, and 3.1% leukopenias NEC. The most frequently reported PTs were neutropenia (n=8), anemia (n=6), and leukopenia (n=5). Three AEs of anemia were serious and led to study discontinuation (as already described) and also presented under the AESI Hematopoietic Cytopenia.

In reviewing the summary of laboratory values over time (which was evaluated through the resubmission data cutoff date of March 6, 2023, not the 90-day SUR), the proportion of participants in the Any CZP Dose group with a shift in hematology from normal to high/low was <5% for most parameters. For parameters with ≥5% of participants showing a shift in hematology values, the Applicant noted the following:

- Normal to high: monocytes/leukocytes (15.0%), lymphocytes (9.3%), lymphocytes/leukocytes (7.8%), hematocrit (7.3%), eosinophils (5.2%), eosinophils/leukocytes (5.2%)
- Normal to low: hemoglobin (10.9%), eosinophils (6.7%), monocytes (5.2%), neutrophils/leukocytes (5.2%)

The proportion of participants who developed markedly abnormal hematology values (as defined in 8.2.3) were also summarized. The hematology abnormalities that were reported in ≥15% of participants in the Any CZP Dose group included the following:

- Hematocrit (38.9%)
- Neutrophils (30.1%)
- Leukocytes (29.5%)
- Eosinophils/leukocytes (15.5%)

Hematological reactions including medically significant cytopenia are labeled risks of treatment

with Cimzia. Overall, the hematologic changes documented in Study RA0043 are consistent with the known safety profile of Cimzia in RA and other indications.

Biochemistry

AEs related to biochemistry values and laboratory values over time were assessed only through the data cutoff for resubmission (March 6, 2023).

The most frequently reported HLTs in the Any CZP Dose group related to biochemistry are listed below:

- Liver function analyses (n=5 [4.8%] in the Original CZP Dose group and n=13 [14.8%] in the Reduced CZP Dose group)
- Skeletal and cardiac muscle analyses (n=3 [2.9%] in the Original CZP Dose group and n=7 [8.0%] in the Reduced CZP Dose group)
- Protein analyses (n=4 [3.8%] in the Original CZP Dose group and n=4 [4.5%] in the Reduced CZP Dose group.

The Applicant noted that most elevations were transient and returned to normal values without a change in CZP administration.

In reviewing the summary of laboratory values over time, the proportion of participants in the Any CZP Dose group with a shift in biochemistry from normal to high/low was <5% for most parameters. For parameters with ≥5% of participants showing a shift in biochemistry values, the Applicant noted the following:

- Normal to high: albumin (9.8%), chloride (7.3%), creatine kinase (CK, 7.3%), protein (6.7%), bilirubin (5.2%)
- Normal to low: bicarbonate (17.1%), urea (7.3%), creatinine (6.7%)

For Any CZP Dose, markedly abnormal biochemistry values (as defined in 8.2.3) that occurred in >20% of participants included the following: urate in the 20 to <40 kg weight category (n=17, 27.0%), CK in the ≥40 kg weight category (n=24, 21.4%), and ALT in the ≥40 kg weight category (n=24, 21.4%). Elevated CK is not a labeled risk of CZP. Despite the number of participants with markedly abnormal CK, there were 16 participants with an AE of “blood creatine phosphokinase increased” balanced across all weight categories, and there were no cases of rhabdomyolysis.

Overall, the biochemistry changes documented in Study RA0043 did not raise concerns for a new safety signal.

Vital Signs

Vitals (systolic and diastolic blood pressures, pulse rate, and temperature) were monitored through the study. For Any CZP Dose, the Applicant determined the proportion of participants with markedly abnormal values:

- Systolic blood pressure (n=19, 9.8%)
- Diastolic blood pressure (n=47, 24.4%)
- Pulse rate (n=28, 14.5%)
- Temperature (n=3, 1.6%)

No trends were revealed, and the Applicant did not determine any safety risks in regards to vital signs.

Electrocardiograms (ECGs) and QT

ECGs were not routinely assessed in Study RA0043.

Immunogenicity

The proportion of participants who were Pre ADAb- and then treatment-induced ADAb+ was 90.5% in the Original CZP Dose and 93.2% in the Reduced CZP Dose. The Applicant evaluated the differences in AEs in those who developed ADAb during the treatment period. However, given that the majority of participants developed ADAb, it is difficult to make any conclusions. Notably, though, there did not appear to be more hypersensitivity events in these participants who developed ADAb. See Section 8.2.5.3 for review of injection reactions (hypersensitivity).

8.2.5. Analysis of Submission-Specific Safety Issues

The protocol specified the following AEs of Special Interest (AESIs):

1. Potential Hy's Law: ≥3 x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with co-existing ≥2 x ULN total bilirubin in the absence of ≥2 x ULN alkaline phosphatase (ALP) with no alternative explanation for the biochemical abnormality
2. Serious infections, including opportunistic infections
3. Malignancies, including lymphoma
4. Congestive heart failure (CHF)
5. Demyelinating-like disorders
6. Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leukopenia
7. Serious bleeding events
8. Lupus and lupus-like syndrome
9. Serious skin reactions (e.g., Stevens Johnson Syndrome, Toxic Epidermal Necrosis, and Erythema Multiforme)

These AESIs are reviewed in the subsections below. In addition, AEs of injection reactions (including hypersensitivity) and psychiatric events are presented separately.

No study participants had AEs consistent with potential Hy's law, malignancies, major cardiovascular event, demyelinating-like disorders, serious bleeding event, lupus/lupus-like

syndrome, serious skin reaction; therefore, these will not be reviewed further below.

8.2.5.1. Infections

TEAEs within the Infections and infestations SOC was the most commonly reported SOC (79.8% in the Any CZP Dose group, 53.3% in the Original CZP Dose group, 84.1% in the Reduced CZP Dose group). The most common infections were nasopharyngitis (n=21, 20.0%) and streptococcal pharyngitis (n=19, 9.8%) in the Original CZP Dose group and nasopharyngitis (n=22, 25.0%) and upper respiratory tract infection (n=23, 26.1%) in the Reduced CZP Dose group.

Serious Infections

For Any CZP Dose, 21 study participants (10.9%) had 26 serious infections. The most frequently reported serious infection was pneumonia (n=6, 3.1%).

- No serious infections occurred while a participant was taking the Original CZP Dose through the time of the 90-day SUR. However, the patient who died after the data cutoff date experienced serious infections of esophageal candidiasis and disseminated TB.
- Reduced CZP Dose
    - Enrolled on the Reduced CZP Dose (n=11)
        - The types of serious infections included sepsis, gastroenteritis, pneumonia, septic shock, liver TB, appendicitis, pilonidal cyst, varicella
    - Enrolled on the Original CZP Dose and dose reduced (n=9)
        - The types of serious infections included pneumonia, fungal pneumonia, tuberculosis, appendicitis, bacteremia, breast abscess, pharyngitis, pyelonephritis, viral infection

Opportunistic Infections

For Any CZP Dose, 6 study participants (3.1%) had 10 opportunistic infections. Below is a description of participants who developed opportunistic infections; some of which were both serious and opportunistic.

- One patient died in the Original CZP Dose group after the 90-day SUR. The esophageal candidiasis and disseminated TB were considered both serious and opportunistic.
- Reduced CZP Dose
    - Enrolled on the Reduced CZP Dose (n=3)
        - The types of events categorized as opportunistic infections included septic shock, liver TB, sepsis, and varicella.
    - Enrolled on the Original CZP Dose and dose reduced (n=2)
        - The types of events categorized as opportunistic infections included fungal pneumonia, tuberculosis, and bacteremia.

In Study RA0043, infections were the most common adverse event. Participants developed both serious and opportunistic infection, as described. The types of infections are consistent with the known safety profile of CZP and other TNFα inhibitors. Although there were less serious and opportunistic infections in the Original CZP Dose group, it is difficult to make any comparisons based on overall low numbers and differences in exposure between the Original CZP Dose group and Reduced CZP Dose group.

8.2.5.2. Hematopoietic Cytopenia

The Standardized MedDRA Query (SMQ) of "hematopoietic cytopenia" (SAEs only) was used to identify this AESI. For Any CZP Dose, 3 study participants (1.6%) had events identified with this SMQ; all had the PT of anemia. The SMQ identified AEs reported in two participants in the Original CZP Dose group and one participant in the Reduced CZP Dose group. One participant in the Original CZP Dose group had concurrent serious TEAE of leukocytosis that led to study discontinuation, and nonserious pyrexia and pharyngotonsillitis, and one participant in the Reduced CZP dose group had concurrent serious death due to septic shock and tuberculosis liver (discussed above). One participant in the Reduced CZP Dose had nonserious cellulitis and leukopenia.

Anemia is a known risk with CZP use. These participants also had concurrent potential contributing medical issues at the time of their anemia.

8.2.5.3. Injection Reactions (Including Hypersensitivity)

Injection reactions identified by the Investigator were categorized as local injection site reactions or systemic injection reactions. Systemic hypersensitivity reactions were further categorized as acute or delayed.

For Any CZP Dose, 29 participants (15.0%) reported injection reactions; the proportion of participants in the Original CZP Dose group (16.2%) was slightly greater than that in the Reduced CZP Dose group (12.5%). Most of these participants (14.0%) had local injection site reactions (including pain, erythema, and reaction), whereas five participants (2.6%) had systemic injection reactions. Most of these events were mild or moderate in intensity. No participants had serious injection reactions. There were no events of anaphylaxis.

The number and types of injection reactions are consistent with the known experience with CZP.

8.2.5.4. Psychiatric Events

For Any CZP Dose, two participants had SAEs categorized as psychiatric events. Both participants were enrolled on the Original CZP Dose but were taking the Reduced CZP Dose at time of the events. One participant had an SAE of suicidal ideation. One participant had SAEs of anxiety and intentional self-injury. The Investigator did not consider these AEs related to CZP. Therefore, there did not appear to be a signal concerning for psychiatric events.

8.2.6. Safety Analyses by Demographic Subgroups

The Applicant analyzed the safety in Study RA0043 by weight categories, age groups, gender, race, and concomitant MTX use. The Applicant noted the following:

- AEs by weight category are presented above in Table 20. For Any CZP Dose, the proportion of SAEs appeared to be smaller in the higher weight category (17.9% in the ≥40 kg group, 31.7% in the 20 to <40 kg group, and 27.8% in the 10 to <20kg group). Comparisons are limited by the smaller number of participants in the lowest weight category and the longer duration of exposure in the highest weight category.
- AEs by age groups showed similar trends to the AEs by weight category. For Any CZP Dose, the overall proportion of participants with AEs were similar across age groups (81.8% in the 2 to <6 years, 96.0% in the 6 to <12 years, 95.3% in the 12 to 17 years). There was a lower proportion of SAEs in the older participants (36.4% in the 2 to <6 years, 26.7% in the 6 to <12 years, 19.6% in the 12 to 17 years). Like the analysis by weight category, comparisons are limited by the smaller number of participants in the younger age group and the longer duration of exposure in the older age group.
- Analysis of AEs by gender and race showed generally similar proportion of AEs as the overall population, likely reflecting the demographics of the study population. The majority of participants in Study RA0043 were female and White, limiting comparisons based on gender and race.
- For Any CZP Dose, the proportion of AEs was similar whether participants were receiving concomitant MTX (94.6% in participants with MTX and 95.6% in participants without MTX). More participants on concomitant MTX (25.7%) reported SAEs (15.6% in participants without MTX). The proportion of participants with AEs leading to discontinuation were similar for both groups (12.8% in participants with MTX vs. 11.1% in participants without MTX). The vast majority of participants (N=148) were receiving concomitant MTX, so comparisons are limited.

Overall, no meaningful differences were observed in safety analyses based on demographics or use of concomitant MTX.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignances were reported in Study RA0043.

Human Reproduction and Pregnancy

A total of 7 pregnancies (n=6 in female participants and n=1 in the female partner of a male participant) occurred in Study RA0043. One female participant reported a spontaneous abortion, but the other pregnancies resulted in live births with no congenital anomalies.

The Applicant conducted a search of pregnancy and lactation cases in participants <18 years of age in the UCB Global Safety Database (September 7, 2007, to March 6, 2024). This search yielded 9 prospective pregnancy cases (one from Study RA0043). Five participants had underlying Crohn's disease; two had JIA with polyarthritis; one had RA. Three of these pregnancies resulted in live births, but outcomes from the other pregnancies were unknown.

No pediatric exposure via breastfeeding was reported for mothers <18 years of age.

Pediatrics and Assessment of Effects on Growth

For Any CZP Dose, changes in weight-for-age and height-for-age percentiles were monitored through the study. Participants generally remained within normal weight and height percentiles throughout the study.

Tanner stage was also monitored through the study. At Week 24 for Any CZP Dose, 8 of 63 males and 15 of 130 females progressed in their Tanner stage. One AE of delayed puberty was reported for a female participant in the Original CZP Dose group. Per report, CZP administration was not changed due to this AE.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No AEs were reported related to inadvertent administration of higher doses of CZP.

Study RA0043 was not designed to evaluate the abuse and dependence potential or withdrawal or rebound of CZP.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant conducted a cumulative search of all postmarketing case reports in pediatric population <18 years of age was performed in the UCB Global Safety Database (September 7, 2007, to March 6, 2024). A total of 932 case reports were identified in patients who received CZP for multiple indications, of which the most common was Crohn's disease (n=428). There

were fewer case reports for RA (n=94), JIA (n=51), AS and axial spondyloarthropathy (n=55), and PsA (n=22). Of the 932 case reports, 210 were serious, and 722 were nonserious. The most frequently reported AEs included off-label use (n=140), drug ineffective (n=79), Crohn's disease (n=57), injection site pain (n=47), and pyrexia (n=46). Generally, the safety events in these postmarket reports are consistent with the known safety profile of CZP in approved adult indications.

Expectations on Safety in the Postmarket Setting

The observed safety profile for CZP in JIA with active polyarthritis in Study RA0043 is generally similar to the observed safety profile of CZP in approved adult indications including RA as well as the known safety profile of other TNFα inhibitors in JIA with active polyarthritis, including pJIA. Therefore, the safety profile of CZP in the postmarket setting is expected to be consistent with the known risks associated with TNFα inhibitors in JIA with active polyarthritis and other indications. There are no new safety issues that cause concern when considering how the drug may be used in the postmarket setting.

8.2.9. Integrated Assessment of Safety

Study RA0043 was the single, open-label study conducted to evaluate the PK, safety, and efficacy of CZP in participants with JIA with active polyarthritis. The safety assessment of CZP for the proposed pJIA indication is primarily based on the safety data from 193 participants with JIA with active polyarthritis treated with weight-tiered dosing for CZP. Two dose regimens (Original CZP Dose and Reduced CZP Dose) were assessed. Three deaths occurred in the study. Two of these deaths were due to miliary TB and were related to CZP (one occurred in the Original CZP Dose group; the other in the Reduced CZP Dose group). The most common SAE was pneumonia (n=6). Other serious infections (other than miliary TB and pneumonia) included gastroenteritis, appendicitis, pilonidal cyst, varicella, breast abscess, pharyngitis, pyelonephritis, viral infection, septic shock, and bacteremia. Opportunistic infections occurred in Study RA0043 and included esophageal candidiasis, miliary/disseminated TB, TB, and varicella. The most common AEs included nasopharyngitis, upper respiratory tract infection, and headache. In general, the types and numbers of adverse events were similar across both dose regimens and across weight categories. Numerical differences could be attributed to the small number of participants in the lowest weight category and the longer duration of exposure in the higher weight categories. Additionally, the different doses were not administered concurrently, and the study was not designed to compare these 2 dose regimens. Overall, the safety profile in pediatric patients with JIA with active polyarthritis on Any CZP Dose was similar to the previously established safety profile in adults with RA treated with CZP. No new safety signals were identified.

8.3. Statistical Issues

Study RA0043 is an ongoing, multicenter, open-label study to assess the PK, immunogenicity,

safety, and efficacy of CZP in children and adolescents with moderately-to-severely active JIA with polyarthritis. The primary assessments were the analysis of PK and safety. Efficacy was analyzed descriptively as a secondary endpoint. No statistical issues were identified.

8.4. Conclusions and Recommendations

The Applicant resubmitted updated data from Study RA0043 to support CZP for the treatment of active pJIA in patients ages 2 to 17 years. The resubmission of S-275 also is intended to fulfill a PREA PMR (PMR 2563-1) required at the time of the approval for the RA indication to provide an assessment of pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance, and immunogenicity in a pediatric population ≥2 to <17 years with pJIA. Study RA0043 was designed and conducted as an open-label, PK, safety, and tolerability study in pediatric subjects ages 2 to 17 years-old with JIA with active polyarthritis. The primary objectives were to evaluate the PK and safety including immunogenicity in pediatric participants with JIA with active polyarthritis. Evaluation of the descriptive efficacy of CZP in JIA with active polyarthritis was a secondary objective.

The efficacy of CZP in pJIA is based on matching systemic exposure and extrapolation of established efficacy of CZP in adult RA. Because of the similarities between the clinical presentation, disease progression, and responsiveness to therapies, including TNFα inhibitors, between adult RA and pJIA, efficacy extrapolation was considered an acceptable approach. As discussed in Section 6, the Clinical Pharmacology team determined that the exposures in patients with JIA with active polyarthritis treated with the Original CZP Dose in Study RA0043 were within the range of exposures seen in Study RA0138 in adult RA patients treated with CZP. Therefore, the Applicant provided an adequate PK bridge for CZP to support the extrapolation of efficacy in the adult RA population to the pJIA population. In addition, numerical trends of improvement from baseline were observed for the efficacy endpoints in Study RA0043 (e.g., PedACR responses) in participants with JIA with active polyarthritis for both dose regimens, providing additional support of the efficacy of CZP in pJIA.

The safety assessment of CZP for the proposed pJIA indication is primarily based on the safety data from 193 participants with JIA with active polyarthritis treated with weight-tiered dosing for CZP. Two dose regimens (Original CZP Dose and Reduced CZP Dose) were assessed. Three deaths occurred in the study. Two of these deaths were due to miliary TB and were related to CZP (one occurred in the Original CZP Dose group; the other in the Reduced CZP Dose group). The most common SAE was pneumonia (n=6). Other serious infections (other than miliary TB and pneumonia) included gastroenteritis, appendicitis, pilonidal cyst, varicella, breast abscess, pharyngitis, pyelonephritis, viral infection, septic shock, and bacteremia. Opportunistic infections occurred in Study RA0043 and included esophageal candidiasis, miliary/disseminated TB, TB, and varicella. The most common AEs included nasopharyngitis, upper respiratory tract infection, and headache. In general, the types and numbers of adverse events were similar across both dose regimens and across weight categories. Numerical differences could be attributed to the small number of participants in the lowest weight category and the longer

duration of exposure in the higher weight categories. Additionally, the different dose were not administered concurrently, and the study was not designed to compare these 2 dose regimens. Overall, the safety profile in pediatric patients with JIA with active polyarthritis on Any CZP Dose was similar to the previously known safety profile in adults with RA treated with CZP. No new safety signals were identified for either dose regimen.

During the review cycle, (b) (4) Rather, patients with pJIA could be dosed by healthcare providers with the lyophilized formulation available in a vial. Study RA0043 was conducted with the PFS. Based on previous bridging studies and analytical similarity between the formulation in the PFS and the vial (see Section 6), alongside clinical data supporting efficacy and safety of the vial and PFS in adult RA, the use of the vial for the lower weight groups (10 to <20 kg and 20 to <40 kg) is reasonable. Labeling updates (see Section 11) were made to reflect use of the vial for these lower weight groups for pJIA.

In conclusion, the efficacy and safety evidence provided in this submission support a favorable benefit/risk profile of CZP for the treatment of pJIA patients ages 2 to 17 years following the proposed weight-tiered dosing (Original CZP Dose). The safety of CZP in pJIA was consistent with the known safety of CZP and offers an acceptable risk for the therapeutic benefits. Approval of CZP will provide an additional treatment option in the United States. Therefore, we recommend approval of CZP for active pJIA in pediatric patients 2 to 17 years of age. We also recommend that PMR 2563-1 be considered fulfilled based on the results of Study RA0043 and the resubmission of S-275. See Section 10 for details.

9 Advisory Committee Meeting and Other External Consultations

No issues were identified warranting advisory committee (AC) input. As discussed in the regulatory history (Section 3.2), the FDA/University of Maryland CERSI workshop titled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis" (October 2, 2019) served as the public discussion of the PK-based extrapolation approach from adult RA to pJIA. Therefore, no advisory committee meeting was convened for BLA 125160/S-275.

10 Pediatrics

BLA 125160/S-275 was submitted to fulfill the PREA post-marketing requirement (PMR) 2563-1 issued by FDA following the approval of CZP in adult RA to provide an "assessment of pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance and immunogenicity in the pediatric population ≥2 years to <17 years with polyarticular JIA." Study RA0043 has adequately addressed all PMR requirements, including assessments of PK, safety, immunogenicity in pediatric patients between the ages 2 to 17 years with active polyarticular JIA. The review team recommends that the PMR be considered fulfilled. The submission was reviewed at the FDA Pediatric Review Committee (PeRC) on August 6, 2024. The PeRC agreed with the Division's assessment and recommendation that the study fulfills the intent of the PMR.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Table 21 presents a high-level summary of the labeling proposal and subsequent interactions between the Applicant and the Agency.

Table 21. Summary of Significant Labeling Changes

Section	Labeling Changes
Section 1 Indications and Usage	• The Applicant proposed the indication of "Treatment of (b) (4) (b) (4) active polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) in patients 2 years of age and older" which was revised as follows to accurately reflect the appropriate patient population for which the efficacy is supported based on the extrapolation of efficacy from adult RA: Treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older. Aligning revisions to references to the pJIA indication were also implemented throughout the updated labeling
Section 2 Dosage and Administration	• Statement that (b) (4) (b) (4) was removed as it does not further inform dosage recommendations • The following text was added: There is no dosage form for Cimzia that allows for patient self-administration for doses below 200 mg. Doses less than 200 mg require administration by a health care professional using the vial kit • Description of color of liquid in prefilled syringe was clarified adding the following in italics: "It should be clear *to opalescent* and colorless to yellow..."
Section 5 Warnings and Precautions	• Section 5.10 Immunization was updated to include the following: Avoid use of live vaccines during or immediately prior to initiation of therapy with Cimzia. Update immunizations in agreement with current immunization guidelines prior to initiating Cimzia therapy
Section 6.1 Clinical Trials Experience	• Description added of Study RA0043 in patients with JIA with active polyarthritis 2 years and older with statement that the safety profile observed was similar to the safety profile in adult RA patients treated with Cimzia • Study population in Study RA0043 revised from (b) (4) (b) (4) to JIA with active polyarthritis to more accurately reflect the study population that included JIA subtypes other than pJIA ○ Aligning revisions to descriptions of the study population for Study RA0043 were implemented throughout the updated labeling • Descriptive statements on observed serious infections and TB and opportunistic infections were included in the relevant subsections

Section 6.2 Immunogenicity	• Immunogenicity statement updated consistent with "guidance for Industry -- *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format* https://www.fda.gov/media/155871/download • Statement that [redacted] was removed as conclusions [redacted] are limited by the single-arm, open-label study design
Section 7.2 Live Vaccines	• Updated to align with Section 5.10 (see above)

Section 8.4 Pediatric Use	• Addition of statements describing pediatric populations in which safety and efficacy information are available
	• Clarification of the description of data supporting use of Cimzia in pJIA:
	  ○ Data from adequate and well-controlled studies in adults with RA
	  ○ PK data from adults with RA and pediatric patients with JIA with active polyarthritis
	  ○ Safety data from Study RA0043 in patients 2 to less than 18 years of age with JIA with active polyarthritis
	• Statement regarding comparable PK between adults with RA and pediatric patients with JIA with active polyarthritis added.
	• Updates to statements of populations in which the safety and effectiveness of Cimzia have not been established in pediatric patients

Section 12.3 Pharmacokinetics, Pediatrics	• Description of PK data in JIA with active polyarthritis • Specification of the body weight groups for which similar peak plasma concentrations were observed in JIA with active polyarthritis patients • Addition of statement that similar to the adult indications, body weight and anti-certolizumab antibodies titers affected certolizumab pegol PK with higher body weights and presence of ADA associated with lower exposures and no impact from use of concomitant methotrexate on CZP concentrations.
Section 14 Clinical Studies, pJIA	• Addition of Section 14.3 describing the support for the efficacy of Cimzia in pJIA based on PK exposure and extrapolation from RA patients. • Description of Study RA0043 design added. • As efficacy established based on PK-based extrapolation and efficacy was assessed descriptively as secondary endpoints in open-label Study RA0043, detailed description of efficacy results was replaced with description that the efficacy was generally consistent with the responses in patients with RA. • NCT number was added
Section 16 How Supplied/ Storage and Handling	• How Supplied information reformatted into tabular format for readability

Other Prescription Drug Labeling

Revisions to patient labeling were made to align with the revised prescribing information, including the addition of the pJIA indication and updates to the guidance on not receiving live vaccines to align with Section 5 and 7 of the prescribing information (PI). In addition, storage information was added to align with the PI and Instructions for Use. Revisions to the IFU included adding storage information instructions not to freeze, not to shake, to protect Cimzia from light, and not to use if the medicine is expired.

Labeling consultants, including DMEPA, OPDP, and DMPP, have reviewed the submitted labeling and their recommendations, which pertain primarily to internal consistency, improving readability, and clarity of the labeling, have been considered and conveyed to the Applicant. All labeling changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

No new risk management plans are submitted in BLA 125160/S-275. As no new safety signals have been identified, a Risk Evaluation and Management Strategy (REMS) is not recommended.

13 Postmarketing Requirements and Commitment

There are no potential or new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement (PMR) or postmarketing commitment (PMC).

14 Division Director (or designated signatory authority) (Clinical) Comments

I concur with the review and conclusions by the review team, as detailed in this document. The regulatory action for S-275 for certolizumab pegol for treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older is Approval. The data provided in BLA 125160/S-275 fulfills the PREA PMR 2563-1. No postmarketing required studies or commitments are warranted based on this submission.

15 Appendices

15.1. References

Brewer EJ, Bass J, Baum J, et al., 1997, Current proposed revision of JRA criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association, *Arthritis Rheum*, 20 (Suppl): 195-9.

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Petty RE, Southwood TR, Manners P, et al., 2001, International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, *J Rheumatol*, 31(2):390–392.

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Ringold S, Angeles-Han ST, Beukelman T, et al. 2019, 2019 American College of Rheumatology/ Arthritis Foundation Guidelines for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis, *Arthritis Care & Res*, 71:717-734.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study RA0043

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 49 principal investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in the study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) Not applicable

Covered Clinical Study (Name and/or Number): Study RA0138

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13 principal investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in the study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) Not applicable

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

Bioanalytical Methods: Key studies supporting this pJIA resubmission were the pediatric phase 3 study in pJIA – Study RA0043 and the adult phase 1 study in RA – Study RA0138. For both studies, plasma CZP and anti-CZP antibody (ADAb) levels were measured with respective electrochemiluminescent immunoassay (ECLIA) methods that meet current regulatory guidances.

An overview of the bioanalytical methods used for the measurement of plasma CZP concentrations and ADAb assessments in Studies RA0043 and RA0138 is shown in **Table 22**.

Table 22. Bioanalytical Methods Summary

Study numbers	Study phase	Target indication	Bioanalytical method	
			Plasma CZP concentration method	ADAb method
RA0138	1	RA	PK Method #2	ADAb-3
RA0043	3	pcJIA	PK Method #2	ADAb-3

Source: Summary of Biopharmaceutic Studies, Table 1-1.

Determination of CZP concentrations in plasma: PK Method #2, which was used for study participant sample measurements in Studies RA0043 and RA0138. PK Method #2 was an ECLIA method that measures CZP in human lithium heparin plasma. CZP is captured by recombinant

human TNFα, which is coated overnight at 2 to 8°C onto a 96 well Meso-Scale Discovery (MSD) standard bind plate. Following a wash step to remove any unbound capture reagent, the plate is blocked using assay diluent (0.5% skimmed milk powder in assay buffer) for 1 hour with no agitation. Following a wash step, samples, calibrators, and quality control's post minimum required dilution (MRD) are incubated for 1 hour with shaking at 300rpm. The CZP in the samples, calibrators, and quality control samples binds to the TNFα bound to the plate and any unbound substances are washed off. The primary detection reagent, a rabbit anti-polyethylene glycol (PEG) conjugated to biotin is added and subsequently any unbound antibody is washed off. The secondary detection reagent, streptavidin-SulfoTAG causes a luminescence signal emission when an electrochemiluminescence substrate is added and the current applied to the electrodes built into the MSD plate. The amount of light emitted is directly proportional to the amount of CZP in the sample or standard. The analyte concentration of unknown samples is determined by comparison against a standard curve. A summary of the PK method validation is shown in **Table 23** and **Table 24**.

All 78 study participants in the Original CZP Dose and all 85 study participants in the Reduced CZP Dose who had post-Baseline PK samples originally analyzed with the legacy assay had at least 1 PK sample re-analyzed with the ECLIA assay. The majority of post-Baseline PK samples originally analyzed with the legacy assay were re-analyzed with the ECLIA assay (87.0% for the Original CZP Dose and 96.0% for the Reduced CZP Dose). The percentages of the post-Baseline PK samples that were only analyzed with the ECLIA assay were 30.1% for the Original CZP Dose and 37.4% for the Reduced CZP Dose, respectively).

Table 23. Summary of PK Method Performance of Method Validation #2 in Study RA0138

Bioanalytical method validation report name, amendment and hyperlinks	**Validation of a Method for the Detection of CDP870 in Human Lithium Plasma Using MSD Report code: NCD2961rep (LGC298377QB112). Core-validation data submitted in nr-axSpA submission (adult nr-axSpA submission - BLA125160, Sequence 0561 [Module 2.7.1]).**	
Method performance in study RA0138: Report name: Determination of Certolizumab Pegol in Human Plasma from Clinical Study RA0138 using an MSD ECL Assay; Report code: NCD3516-RA0138rep		
Assay performed according to method validation #2; Phase 1 study		
Assay passing rate	41 of 61 runs were accepted; passing rate = 67.2%	NCD3516-RA0138rep Page 16 and Table 1
Standard curve performance	Cumulative bias range observed: -7.2% to 7.2% RE Cumulative precision observed: 10.0% CV	NCD3516-RA0138rep Page 16 and Table 8
QC performance	Cumulative bias range observed:-6.0% to 5.0% RE Cumulative precision observed: 18.9% CV Cumulative %TE observed 23.9	NCD3516-RA0138rep Page 16 and Table 11
Method reproducibility	Incurred sample reanalysis was performed 40 study samples and 66.7% of samples met the pre-specified criteria.	NCD3516-RA0138rep Page 16 and Table 19
Study sample analysis/stability	All samples fell within established stability.	NCD3516-RA0138rep Page 16 and 8294-355rep and 8294-355rep add1, 8294-355rep add2, 8294-355rep add3, and 8294-355rep add4
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators used: 10. Performance: see above.	NCD3516-RA0138rep Table 7

Source: Summary of Biopharmaceutic Studies, Table 4-3.

Table 24. Summary of PK Method Performance of Method Validation #2 in Study RA0043

Bioanalytical method validation report name, amendment and hyperlinks	**Validation of a Method for the Detection of CDP870 in Human Lithium Plasma Using MSD Report code: NCD2961rep (LGC298377QB112). Core-validation data submitted in nr-axSpA submission (adult nr-axSpA submission - BLA125160, Sequence 0561 [Module 2.7.1]).**	
Method performance in study RA0043: Report name: Determination of Certolizumab Pegol in Human Plasma from Clinical Study RA0043 using an MSD ECL Assay; Report code: NCD3523-RA0043rep		
Assay performed according to method validation #2; Phase 3 study		
Assay passing rate	153 of 178 runs were accepted; passing rate = 86%	NCD3523-RA0043rep Page 20 and Table1
Standard curve performance	Cumulative bias range observed: -8.0 to 5.8 %RE Cumulative precision observed: ≤ 7.5%	NCD3523-RA0043rep Page 20 and Table 19 and Page 306 Figure 1.
QC performance	Cumulative bias range observed -2 to 4.8 %RE Cumulative precision observed: ≤ 25.1%	NCD3523-RA0043rep Page 20 and Table 21
Method reproducibility	Incurred sample reanalysis was performed, and 238 of 271 (87.7%) met pre-defined acceptance criteria	NCD3523-RA0043rep Page 20 and Table 30
Study sample analysis/stability	All samples fell within established stability.	NCD3523-RA0043rep Page 28 and 8294-355rep and 8294-355rep add1, 8294-355rep add2, 8294-355rep add3, and 8294-355rep add4
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators used: 10. Performance: see above.	NCD3523-RA0043rep and Table 1

CV=coefficient of variation; ECL=electrochemiluminescence; ISR=incurred sample reanalysis; MSD=Meso-Scale Discovery; nr-axSpA=nonradiographic axial spondyloarthritis; PK=pharmacokinetic; QC=quality control; RE=relative error

Source: Summary of Biopharmaceutic Studies, Table 4-3.

Immunogenicity/ADAb methods: The ADAb-3 method was used to assess ADAb in Studies RA0043 and RA0138. The presence of ADAb in human plasma was determined using a bridging ECLIA assay method (referenced as Method ADAb-3). An industry standard tiered approach (Tier 1 Screening Assay, Tier 2 Confirmatory Assay, Tier 3 Titer Assay) in agreement with the current FDA guidances was applied to evaluate ADAb levels in Studies RA0043 and RA0138. A summary of the ADAb method validation is shown in **Table 25** and method performance for Studies RA0138 and RA0043 are shown in **Table 26** and **Table 27**.

The percentages of post-Baseline ADAb samples that were originally analyzed with ELISA and reanalyzed with ECLIA ranged from 96.8% to 98.9% across the Original CZP Dose, the Reduced CZP Dose, the Complete Original CZP Dose, and the Complete Reduced CZP Dose. Of all the samples analyzed with ECLIA, the percentages of post-Baseline ADAb samples that were previously analyzed with ELISA ranged from 64.6% to 74.3% and the percentages of the post-Baseline ADAb samples that were only analyzed with ECLIA ranged from 26.0% to 35.4% across the Original CZP Dose, the Reduced CZP Dose, the Complete Original CZP Dose, and the Complete Reduced CZP Dose.

Table 25. Summary of ADAb Method Performance and Validation

Validation ID	Description
Method ID	16269 (NDC3323rep)
Validation ID	Partial Re-Validation of an Immunogenicity Method for the Determination of Anti-CDP870 Antibodies in Healthy Human Plasma
Bioanalytical site	(b) (4)
Analyte	Anti-CDP870
Drug	CDP870; CDP870-RS-003
Tiered analysis approach	Screening, confirmation, titration
Platform	ECL MSD Sector Imager S600
Assay format	Semi-homogeneous direct assay
Sample pre-treatment	Acid dissociation in 300mM acetic acid pH 2.0 (30 mins at 25°C)
Capture reagent	Biotin-CDP870 prepared in mastermix at 0.750µg/mL (in well concentration of 0.500µg/mL)
Detection reagent	SulfoTag-CDP870 prepared in mastermix at 1.08µg/mL (in well concentration of 0.720µg/mL)
Method description	Samples are diluted at 1 in 10 with 300mM acetic acid pH 2.0. 1 volume of acidified samples is neutralized with 9 volumes of mastermix solution (SuperBlock in PBS solution containing 0.750µg/mL Biotin-CDP870 and 1.08µg/mL SulfoTag-CDP870 is first added to the acidified sample followed by a separate neutralization step containing 1.5M Tris diluted with SuperBlock in PBS). In well concentrations = Biotin-CDP870 (0.500µg/mL), SulfoTag-CDP870 (0.720µg/mL), Tris (33.7mM), CDP870 in confirmatory assay (45.0µg/mL). Incubation of mixture overnight at +25°C, shaking at 600rpm. MSD Streptavidin coated plate overnight blocked with SuperBlock in PBS at RT (nominally +20°C), without shaking. MSD plate washed with wash buffer (1x PBS). Sample mixture added to blocked MSD plate and incubated for 1 hour at +25°C, shaking at 300 rpm. MSD plate washed with wash buffer (1x PBS), addition of read buffer to MSD plate and read.
Positive control	Anti-CDP870 rabbit IgG anti-Id (BSN.3973.rbIgG.137)
Negative control	Pooled healthy lithium heparin plasma
Matrix	Human lithium heparin plasma
MRD	100-fold

Assay diluent	SuperBlock		
Drug concentration in the confirmatory tier	Prepared in mastermix at 67.5µg/mL (in well concentration of 45.0µg/mL)		
Validation parameters	**Method validation summary**		
Screening cut-point (floating, multiplicative, 95.0% upper limit)	**Pop (healthy vs disease status)**	**Assessment**	**SCP factor**
	Healthy (n=56) (NCD3323rep validation report Section 11.4)	Using commercially available healthy lithium heparin plasma samples calculated from 6 assessments (2 analysts, 3 batches each) following a balanced design using mixed effect model for outlier exclusion using conditional residuals and BLUPs for analytical and biological outlier exclusion. Parametric approach using log-transformed normalized data Each batch consisted of 4 plates.	1.12
Confirmatory cut-point (% inhibition, floating multiplicative, 99.0% upper limit)	**Pop (healthy vs disease status)**	**Assessment**	**CCP factor**
	Healthy (n=56) (NCD3323rep validation report Section 11.4)	Calculated from 6 assessments (2 analysts, 3 batches each) following a balanced design using mixed effect model for outlier exclusion using conditional residuals and BLUPs for analytical and biological outlier exclusion. Parametric approach using inhibition ratio data in drug displacement assay.	0.817
Titer cut-point (floating, multiplicative, 99.0% upper limit)	**Pop (healthy vs disease status)**	**Assessment**	**TCP factor**
	Healthy (n=56) (NCD3323rep validation report Section 11.4 and Section 11.5)	The TCP was calculated corresponding to 99.0% upper limit of the SCP. The TCP of 1.17 was confirmed as suitable based on titration precision of PC curve of cut-point assessment and sensitivity investigation (n=36), MSR of 2.69.	1.17

Control precision (NCD3323rep validation report Section 11.7, Table 21 to Table 25, Table 36)	**Level**	**Conc. (ng/mL)**	**Screen % CV signal**		**Confirm % CV signal**				
			Intra-assay (y/z)[a]	**Inter-assay**	**Intra-assay (y/z)[a]**	**Inter-assay**			
	HPC	20,000	3.0/5.1	12.9	7.7/45.0	13.2			
	MPC	1000	4.1/20.4	13.3	7.2/25.9	15.9			
	cLPC	100	4.0/8.3	9.3	4.7/23.2	12.8			
	sLPC	54.4	2.6/17.8	9.8	11.1/14.2	10.0			
	NC	0.00	5.4/19.1	17.0	8.4/14.8	12.0			
	MPC and HPC selected based on previous validated method. LPC selected based on 99.0% CI of sensitivity and suitable PC scoring.								
	Titer PC		**MSR (inter-assay)**		**% CV (inter-assay) (screening assay)**				
	250ng/mL		Healthy pool (n=36)	2.69	Healthy	10.3			
			Healthy individual (n=5)	1.83	Healthy	9.0			
Sensitivity (PC antibody in neat matrix) (NCD3323rep validation report Section 11.6, Table 19 to Table 20)	**Assay type**		**Cut-point (pop)**		**Conc. (ng/mL) (50, 95, and 99% CI)**				
	Screen		1.12 (healthy)		17.6, 38.4, 54.4				
	Confirm		0.817 (healthy)		29.6, 67.3, 97.6				
Drug tolerance (PC antibody/drug in neat matrix) (NCD3323rep validation report, Section 11.9, Table 28 to Table 30)	**Assay type**	**Cut-point (pop)**	**PC conc.[b] (ng/mL)**	**Tolerated drug conc. (µg/mL)**	**Assay sensitivity in presence of drug**				
					Drug[b] (µg/mL)	**Sensitivity (ng/mL)**			
	Screen	1.12 (healthy)		100	100	<54.4			
			1000	100	75	<54.4			
			250	100	50	<54.4			
			100	100	20	<54.4			
			54.4	100	10	<54.4			
			N/A		2	<54.4			
	Confirm	0.817 (healthy)	20,000	100	100	76.4			
			1000	100	75	62.5			
			250	100	50	<54.4			
			100	100	20	<54.4			
			54.4	50	10	<54.4			
			N/A		2	<54.4			
	100ng/mL PC tolerance to 100µg/mL drug acceptable, meets expectations of previous validated method.								

Target tolerance (NCD3323rep validation report Section 11.10, Table 31)	**Assay type**	**Cut-point (pop)**	**PC conc. (ng/mL)**	**Tolerated target conc. (pg/mL)**	**Impact assay**
	Screen	1.12 (healthy)	20,000	1000	*No false negative results in the screening or confirmatory assay for 54.4-20,000ng/mL of PC in the presence of up to 1000pg/mL of TNFα.* *No false positives observed in the NC in the presence of up to 1000pg/mL of TNFα.*
			1000	1000	
			250	1000	
			100	1000	
			54.4	1000	
			0.00	1000	
	Confirm	0.817 (healthy)	20,000	1000	
			1000	1000	
			250	1000	
			100	1000	
			54.4	1000	
			0.00	1000	
	PC and NC tolerance to 1000pg/mL target acceptable, meets expectations of previous validated method.				
Selectivity	Not required to be reported for this partial validation.				
Hook effect	Not required for this partial validation.				
Hemolysis	Not required for this partial validation.				
Lipemia	Not required for this partial validation.				
Icteric (NCD3323rep validation report Section 11.12, Table 34)	No effect in blank, LPC (54.4ng/mL) and HPC (20,000ng/mL) spiked matrix in 0.0300mg/mL bilirubin in plasma (in screening and confirmatory assay)				
Thawed matrix stability	Not required for this partial validation.				
Freeze-thaw stability	Not required for this partial validation.				
Acceptance limits for system suitability controls (NCD3323rep validation report Section 11.8, Table 27	**PC conc. (ng/mL)**	**Limits** (b) (4)			
	HPC/NC (lower and upper limit)				
	MPC/NC (lower and upper limit)				
	cLPC/NC (upper limit)				
	sLPC/NC (upper limit)				
	NC (upper limit)				

	Tier	Control	Run acceptance criteria
Run acceptance criteria (NCD3323rep validation report Section 11.1)	Screen	NC ([b) (4)] replicates)	≤ [b) (4)] % CV between duplicates. [b) (4)] out of [b) (4)] replicates should have acceptable % CV between duplicates
			Mean NC signal ≤ upper limit ([b) (4)] %)
			Intra-assay precision ≤ [b) (4)] %. [b) (4)] replicate can be excluded as outlier value
		LPC ([b) (4)] replicates)	≤ [b) (4)] % CV between duplicates [b) (4)] out of [b) (4)] replicates should have acceptable % CV between duplicates
		HPC ([b) (4)] replicates)	HPC (both replicates) and LPC (both replicates) ≥ SCP
	Confirm	NC-I ([b) (4)] replicates)	≤ [b) (4)] % CV between duplicates [b) (4)] out of [b) (4)] replicates should have acceptable % CV between duplicates
			Intra-assay precision ≤ [b) (4)] %. [b) (4)] replicate can be excluded based on outlier determination
			All replicates should have inhibition ratio > CCP
		LPC-I ([b) (4)] replicates)	≤ [b) (4)] % CV between duplicates. [b) (4)] out of [b) (4)] replicates should have acceptable % CV between duplicates
		HPC-I ([b) (4)] replicates)	LPC-I ([b) (4)] replicates) inhibition ratio ≤ CCP
			HPC-I ([b) (4)] replicates) inhibition ratio ≤ CCP
	Titer	Titer controls	≤ [b) (4)] % CV for dilutions involved in titer calculation
			Titer is within MSR limits
Sample acceptance criteria	Screen	≤ [b) (4)] % CV between duplicates	Samples with mean replicate response [b) (4)] are considered "potential positive" and progress to confirmatory analysis.
			Samples with mean replicate response [b) (4)] are reported as "negative."
	Confirm	≤ [b) (4)] % CV between duplicates	Samples with inhibition ratio [b) (4)] are considered "positive" and progress to titer analysis.
			Samples with inhibition ratio [b) (4)] are reported as "negative."
	Titer	≤ [b) (4)] % CV (for titer calculation dilutions – flanking points)	≥ [b) (4)] dilution must be [b) (4)]
			The sample titer is dilution factor (including the MRD) calculated via linear interpolation between the flanking point of the TCP or by reporting the end point titer.

Source: Integrated Summary of Immunogenicity, Table 9-5.

Table 26. Summary of ADAb Method Performance in Study RA0138

Method performance in RA0138; Report name: Determination of Anti CDP870 Antibodies in Human Plasma Samples from Phase 1b Clinical Study Number RA0138 Using a MSD ECL Assay; Report code: NCD3515-RA0138rep			
Title of study	Determination of Anti CDP870 Antibodies in Human Plasma Samples from Phase 1b Clinical Study Number RA0138 Using a MSD ECL Assay		
Screening assay performance	4 out of 4 screening runs were accepted (100% acceptance rate).		
Confirmatory assay performance	6 out of 6 confirmatory runs were accepted (100% acceptance rate).		
Titration assay performance	24 out of 24 titer runs were accepted (100% acceptance rate).		
Screening pre-dose false positive rate	12.5%		
LPC failure rate	0 out of 34 runs were rejected due to unacceptable LPC response below SCP (0% failure rate)		
Control responses precision– Replicate (RLU) range during sample analysis	**Level**	**Conc. (ng/mL)**	**Precision range (% CV)**
	NC	0	0-17
	sLPC	54.4	0-11.6
	cLPC	100	0.9-17.6
	HPC	20,000	0-13.3

Source: Integrated Summary of Immunogenicity, Table 9-6.

Table 27. Summary of ADAb Method Performance in Study RA0043

Method performance in RA0043; Report name: Determination of Anti-CDP870 Antibodies in Human Plasma Samples from Clinical Study RA0043 using an MSD ECL Assay; Report code: NCD3522-RA0043rep			
Title of study	Determination of Anti-CDP870 Antibodies in Human Plasma Samples from Clinical Study RA0043 using an MSD ECL Assay		
Screening assay performance	5 out of 6 screening runs were accepted (83% acceptance rate).		
Confirmatory assay performance	198 out of 239 confirmatory runs were accepted (83% acceptance rate).		
Titration assay performance	410 out of 481 titer runs were accepted (85% acceptance rate).		
Screening pre-dose false positive rate	12 out of 174 baseline samples were reported as screen positive (FPR=6.9%).		
LPC failure rate	sLPC: 54 out of 1408 runs were rejected due to unacceptable LPC response below SCP (3.8% failure rate). cLPC:3 out of 418 runs were rejected due to unacceptable LPC response below SCP (0.7% failure frate).		
Control responses precision– Replicate (RLU) range during sample analysis	**Level**	**Conc. (ng/mL)**	**Precision range (% CV)**
	NC	0	0-28.3
	sLPC	54.4	0-18.2
	cLPC	100	0-14.2
	HPC	20,000	0-16.0

Source: Integrated Summary of Immunogenicity, Table 9-7.

Storage and stability of samples from RA0043: Within the CRL dated 22 Mar 2017, which the Agency issued in response to the initial pJIA submission – BLA 125160, Sequence 0426, concerns regarding freeze thaw and long-term stability of study samples had been raised. These concerns have been addressed through demonstrating the stability of CZP over time and through freeze-thaw cycles, and the currently available data support sufficient number of freeze thaw cycles and length of stability period. All samples included in the analysis met the requirements for freeze-thaw cycles and stability.

The (b) (4) validated stability period was reported as 897 days at (b) (4) °C in the original pJIA submission. Further stability has been provided by the Applicant demonstrating 3146 days. Samples were stored for a maximum of up to 3977 days between the date of collection and the date of sample analysis. Samples are stable for 3146 days in a freezer set to (b) (4) °C. The results from samples analyzed outside of the currently demonstrated stability are not scientifically valid. Of the 193 samples selected for incurred sample reanalysis, 167 samples (86.5%) met the acceptance criteria of being within (b) (4) % of their mean value. Acceptable stability of analyte was demonstrated for benchtop conditions (room temperature for up to 25 days), frozen at -20 Deg

C and (b) (4) Deg C (819 days and 897 days respectively) and over 14 freeze/thaw cycles from (b) (4) Deg C to room temperature. Long term frozen stability of the analyte in Lithium Heparin plasma was also confirmed up to 3146 days. This was performed within a separate regulated validation at (b) (4)

15.4. Clinical Appendices

Table 28. Study RA0043 Schedule of Assessments

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

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, (17[b]), 20, 24	32 and every 8 weeks thereafter[c]	Unsch. Visit[d]	Early Disc/ EOT	Final Visit[e]
Visit (±3 days)[a]	1	2	3	4	5 to 10	11 onwards			FV
Parent's Assessment of Arthritis Pain	X	X	X	X	X	X		X	
Parent's Global Assessment of Overall Well-Being	X	X	X	X	X	X		X	
CID and clinical remission[r]			X	X	X	X		X	
Duration of morning stiffness		X	X	X	X	X		X	
JADAS-71		X	X	X	X	X		X	
FPS-R[s]		X			X	X		X	
Patient's Assessment of Arthritis Pain[t], acute		X							
Patient's Assessment of Arthritis Pain[t], standard		X			X[t]	X		X	
Fatigue Assessment Scale		X	X	X	X[u]	X		X	
Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey (parent/caregiver-reported)		X			X	X		X	
Concomitant medications and procedures[v]	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X
IXRS contact	X	X	X	X	X	X		X	X
CZP plasma concentrations		X	X		X[b]	X[w]			
ADAbs		X	X		X[b]	X[w]			

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, (17[b]), 20, 24	32 and every 8 weeks thereafter[c]	Unsch. Visit[d]	Early Disc/ EOT	Final Visit[e]
Visit (±3 days)[a]	1	2	3	4	5 to 10	11 onwards			FV
Autoantibodies (ANA and anti-dsDNA antibodies)[l]		X[x]			X[y]	X[y]		X	
CZP administration[z]		X		X	X	X			

ADAb=anti-CZP antibody(ies); AE=adverse event; ANA=antinuclear antibody; anti-dsDNA=anti-double-stranded deoxyribonucleic acid; BCG=Bacille Calmette-Guérin; BP=blood pressure; CID=Clinically Inactive Disease; CHAQ=Childhood Health Assessment Questionnaire; CRM=clinical remission on medication; CRP=C-reactive protein; CZP=certolizumab pegol; Disc=discontinuation; DNA=deoxyribonucleic acid; eCRF=electronic Case Report Form; EOT=End of Treatment; HBcAb=hepatitis B core antibody; FPS-R=Faces Pain Scale-Revised; HBsAb=hepatitis B surface antibody; HBsAg= hepatitis B surface antigen; HBV=hepatitis B virus; HCVAb=hepatitis C virus antibody; IGRA=interferon-gamma release assay; IXRS=interactive voice/web response system; JADAS-71=Juvenile Arthritis Disease Activity Score 71-joint; JIA=juvenile idiopathic arthritis; PK=pharmacokinetic; PRINTO/PRCSG=Paediatric Rheumatology International Trials Organisation/Pediatric Rheumatology Collaborative Study Group; Q2W, Q4W=every 2 weeks, every 4 weeks; TB=tuberculosis; TST=tuberculin purified protein derivative skin test; Unsch=Unscheduled; VAS=visual analog scale

[a] Screening Visit was completed at least 4 to 12 working days prior to the Baseline Visit, depending on regional requirements and laboratory assessments required for the study participant (please refer to Section 4.4.6 and the laboratory manual). For all other visits, the Visit window was ±3 days relative to Baseline.

[b] Certolizumab pegol plasma concentration and ADAbs were measured at Weeks 4, 12, 16, and 24. A postdose CZP plasma sample was collected at approximately 5 to 7 days following the Week 16 Visit (ie, required an additional clinic site visit for blood collection at Week 17). Samples for CZP plasma concentration and anti CZP antibodies were collected as separate samples.

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

[d] Vital signs, concomitant medications, concomitant procedures, and AEs were assessed at every Unscheduled Visit. Other PK and safety assessments were performed as related to nature of the visit. For Unscheduled Visits related to the dose changes, see Section 3.5.2.1. For these Unscheduled Visits, the same visit window applied, ie, ±3 days.

[e] The Final Visit was performed 12 weeks after the final dose of CZP.

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

[g] Change in height and weight over the last 6 months and over the last year were collected via parent-/self-report, if not available from medical records.

Source: UCB Updated Interim Clinical Study Report, dated December 12, 2023; Table 3-4, pages 51-53

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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