Clinical trial results:
A Multicenter, Open-Label Study to Assess the Pharmacokinetics, Safety, and Efficacy of Certolizumab Pegol in Children and Adolescents With Moderately to Severely Active Polyarticular-Course Juvenile Idiopathic Arthritis

Summary

EudraCT number	2009-018027-33
Trial protocol	Outside EU/EEA
Global end of trial date	08 April 2024

Results information

Result version number	v1 (current)
This version publication date	12 October 2024
First version publication date	12 October 2024

Trial information

Trial identification

Sponsor protocol code	RA0043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01550003
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biopharma SRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, 1070
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2024
Global end of trial reached?	Yes
Global end of trial date	08 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the Pharmacokinetic (PK) and safety including the immunogenicity of certolizumab pegol (CZP) administered subcutaneously (sc) in children and adolescents with moderate to severe polyarticular-course juvenile idiopathic arthritis (JIA)

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable

Actual start date of recruitment	08 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Mexico: 38
Country: Number of subjects enrolled	Russian Federation: 64
Country: Number of subjects enrolled	United States: 68
Worldwide total number of subjects	193
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	86
Adolescents (12-17 years)	107
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll participants in March 2012 and concluded in April 2024.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Any CZP Dose - Weight group: 10 - < 20 kg

Arm description:

Participants received Certolizumab Pegol (CZP) subcutaneously (sc) as a fixed dose based on their body weight every 2 weeks (Q2W) or every 4 weeks (Q4W) throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.

Arm type	Experimental
Investigational medicinal product name	Certolizumab Pegol
Investigational medicinal product code	CDP870
Other name	CZP, Cimzia®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received CZP at pre-defined timepoints.

Arm title	Any CZP Dose - Weight group: 20 - <40 kg

Arm description:

Participants received CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.

Arm type	Experimental
Investigational medicinal product name	Certolizumab Pegol
Investigational medicinal product code	CDP870
Other name	CZP, Cimzia®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received CZP at pre-defined timepoints.

Arm title	Any CZP Dose - Weight group: >= 40 kg

Arm description:

Participants received CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.

Arm type	Experimental

Investigational medicinal product name	Certolizumab Pegol
Investigational medicinal product code	CDP870
Other name	CZP, Cimzia®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received CZP at pre-defined timepoints.

Number of subjects in period 1	Any CZP Dose - Weight group: 10 - < 20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >= 40 kg
Started	18	63	112
Original CZP Dose	7	34	64
Reduced CZP Dose	11	29	48
Completed	0	0	0
Not completed	18	63	112
Patient reached adulthood	-	1	-
By medical decision and approved by the sponsor	-	-	1
Subject is in college/unable to come to visits	-	-	1
Missing	1	-	2
Site closure	-	2	-
Sponsor's decision	1	5	4
Study closed	-	1	-
Adverse event, non-fatal	-	9	15
Switching to adult rheumatologist	-	-	1
Non-compliance	-	-	1
Protocol Noncompliance	1	-	-
Protocol deviation	-	3	2
Study closure	-	1	1
Transitioned to adult rheumatology	-	-	1
Discontinuation	-	1	-
Treatment or 12 week follow up visit completed	-	-	1
Patient not compliance	-	-	1
Per Sponsor request	1	-	1
Subject mother passed away	-	1	-
Subject moved to rheumatology and out of study	-	1	1
Early discontinuation at request of sponsor	-	2	4
Sponsor's order	-	3	3
Subject was able to obtain commercial cimzia	-	-	1

Pregnancy	-	1	-
Lost to follow-up	1	4	8
Consent withdrawn	2	11	23
Study closure as announced by sponsor	7	6	24
Patient transition to adult care	-	-	1
Lack of efficacy	4	11	15

Baseline characteristics

Reporting groups	
Reporting group title	Any CZP Dose - Weight group: 10 - < 20 kg
Reporting group description:	
Participants received Certolizumab Pegol (CZP) subcutaneously (sc) as a fixed dose based on their body weight every 2 weeks (Q2W) or every 4 weeks (Q4W) throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.	
Reporting group title	Any CZP Dose - Weight group: 20 - <40 kg
Reporting group description:	
Participants received CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.	
Reporting group title	Any CZP Dose - Weight group: >= 40 kg
Reporting group description:	
Participants received CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.	

Reporting group values	Any CZP Dose - Weight group: 10 - < 20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >= 40 kg
Number of subjects	18	63	112
Age Categorical Units: participants			
24 months - <12 years	18	55	13
12 - <18 years	0	8	99
Age Continuous Units: years			
arithmetic mean	5.4	9.1	14.5
standard deviation	± 1.3	± 2.0	± 2.2
Sex: Female, Male Units: participants			
Female	11	43	76
Male	7	20	36

Reporting group values	Total		
Number of subjects	193		
Age Categorical Units: participants			
24 months - <12 years	86		
12 - <18 years	107		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: participants			
Female	130		
Male	63		

End points

End points reporting groups

Reporting group title	Any CZP Dose - Weight group: 10 - < 20 kg
Reporting group description:	
Participants received Certolizumab Pegol (CZP) subcutaneously (sc) as a fixed dose based on their body weight every 2 weeks (Q2W) or every 4 weeks (Q4W) throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.	
Reporting group title	Any CZP Dose - Weight group: 20 - <40 kg
Reporting group description:	
Participants received CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.	
Reporting group title	Any CZP Dose - Weight group: >= 40 kg
Reporting group description:	
Participants received CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.	
Subject analysis set title	Reduced CZP Dose -Weight group: 10 - <20 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received CZP 50 milligrams (mg) sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 50 mg sc Q4W (maintenance dose) from Week 8 onwards.	
Subject analysis set title	Reduced CZP Dose - Weight group: 20 - <40 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received CZP 100 mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 50 mg sc Q2W (maintenance dose) from Week 6 onwards.	
Subject analysis set title	Reduced CZP Dose - Weight group: >=40 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received CZP 200 mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 100 mg sc Q2W (maintenance dose) from Week 6 onwards.	
Subject analysis set title	Original CZP dose - Weight group: 10 - <20 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received CZP 100 mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 50 mg sc Q2W (maintenance dose) from Week 6 onwards.	
Subject analysis set title	Original CZP Dose - Weight group: 20 - <40 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received CZP 200 mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 100 mg sc Q2W (maintenance dose) from Week 6 onwards.	
Subject analysis set title	Original CZP Dose - Weight group: >=40 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received CZP 400 mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200 mg sc Q2W (maintenance dose) from Week 6 onwards.	
Subject analysis set title	Reduced CZP Dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received reduced CZP sc as a fixed dose based on their body weight Q2W or Q4W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.	
Subject analysis set title	Original CZP dose

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received original CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.

Primary: Certolizumab Pegol (CZP) Plasma Concentration level at Week 16

End point title	Certolizumab Pegol (CZP) Plasma Concentration level at Week 16[1]

End point description:

Certolizumab Pegol (CZP) plasma concentration level was measured in micrograms per mililiter (ug/ml). The Pharmacokinetic Per-Protocol (PK-PP) Set was a subset of the SS consisting of those study participants who took at least 1 dose of study medication, provided measurable plasma CZP concentration samples (with recorded sampling date/time or for which date/time can be reasonably assumed). Here, " Number of Participants Analyzed" signifies participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Week 16

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Reduced CZP Dose -Weight group: 10 - <20 kg	Reduced CZP Dose - Weight group: 20 - <40 kg	Reduced CZP Dose - Weight group: >=40 kg	Original CZP dose - Weight group: 10 - <20 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	24	36	5
Units: ug/ml				
geometric mean (confidence interval 95%)	1.6166 (0.4720 to 5.5368)	9.2277 (5.1453 to 16.5491)	13.8928 (11.0030 to 17.5416)	22.9060 (13.3380 to 39.3374)

End point values	Original CZP Dose - Weight group: 20 - <40 kg	Original CZP Dose - Weight group: >=40 kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	49		
Units: ug/ml				
geometric mean (confidence interval 95%)	25.7752 (16.9024 to 39.3058)	33.5680 (25.7883 to 43.6945)		

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab Pegol (CZP) Plasma Concentration level at Week 48

End point title	Certolizumab Pegol (CZP) Plasma Concentration level at Week 48[2]

End point description:

Certolizumab Pegol (CZP) plasma concentration level was measured in ug/mL. The Pharmacokinetic Per-Protocol (PK-PP) Set was a subset of the SS consisting of those study participants who took at least 1 dose of study medication, provided measurable plasma CZP concentration samples (with recorded sampling date/time or for which date/time can be reasonably assumed). Here, "Number of Participants Analyzed" signifies participants evaluable for this outcome measure. Here, 99999 signifies that as pre-specified in the SAP, Geometric Mean and 95% confidence interval were not calculated if the number of values below lower limit of quantification (LLOQ) was greater than (>)1/3. If n less than (<) 3, only the minimum and maximum were reported, other statistics were not calculated.

End point type	Primary

End point timeframe:

Week 48

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Reduced CZP Dose -Weight group: 10 - <20 kg	Reduced CZP Dose - Weight group: 20 - <40 kg	Reduced CZP Dose - Weight group: >=40 kg	Original CZP dose - Weight group: 10 - <20 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	24	31	2
Units: ug/ml				
geometric mean (confidence interval 95%)	4.7404 (1.7596 to 12.7710)	8.4459 (5.0002 to 14.2661)	12.2987 (8.6950 to 17.3962)	99999 (99999 to 99999)

End point values	Original CZP Dose - Weight group: 20 - <40 kg	Original CZP Dose - Weight group: >=40 kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	25		
Units: ug/ml				
geometric mean (confidence interval 95%)	20.7048 (11.1744 to 38.3636)	25.5940 (14.6913 to 44.5878)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Anti-Certolizumab Pegol (anti-CZP) Antibody level at Week 16

End point title	Number of participants with Anti-Certolizumab Pegol (anti-CZP) Antibody level at Week 16[3]

End point description:

Number of participants with anti-CZP antibodies were reported. Safety Set (SS) consisted of all study participants in the Enrolled Set (ES) who have received at least 1 dose of study medication. Here, "Number of Participants Analyzed" signifies participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Week 16

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Reduced CZP Dose	Original CZP dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	97		
Units: participants	69	77		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Anti-Certolizumab Pegol (anti-CZP) Antibody level at Week 48

End point title	Number of participants with Anti-Certolizumab Pegol (anti-CZP) Antibody level at Week 48[4]

End point description:

Number of participants with anti-CZP antibodies were reported. Safety Set (SS) consisted of all study participants in the Enrolled Set (ES) who have received at least 1 dose of study medication. Here, "Number of Participants Analyzed" signifies participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Week 48

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Reduced CZP Dose	Original CZP dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	72	60		
Units: participants	58	47		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with serious treatment-emergent adverse events (TEAEs) during the study

End point title	Number of participants with serious treatment-emergent adverse events (TEAEs) during the study[5]

End point description:

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose: results in deaths, is life-threatening, requires in patient hospitalization or prolongation of existing hospitalization, is a congenital anomaly or birth defect and other important medical events which based on medical or scientific judgement may jeopardize the patients, or may require medical or surgical intervention to prevent any of the above. TEAEs are defined as AEs starting on or after first administration of CZP and up to 70 days after last dose of study medication. Safety Set (SS) consisted of all study participants in the Enrolled Set (ES) who have received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

From Baseline (Week 0) up to the Final Visit (70 days after final dose of CZP) (maximum up to 12 years)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Any CZP Dose - Weight group: 10 - < 20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >= 40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	63	112	
Units: participants	5	20	21	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with treatment-emergent adverse events (TEAEs) leading to permanent withdrawal of the Investigational Medicinal Product (IMP) during the study

End point title	Number of participants with treatment-emergent adverse events (TEAEs) leading to permanent withdrawal of the Investigational Medicinal Product (IMP) during the study[6]

End point description:

An AE is any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP. TEAEs are defined as AEs starting on or after first administration of CZP and up to 70 days after last dose of study medication. TEAEs leading to permanent withdrawal of the IMP during the study were reported in this outcome measure. Safety Set (SS) consisted of all study participants in Enrolled Set (ES) who have received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

From Baseline (Week 0) up to the Final Visit (70 days after final dose of CZP) (maximum up to 12 years)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Any CZP Dose - Weight group: 10 - < 20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >= 40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	63	112	
Units: participants	0	9	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants meeting American College of Rheumatology Pediatric 30 % (PedACR30) Response Criteria at Week 16

End point title	Percentage of Participants meeting American College of Rheumatology Pediatric 30 % (PedACR30) Response Criteria at Week 16

End point description:

PedACR30-at least 30% improvement from baseline in 3 of any 6 core set measures, with no more than 1 of remaining variables worsening by >30%:
• Number of joints with active arthritis
• Number of joints with limitation of range of motion
• Physician's Global Assessment of Disease Activity (using VAS: 100mm; 0= very good, and 100= very poor)
• CHAQ (30 questions, 8 domains, scores for each domain are averaged to calculate total score [0= no disability to 3= very severe disability])
• Parent's Global Assessment of Overall Well-Being (using VAS: 100mm; 0= Very well to 100= Very poor)
• C-reactive protein(CRP)
FAS: all study participants in SS who have no more than one of 6 core components missing at baseline (count of joints with active arthritis, count of joints with limitation of range of motion, Physician's Global Assessment of Disease Activity score, CHAQ score, Parent's Global Assessment of Overall Well-Being score and CRP result) for calculating PedACR30/50/70/90.

End point type	Secondary

End point timeframe:

Week 16

End point values	Any CZP Dose - Weight group: 10 - < 20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >= 40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	63	112	
Units: percentage of participants				
number (confidence interval 95%)	83.3 (58.6 to 96.4)	77.8 (65.5 to 87.3)	79.5 (70.8 to 86.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants meeting American College of Rheumatology Pediatric 70 % (PedACR70) Response Criteria at Week 16

End point title	Percentage of Participants meeting American College of Rheumatology Pediatric 70 % (PedACR70) Response Criteria at Week 16

End point description:

PedACR70- at least 70% improvement from baseline in 3 of any 6 following core set measures, with no more than 1 of remaining variables worsening by >30%:
- Number of joints with active arthritis
- Number of joints with limitation of range of motion
- Physician's Global Assessment of Disease Activity (using VAS: 100mm; 0= very good, and 100= very poor)
- CHAQ (30 questions, 8 domains, scores for each domain are averaged to calculate total score [0= no disability to 3= very severe disability])
- Parent's Global Assessment of Overall Well-Being (using VAS: 100mm; 0= Very well to 100= Very poor)
- CRP

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

End point type	Secondary

End point timeframe:

Week 16

End point values	Any CZP Dose - Weight group: 10 - < 20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >= 40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	63	112	
Units: percentage of participants				
number (confidence interval 95%)	44.4 (21.5 to 69.2)	57.1 (44.0 to 69.5)	54.5 (44.8 to 63.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants meeting American College of Rheumatology Pediatric 50 % (PedACR50) Response Criteria at Week 16

End point title	Percentage of Participants meeting American College of Rheumatology Pediatric 50 % (PedACR50) Response Criteria at Week 16

End point description:

PedACR50- at least 50% improvement from baseline in 3 of any 6 core set measures, with no more than 1 of remaining variables worsening by >30%:
- Number of joints with active arthritis
- Number of joints with limitation of range of motion
- Physician's Global Assessment (PGA) of Disease Activity (using VAS: 100mm; 0= very good, and 100= very poor)
- Childhood Health Assessment Questionnaire (CHAQ) (30 questions, 8 domains, scores for each domain are averaged to calculate total score [0= no disability to 3= very severe disability])
- Parent's Global Assessment of Overall Well-Being (using VAS: 100mm; 0= Very well to 100= Very poor)

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

End point type	Secondary

End point timeframe:

Week 16

End point values	Any CZP Dose - Weight group: 10 - < 20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >= 40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	63	112	
Units: percentage of participants				
number (confidence interval 95%)	66.7 (41.0 to 86.7)	71.4 (58.7 to 82.1)	74.1 (65.0 to 81.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants meeting American College of Rheumatology Pediatric 90 % (PedACR90) Response Criteria at Week 16

End point title	Percentage of Participants meeting American College of Rheumatology Pediatric 90 % (PedACR90) Response Criteria at Week 16

End point description:

PedACR90- at least 90% improvement from baseline in 3 of any 6 following core set measures, with no more than 1 of remaining variables worsening by >30%:
- Number of joints with active arthritis
- Number of joints with limitation of range of motion
- Physician's Global Assessment of Disease Activity (using VAS: 100mm; 0= very good, and 100= very poor)
- CHAQ (30 questions, 8 domains, scores for each domain are averaged to calculate total score [0= no disability to 3= very severe disability])
- Parent's Global Assessment of Overall Well-Being (using VAS: 100mm; 0= Very well to 100= Very poor)
- CRP

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

End point type	Secondary

End point timeframe:

Week 16

End point values	Any CZP Dose - Weight group: 10 - < 20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >= 40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	63	112	
Units: percentage of participants				
number (confidence interval 95%)	22.2 (6.4 to 47.6)	25.4 (15.3 to 37.9)	29.5 (21.2 to 38.8)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline (Week 0) up to the Final Visit (70 days after final dose of CZP) (maximum up to 12 years)

Adverse event reporting additional description:

TEAEs were defined as AEs starting on or after first administration of CZP and up to 70 days after last dose of study medication. Safety Set (SS) consisted of all study participants in the Enrolled Set (ES) who have received at least 1 dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Any CZP Dose - Weight group: 10 - <20 kg

Reporting group description:

Participants received CZP sc as a fixed dose based on their body weight Q2W or Q4W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.

Reporting group title	Any CZP Dose - Weight group: 20 - <40 kg

Reporting group description:

Participants received CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.

Reporting group title	Any CZP Dose - Weight group: >=40 kg

Reporting group description:

Participants received CZP sc as a fixed dose based on their body weight Q2W throughout the study. Participants started with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study.

Serious adverse events	Any CZP Dose - Weight group: 10 - <20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >=40 kg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)	20 / 63 (31.75%)	21 / 112 (18.75%)
number of deaths (all causes)	0	0	3
number of deaths resulting from adverse events	0	0	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hair follicle tumour benign			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy on contraceptive			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Drug abuse			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Alcoholism			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Jaw fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Nervous system disorders			
Idiopathic generalised epilepsy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Leukocytosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal motility disorder			

subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory bowel disease			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal suppression			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot deformity			

subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	5 / 63 (7.94%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 0	2 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated tuberculosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Breast abscess			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis liver			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tuberculosis			

subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serratia bacteraemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pyelonephritis acute			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Any CZP Dose - Weight group: 10 - <20 kg	Any CZP Dose - Weight group: 20 - <40 kg	Any CZP Dose - Weight group: >=40 kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 18 (88.89%)	59 / 63 (93.65%)	98 / 112 (87.50%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 18 (16.67%)	12 / 63 (19.05%)	11 / 112 (9.82%)
occurrences (all)	6	18	20
Cyst			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	2 / 112 (1.79%)
occurrences (all)	1	0	2
Condition aggravated			

subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	2 / 112 (1.79%)
occurrences (all)	1	1	2
Injection site reaction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	6 / 112 (5.36%)
occurrences (all)	0	2	9
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	5 / 63 (7.94%)	9 / 112 (8.04%)
occurrences (all)	0	6	11
Injection site pain			
subjects affected / exposed	2 / 18 (11.11%)	5 / 63 (7.94%)	10 / 112 (8.93%)
occurrences (all)	2	25	30
Drug intolerance			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	2 / 112 (1.79%)
occurrences (all)	1	0	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	3 / 112 (2.68%)
occurrences (all)	1	3	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 18 (11.11%)	10 / 63 (15.87%)	11 / 112 (9.82%)
occurrences (all)	2	16	21
Oropharyngeal pain			
subjects affected / exposed	0 / 18 (0.00%)	6 / 63 (9.52%)	15 / 112 (13.39%)
occurrences (all)	0	12	19
Rhinorrhoea			
subjects affected / exposed	1 / 18 (5.56%)	6 / 63 (9.52%)	6 / 112 (5.36%)
occurrences (all)	1	8	12
Nasal congestion			
subjects affected / exposed	2 / 18 (11.11%)	2 / 63 (3.17%)	2 / 112 (1.79%)
occurrences (all)	2	4	2
Epistaxis			
subjects affected / exposed	0 / 18 (0.00%)	4 / 63 (6.35%)	7 / 112 (6.25%)
occurrences (all)	0	4	18
Psychiatric disorders			

Depression			
subjects affected / exposed	0 / 18 (0.00%)	2 / 63 (3.17%)	8 / 112 (7.14%)
occurrences (all)	0	2	11
Anxiety			
subjects affected / exposed	0 / 18 (0.00%)	2 / 63 (3.17%)	7 / 112 (6.25%)
occurrences (all)	0	2	7
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences (all)	1	1	0
Mycobacterium tuberculosis complex test positive			
subjects affected / exposed	1 / 18 (5.56%)	2 / 63 (3.17%)	1 / 112 (0.89%)
occurrences (all)	1	2	1
Hepatic enzyme increased			
subjects affected / exposed	2 / 18 (11.11%)	1 / 63 (1.59%)	6 / 112 (5.36%)
occurrences (all)	2	1	7
C-reactive protein increased			
subjects affected / exposed	2 / 18 (11.11%)	1 / 63 (1.59%)	6 / 112 (5.36%)
occurrences (all)	2	2	6
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	3 / 63 (4.76%)	6 / 112 (5.36%)
occurrences (all)	0	3	8
Alanine aminotransferase increased			
subjects affected / exposed	1 / 18 (5.56%)	5 / 63 (7.94%)	9 / 112 (8.04%)
occurrences (all)	1	5	12
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 18 (5.56%)	5 / 63 (7.94%)	10 / 112 (8.93%)
occurrences (all)	1	8	12
Transaminases increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences (all)	1	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural			

complications			
Ligament sprain			
subjects affected / exposed	0 / 18 (0.00%)	5 / 63 (7.94%)	9 / 112 (8.04%)
occurrences (all)	0	6	11
Joint injury			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	2 / 112 (1.79%)
occurrences (all)	1	2	5
Radius fracture			
subjects affected / exposed	2 / 18 (11.11%)	0 / 63 (0.00%)	3 / 112 (2.68%)
occurrences (all)	2	0	3
Contusion			
subjects affected / exposed	0 / 18 (0.00%)	3 / 63 (4.76%)	6 / 112 (5.36%)
occurrences (all)	0	4	7
Congenital, familial and genetic disorders			
Lichen spinulosus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 18 (0.00%)	1 / 63 (1.59%)	6 / 112 (5.36%)
occurrences (all)	0	1	9
Headache			
subjects affected / exposed	2 / 18 (11.11%)	7 / 63 (11.11%)	30 / 112 (26.79%)
occurrences (all)	2	16	56
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 18 (0.00%)	5 / 63 (7.94%)	4 / 112 (3.57%)
occurrences (all)	0	6	4
Neutropenia			
subjects affected / exposed	1 / 18 (5.56%)	4 / 63 (6.35%)	3 / 112 (2.68%)
occurrences (all)	2	5	7
Thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			

Middle ear effusion			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	1 / 112 (0.89%)
occurrences (all)	1	1	1
Ear pain			
subjects affected / exposed	1 / 18 (5.56%)	3 / 63 (4.76%)	1 / 112 (0.89%)
occurrences (all)	1	5	1
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	1 / 112 (0.89%)
occurrences (all)	1	1	2
Ocular hyperaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Hypermetropia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Iritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences (all)	2	0	2
Uveitis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 63 (3.17%)	0 / 112 (0.00%)
occurrences (all)	1	3	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 18 (5.56%)	3 / 63 (4.76%)	13 / 112 (11.61%)
occurrences (all)	2	5	19
Diarrhoea			
subjects affected / exposed	3 / 18 (16.67%)	5 / 63 (7.94%)	13 / 112 (11.61%)
occurrences (all)	4	5	14
Vomiting			
subjects affected / exposed	3 / 18 (16.67%)	6 / 63 (9.52%)	14 / 112 (12.50%)
occurrences (all)	3	8	22
Abdominal pain			
subjects affected / exposed	0 / 18 (0.00%)	8 / 63 (12.70%)	8 / 112 (7.14%)
occurrences (all)	0	9	12
Salivary gland mass			

subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Retained deciduous tooth			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	3 / 18 (16.67%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences (all)	3	1	0
Stomatitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	4 / 112 (3.57%)
occurrences (all)	1	2	4
Abdominal discomfort			
subjects affected / exposed	0 / 18 (0.00%)	4 / 63 (6.35%)	2 / 112 (1.79%)
occurrences (all)	0	4	2
Skin and subcutaneous tissue disorders			
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 63 (3.17%)	1 / 112 (0.89%)
occurrences (all)	1	2	2
Urticaria			
subjects affected / exposed	1 / 18 (5.56%)	4 / 63 (6.35%)	2 / 112 (1.79%)
occurrences (all)	1	7	2
Rash			
subjects affected / exposed	1 / 18 (5.56%)	7 / 63 (11.11%)	10 / 112 (8.93%)
occurrences (all)	1	7	13
Dermatitis atopic			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	0 / 112 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	5 / 112 (4.46%)
occurrences (all)	1	0	5
Back pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 63 (3.17%)	6 / 112 (5.36%)
occurrences (all)	0	3	7
Pain in extremity			

subjects affected / exposed	0 / 18 (0.00%)	4 / 63 (6.35%)	10 / 112 (8.93%)
occurrences (all)	0	6	13
Arthralgia			
subjects affected / exposed	2 / 18 (11.11%)	6 / 63 (9.52%)	10 / 112 (8.93%)
occurrences (all)	2	11	17
Juvenile idiopathic arthritis			
subjects affected / exposed	3 / 18 (16.67%)	12 / 63 (19.05%)	20 / 112 (17.86%)
occurrences (all)	3	19	37
Joint swelling			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	4 / 112 (3.57%)
occurrences (all)	1	0	6
Tendonitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	2 / 112 (1.79%)
occurrences (all)	2	1	2
Infections and infestations			
Latent tuberculosis			
subjects affected / exposed	2 / 18 (11.11%)	7 / 63 (11.11%)	2 / 112 (1.79%)
occurrences (all)	2	7	2
Upper respiratory tract infection			
subjects affected / exposed	4 / 18 (22.22%)	16 / 63 (25.40%)	28 / 112 (25.00%)
occurrences (all)	11	41	62
Respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)	12 / 63 (19.05%)	11 / 112 (9.82%)
occurrences (all)	6	22	15
Viral infection			
subjects affected / exposed	2 / 18 (11.11%)	7 / 63 (11.11%)	13 / 112 (11.61%)
occurrences (all)	2	12	17
Pharyngitis streptococcal			
subjects affected / exposed	0 / 18 (0.00%)	10 / 63 (15.87%)	9 / 112 (8.04%)
occurrences (all)	0	16	18
Pharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	9 / 63 (14.29%)	7 / 112 (6.25%)
occurrences (all)	1	11	9
Sinusitis			
subjects affected / exposed	0 / 18 (0.00%)	5 / 63 (7.94%)	12 / 112 (10.71%)
occurrences (all)	0	6	20

Tonsillitis			
subjects affected / exposed	2 / 18 (11.11%)	9 / 63 (14.29%)	6 / 112 (5.36%)
occurrences (all)	3	9	11
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	5 / 63 (7.94%)	10 / 112 (8.93%)
occurrences (all)	1	8	16
Conjunctivitis			
subjects affected / exposed	2 / 18 (11.11%)	3 / 63 (4.76%)	7 / 112 (6.25%)
occurrences (all)	2	3	7
Bronchitis			
subjects affected / exposed	1 / 18 (5.56%)	6 / 63 (9.52%)	6 / 112 (5.36%)
occurrences (all)	1	6	6
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	4 / 63 (6.35%)	10 / 112 (8.93%)
occurrences (all)	0	4	23
Rhinitis			
subjects affected / exposed	0 / 18 (0.00%)	8 / 63 (12.70%)	7 / 112 (6.25%)
occurrences (all)	0	12	9
Gastroenteritis			
subjects affected / exposed	0 / 18 (0.00%)	4 / 63 (6.35%)	11 / 112 (9.82%)
occurrences (all)	0	4	19
Nasopharyngitis			
subjects affected / exposed	4 / 18 (22.22%)	17 / 63 (26.98%)	32 / 112 (28.57%)
occurrences (all)	8	46	68
Ear infection			
subjects affected / exposed	2 / 18 (11.11%)	4 / 63 (6.35%)	4 / 112 (3.57%)
occurrences (all)	2	5	6
Varicella			
subjects affected / exposed	4 / 18 (22.22%)	4 / 63 (6.35%)	0 / 112 (0.00%)
occurrences (all)	4	4	0
COVID-19			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	6 / 112 (5.36%)
occurrences (all)	1	0	9
Tooth infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	1 / 112 (0.89%)
occurrences (all)	2	0	1

Viral rash			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	1 / 112 (0.89%)
occurrences (all)	1	1	1
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 63 (3.17%)	0 / 112 (0.00%)
occurrences (all)	1	3	0
Bacteriuria			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	1 / 112 (0.89%)
occurrences (all)	1	2	1
Otitis media acute			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	2 / 112 (1.79%)
occurrences (all)	1	1	2
Ascariasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 63 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Impetigo			
subjects affected / exposed	1 / 18 (5.56%)	3 / 63 (4.76%)	2 / 112 (1.79%)
occurrences (all)	1	3	2
Gastroenteritis viral			
subjects affected / exposed	1 / 18 (5.56%)	3 / 63 (4.76%)	2 / 112 (1.79%)
occurrences (all)	1	3	2
Respiratory tract infection viral			
subjects affected / exposed	2 / 18 (11.11%)	4 / 63 (6.35%)	1 / 112 (0.89%)
occurrences (all)	2	4	1
Viral pharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 63 (1.59%)	4 / 112 (3.57%)
occurrences (all)	1	1	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2011	Protocol Amendment 1, dated 26 Aug 2011, was implemented prior to the start of enrollment and submitted to Food and Drug Administration (FDA). The primary purpose of this substantial protocol amendment was to revise the protocol in line with change requests from health authorities following discussions on the CZP pediatric arthritis development program. In addition, a list of anticipated SAEs for CZP in the juvenile idiopathic arthritis (JIA) population was added based on the FDA Final Rule on safety reporting for investigational new drug studies. Further key revisions included updates of eligibility criteria, updates of the protocol to current terminology used in the rheumatology community and to current company standards, and clarification of assessments and concomitant medications.
06 May 2013	Protocol Amendment 3 was dated 06 May 2013, and a total of 54 study participants had entered the study at the time of this amendment. The primary purpose of this substantial amendment was to update the exclusion criteria and guidelines related to tuberculosis (TB) detection and monitoring in order to comply with the revised UCB TB Task Force policy applied to all UCB-sponsored studies that include study participants with immunological diseases who are at risk of developing or reactivation of TB infection, which might be associated with the class of tumor necrosis factor inhibitor (TNFi), including the investigational medicinal product (IMP). These instructions are evidence-based and reflect the updated recommendations of various national guidelines (eg, diagnosis of latent TB infection [LTBI] [Centers for Disease Control and Prevention]). This guideline includes the preference of use of tuberculin purified protein derivative skin test (TST) over interferon-gamma release assay (IGRA) in children below the age of 5 years. With the implementation of Protocol Amendment 3, TST was mandatory for study participants from 2 to 4 years of age in this study, unless the study participant had received a Bacille Calmette-Guérin (BCG) vaccination, and IGRA testing was required for study participants from 5 to 17 years of age. An independent Data and Safety Monitoring Board (DSMB) was implemented to conform to the standards for pediatric clinical studies. The DSMB reviewed emerging safety, PK, and efficacy data from the study. Activities were defined in the DSMB charter. Furthermore, this substantial amendment introduced a full interim analysis at Week 24 (Visit 10) involving a complete data analysis for the inclusion in the marketing application for the JIA indication.
06 May 2013	Continuation of Protocol Amendment 3: At the same time, the planned analysis at Week 16 (Visit 8) was reduced to an analysis of the American College of Rheumatology Pediatric 30% (PedACR30) response rate required to confirm adequate response of the study population to CZP treatment and to confirm continuation of RA0043. Key revisions also included modifications and clarifications of eligibility criteria related to the diagnosis of JIA, use of disease-modifying antirheumatic drug (DMARDs) and methotrexate (MTX), TB, hepatitis screening panel, Follow-up Period for pregnancy and contraception, and infections. Further revisions were made to clarify study-related procedures (eg, the process of analyzing CZP plasma concentrations in the first cohort of study participants and the completion of parent-reported questionnaires), to clarify the CZP assay methodology, and to correct errors in the previous protocol version (eg, in relation to the core set measures of the American College of Rheumatology Pediatric (PedACR). In addition, the definition of the Physician’s Global Assessment criterion for Clinically Inactive Disease (CID) and clinical remission (CRM) previously defined as "clinical remission on medication") was changed to conform to the most current standard as defined by Wallace et al, 2011.

01 August 2013	Protocol Amendment 4, dated 01 Aug 2013, was implemented after a total of 78 study participants had entered the study. The primary purpose of this substantial amendment was to implement a change in the dosing algorithm for children and adolescents who were participating currently in RA0043 at the time. Based on the results of the interim population pharmacokinetic (PopPK) analysis conducted in Jun 2013 (report Aug 2013) that included data from 34 pediatric study participants, new enrollment into RA0043 was suspended, effective 17 Jul 2013, and the maintenance dose for study participants already in RA0043 was reduced with Protocol Amendment 4. An overall dose reduction for pediatric study participants of 50% of the dose used in RA0043 at that time was proposed to provide a pragmatic dose that would yield a closer match to the plasma concentration range achieved in adults with the approved dose for RA (CZP 400mg at Weeks 0, 2, and 4 [Visits 2, 4, and 5, respectively] followed by CZP 200mg Q2W thereafter). Additional Unscheduled Visits were implemented, as required, in order to closely monitor the study participants over a period of 12 weeks after the dose change.
20 January 2014	Protocol Amendment 5, dated 20 Jan 2014, was implemented after a total of 78 study participants had entered the study. The primary purpose of this substantial amendment was to reopen enrollment under the new Reduced CZP Dose, as defined in Protocol Amendment 4 and to update the statistical analyses to account for the changes in the CZP dose. Two CZP dose subgroups were defined as follows: • Original CZP Dose: included all study participants in the Safety Set (SS) who began treatment in accordance with the Original CZP Dose defined for the study (including study participants who underwent a dose reduction under Amendment 4). • Reduced CZP Dose: included all study participants in the SS who began treatment under Protocol Amendment 5 in accordance with the Reduced CZP Dose defined for the study. At the time of Protocol Amendment 4, a total of 78 study participants had entered the study and started treatment on the Original CZP Dose. To allow for a comparison of the group of 78 study participants on the Original CZP Dose with a comparable group of study participants on the revised CZP dose, a further 78 study participants were planned for the Reduced CZP Dose. Thus, the overall number of study participants was increased from 125 to at least 156. Study participants who fulfilled the eligibility criteria but could not enter the study due to the suspended enrollment as of 17 Jul 2013 were allowed to be rescreened. Key changes included the clarification that only study participants who entered the study under Protocol Amendment 5 and began treatment on the Reduced CZP Dose were taken into account for the study stopping rule based on the Week 16 (Visit 8) PedACR30 interim analysis and that a minimum number of 10 study participants in each weight category needed to enter the study for the Reduced CZP Dose.
20 January 2014	Continuation of Protocol Amendment 5: In addition, the requirement that a study participant’s dosing category may only be changed if the 20 kg and 40 kg weight boundaries are crossed due to weight changes of >2.5 kg and >5 kg, respectively, was removed from the protocol. Applying this requirement at the time of dose reduction would have led to potential underdosing of study participants who just crossed the weight boundary, as they would have had their doses reduced by 50% even though, based on their actual weight, they already fell into the next higher weight category. Furthermore, additional changes were made to the exclusion criteria and guidelines related to TB detection and monitoring to adapt the protocol to the current UCB standard, and descriptions of clinically inactive disease (CID) and clinical remission on medication (CRM) were modified for clarity.

22 September 2016	Protocol Amendment 7: The primary purpose of this substantial amendment, dated 22 Sep 2016, was to update the protocol in accordance with current UCB TB detection procedures, including the introduction of yearly TB testing and the extension of the prophylactic TB treatment duration from 4 to 8 weeks. Furthermore, it was clarified that long-term efficacy data from study participants who withdrew from the study after Week 56 or initiated any rescue medication use after Week 56 would be analyzed "as observed" and would no longer be imputed as nonresponse or missing. Moreover, a section on "Suspected transmission of an infectious agent via a medicinal product" was added in accordance with current company standards.
24 June 2019	Protocol Amendment 8: The primary purpose of this substantial amendment, dated 24 Jun 2019, was to reduce the study participants' burden by limiting the frequency of on-site visits, safety sampling, and efficacy assessments. The frequency of on-site visits was reduced from every 8 weeks to every 16 weeks in this long-term study. At the time of implementing Protocol Amendment 8, all ongoing study participants had at least completed the visit for Week 180. As before, on-site CZP administration between scheduled visits was offered as needed. The frequency of safety sampling (blood sampling and urinalysis) was extended from every 8 weeks to every 16 weeks to reduce the study participants' burden in line with the updated on-site CZP administration schedule. Safety data collected previously during the study and close evaluation by the DSMB supported the extension of sampling frequency. This longer interval was also implemented for efficacy assessments to further reduce study participants' burden and was appropriate to describe the long-term efficacy of CZP. UCB also determined there was limited value in collecting ADAb and CZP plasma concentration data after >4 years of CZP exposure. UCB determined that collection of additional samples to determine CZP plasma concentrations and ADAb samples would be of limited utility and an undue burden on the study participants. Discontinuation of blood sample collection for further characterization of CZP PK and immunogenicity was supported by the DSMB as the PK and immunogenicity data available to date were considered sufficient from a safety perspective and for PK characterization.
27 April 2020	Protocol Amendment 9, dated 27 Apr 2020, was undertaken following an interaction with FDA in Jan 2020 in context of the pJIA Pediatric Research Equity Act (PREA) requirement for CZP. The primary purpose of this substantial 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 pcJIA at both the Reduced CZP Dose and Original CZP Dose, and also adequately support the safety assessment of the Original CZP Dose. The ECLIA methods, for which selectivity had previously been assessed in the rheumatoid arthritis (RA) matrix, were validated to meet the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics (FDA, Guidance for Industry – Bioanalytical Method Validation, 2018). Sampling for CZP plasma concentration and ADAb was reinitiated for study participants enrolled following Protocol Amendment 9. All study participants enrolled following Protocol Amendment 9 had plasma concentrations of CZP and ADAb analyzed using the ECLIA methods. In addition, PK and ADAb samples (for which sufficient volume and stability data for PK analysis were available) collected in this study prior to Protocol Amendment 9 were reanalyzed with the ECLIA methods. The collective ECLIA-based PK data for this study form the basis of any future CZP modeling and simulation work. In addition, exclusion criteria related to TB, hepatis B, hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) were updated to align with current clinical guidelines in Protocol Amendment 9. After Protocol Amendment 9, study participants on the Reduced CZP Dose were able to switch to the Original CZP Dose at the discretion of the Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 July 2013	On 16-Jul-2013, the enrollment was temporarily suspended. The decision was not based on safety findings but results from an interim pk-analysis. This analysis had indicated certolizumab pegol plasma levels in the range of those observed in adults with RA but at the upper end of the distribution. As the target was to achieve comparable plasma levels as known from adult patients before, the administered dose was reduced. Protocol Amendment 4 (AMD 4) was created with a 50% reduction of the dose (Reduced Dose, RD). Ongoing patients switched from OD to RD. The first new patient to start on RD was enrolled on 23 April 2014.	23 April 2014

Notes:

Limitations and caveats

None reported