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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cimzia

Certolizumab pegol

Procedure no: EMEA/H/C/001037/P46/041

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Procedure resources	
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LIST OF ABBREVIATIONS

ADAb	anti-CZP antibody
AE	adverse event
CSR	clinical study report
CZP	Cimzia; certolizumab pegol
DBL	database lock
FDA	Food and Drug Administration
JADAS-71	Juvenile Arthritis Disease Activity Score 71-joint
pcJIA	polyarticular-course juvenile idiopathic arthritis
PedACR	American College of Rheumatology Pediatric
PedACR30, 50, 70, 90	American College of Rheumatology Pediatric 30%, 50%, 70%, 90%
PK	pharmacokinetic(s)
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PT	preferred term
Q2W, Q4W	every 2 weeks, every 4 weeks
RA	rheumatoid arthritis
SS	Safety Set
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor-α

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1. Introduction

On 07 October 2024, the MAH submitted a final report for a completed paediatric study for certolizumab pegol (Cimzia), study RA0043, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that RA0043 is a stand alone study.

CHMP comment:

RA0043 was initiated in 2012 pursuant to Food and Drug Administration (FDA) approval of Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) 2563-1, as follows: "Assessment of 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 polyarticular-course juvenile idiopathic arthritis (pcJIA) population was previously agreed with FDA to fulfill the PMR.

In 2017, the PDCO granted a product-specific waiver on its own motion for all subsets of the paediatric population in the specified condition, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments, and that uncertainties pertain to the long-term safety of Cimzia (i.e. CNS development/cognition).

In their decision, the PDCO states that *"several authorized alternative therapies for the treatment of children with chronic idiopathic arthritis are now available. Furthermore, uncertainties pertaining to the long-term safety of Cimzia exist. Dose-dependent vacuolation associated with PEG accumulation has been observed as a consequence of Cimzia administration in monkeys in various tissues including the choroid plexus epithelial cells, choroid plexus stroma, pituitary gland and dorsal root ganglia. Vacuolation was only partially reversible. Furthermore, clinical monitoring of this potential risk of CNS vacuolation is likely not possible in a meaningful way".*

2.2. Information on the pharmaceutical formulation used in the study

Treatment was given with Cimzia prefilled single-use syringe 200mg/mL solution for sc injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- RA0043, 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

2.3.2. Clinical study

RA0043, 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

Description

RA0043 was a Phase 3, multicenter, open-label study to assess the PK, immunogenicity, safety, and efficacy of Cimzia in children and adolescents with moderately-to-severely active polyarticular-course juvenile idiopathic arthritis (pcJIA).

Methods

Study participants

Selection of study population

Inclusion criteria

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

1. An IRB/IEC-approved written ICF was signed and dated by the study participant or by the parent(s) or legal representative. The consent form or a specific assent form, where required, was signed and dated by minors.

2. Study participants/legal representative/parent was considered reliable and capable of adhering to the protocol, visit schedule, or IMP intake according to the judgment of the Investigator.

3. Study participant was able and willing to comply with the requirements of the study.

4. Study participant was 2 to 17 years of age (inclusive) at Baseline (Week 0 [Visit 2]). The minimum age at Baseline (Week 0 [Visit 2]) for study participants enrolled in Russia was 6 years of age.

5. Study participants must have weighed ≥10kg at Baseline (Week 0 [Visit 2]). The minimum weight at Baseline (Week 0 [Visit 2]) for study participants enrolled in Russia was 15kg.

6. Study participants had onset of signs and symptoms consistent with a diagnosis of JIA (according to the International League of Associations for Rheumatology classification of juvenile idiopathic arthritis; second revision, Edmonton, 2001, 2004) and initiation of JIA treatment for at least 6 months prior to Baseline (Week 0 [Visit 2]). Eligible JIA categories included: polyarthritis RF-positive, polyarthritis RF-negative, extended oligoarthritis, juvenile PsA, and ERA.

7. Study participants had active polyarticular-course disease, defined as ≥5 joints with active arthritis at Screening (Visit 1) and at Baseline (Week 0 [Visit 2]).

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

9. If the study participant was using MTX, then the study participant was on MTX for a minimum of 3 months at Screening (Visit 1). In addition, the dose was stable for at least 1 month before Screening (Visit 1) at ≥10 to ≤15mg/m2 per week. If the study participant was not using MTX, then the treatment was previously withdrawn for documented reasons of intolerability or inadequate response. A study participant with no prior MTX use was eligible for the study as long as 1 prior DMARD was used.

10. If the study participant was using oral corticosteroid therapy, the dose was stable for at least 7 days prior to the Baseline arthritis assessment at a maximum dose of 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever was the smaller dose.

CHMP comment:
Inclusion criteria seem adequate.

Exclusion criteria

Study participants were not permitted to enroll in the study if any 1 of the following criteria were met:

1. Study participant was previously exposed to more than 2 biologic agents.

2. Study participant previously failed to respond to treatment with more than 1 TNFi. Lack of response to treatment was defined as no clinical disease improvement within the first 12 weeks of treatment. (Study participant who demonstrated clinical response within 12 weeks of treatment and subsequently lost response after 12 weeks of treatment were eligible.)

3. Study participant was receiving or had received any experimental (biological or nonbiological) therapy (within or outside a clinical study) in the 3 months or 5 half-lives prior to Baseline (Week 0 [Visit 2]), whichever was longer.

4. Study participant was previously treated with a biological therapy for JIA that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.

5. Study participant previously participated in this study or had previously been treated with Cimzia (whether in a study or not).

6. Study participant received any prohibited medication (oral corticosteroids [any dose greater than 10mg or 0.2mg/kg prednisone (or equivalent) per day], im/iv/ia corticosteroids, nonbiologic DMARDs, biologic DMARDs [eg, sulfasalazine, hydroxychloroquine, cyclosporine]).

7. Study participant had a history of systemic JIA, with or without systemic features.

8. Study participant had a secondary, noninflammatory type of rheumatic disease or of joint pains (eg, fibromyalgia) that in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of IMP.

9. Study participant had other inflammatory arthritis (eg, systemic lupus erythematosus, inflammatory bowel disease-related).

10. Study participant had active uveitis or a history of active uveitis within the preceding 6 months.

11. Study participant had:

    a. Known active TB disease

    b. History of active TB involving any organ system

    c. History of or current LTBI

    d. High risk of exposure to TB infection

    e. Current nontuberculous mycobacterial (NTMB) infection or history of NTMB infection.

12. Study participant had a current sign or symptom which may have indicated infection (eg, fever, cough), a history of chronic or recurrent infections within the same organ system (more than 3 episodes requiring antibiotics/antivirals during the 12 months prior to Screening [Visit 1]), had a

recent (within the 6 months prior to Screening [Visit 1]) serious or life-threatening infection (including herpes zoster), or was at a high risk of infection in the Investigator's opinion (eg, study participants with leg ulcers, indwelling urinary catheter, and persistent or recurrent chest infections or permanently bed-ridden or wheelchair bound).

13. Study participant had a history of or current HBV or HCV or HIV 1/2 or had any of the following laboratory abnormalities during the Screening Period:

a. Hepatitis B surface antigen, hepatitis B core antibody (except for isolated, false-positive anti-HBc confirmed with a confirmatory test such as HBV-deoxyribonucleic acid [DNA]): Positive to any of these.

b. Hepatitis C virus positive: defined as hepatitis C antibody positive confirmed via a confirmatory test (for example, HCV polymerase chain reaction)

c. HIV antigen or antibody: Positive to either test

14. Study participant received any live, including attenuated, vaccination within 8 weeks prior to Baseline (Week 0 [Visit 2]) and/or was scheduled for live vaccination during the course of study participation. Nonlive vaccinations were permitted at any time prior to and during the study.

15. Study participant had a history of chronic alcohol or drug abuse based on the Investigator's clinical judgment within the last 1 year.

16. Study participant was breastfeeding, pregnant, or planned to become pregnant during the study or within 12 weeks following the last dose of IMP (or longer if required by local regulations). Female study participant of childbearing potential (ie, postmenarcheal) had a negative result at Screening (Visit 1) and Baseline (Week 0 [Visit 2]) pregnancy tests to be eligible for study entry.

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

18. Study participant had a history of an adverse reaction to PEG.

19. Study participant had a history of a lymphoproliferative disorder including lymphoma or signs and symptoms at any time suggestive of lymphoproliferative disease.

20. Study participant had a concurrent malignancy, or a history of any malignancy.

21. Study participant had a current or recent history (within 6 months prior to Screening [Visit 1]) of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease including blood dyscrasia (eg, pancytopenia, aplastic anemia) and demyelinating disease (eg, multiple sclerosis, myelitis, optic neuritis).

22. Study participant had any other medical or psychiatric condition that, in the opinion of the Investigator or Sponsor, could have jeopardized or compromised the study participant's ability to participate in the study or which otherwise made the study participant unsuitable for inclusion in the study.

23. Study participant had any clinically significant laboratory abnormalities which, in the Investigator's judgment, would have made the study participant unsuitable for inclusion in the study, with specific exclusion of study participants with values of: liver function tests that were >2×upper limit of normal (ULN), serum creatinine that was >1.5×ULN, and white blood cells (WBCs) that were <3.0x109/L or 3000/mm3.

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

25. Study participant had a history of or active systemic/respiratory infection due to fungal, parasitic, or mycotic pathogens including, but not limited, to histoplasmosis, coccidiosis, paracoccidiosis, pneumocystis, blastomyces, and aspergillus. Radiographic evidence suggestive of any of these infections was sufficient grounds for exclusion.

CHMP comment:
Exclusion criteria also seem relevant.

Treatments

Throughout the study, Cimzia dosing was a fixed dose based on weight and given every 2 weeks (Q2W), with the exception of the lowest weight group on the Reduced Cimzia Dose, who received the maintenance dose every 4 weeks (Q4W).

At the onset, study participants were to receive a fixed-dose Cimzia 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, referred to as Original Cimzia Dose. An interim population PK analysis of the first 34 pediatric study participants, conducted in Jun 2013, suggested that while observed Cimzia plasma concentrations remained in the adult range, they were at the upper end of the distribution. A decision was made to reduce the loading and maintenance doses by 50% for ongoing and newly enrolled participants (referred to as the Reduced Cimzia Dose). The Cimzia dose was not reduced due to any safety findings during the study. Following further interaction with FDA in Jan 2020, it was agreed to enroll an additional 30 study participants on the Original Cimzia Dose.

The 2 key dose groups of interest are the Original Cimzia Dose and the Reduced Cimzia Dose.

The Original Cimzia dose group includes all study participants in the Safety Set (SS) who began treatment with the Original Cimzia dose regimen and received 1 or more doses of this regimen, regardless of any subsequent switch to the Reduced Cimzia dose regimen.

The Reduced Cimzia dose group includes all study participants in the SS who began treatment in accordance with the reduced dosing regimen defined for the study.

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

After Week 4 (Visit 5), home-based Cimzia administration by the study participants or parent/caregiver was permitted between scheduled study visits.

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

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

Table 1: Dosing administration of Cimzia

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

CZP=certolizumab pegol; IMP=investigational medicinal product; inj=injection; Q2W=every 2 weeks; Q4W=every 4 weeks

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

Note: The Original CZP Dose described the dosing administration of CZP prior to the implementation of Protocol Amendments 4 and 5 and for study participants enrolled following the implementation of Protocol Amendment 9. The Reduced CZP Dose described the dosing administration of CZP after implementation of Protocol Amendments 4 and 5. Refer to Section 3.5.2.1 of the RA0043 Final CSR for the procedure taken for study participants who were undergoing a dose change.

Note: The first maintenance dose for the 10kg to <20kg weight group on the Reduced CZP Dose was administered at Week 8.

Objectives

The primary objectives of the study were to evaluate the pharmacokinetic (PK) and safety including immunogenicity of Cimzia administered subcutaneously (sc) in children and adolescents with moderately-to-severely active pcJIA. The secondary objective of the study was to assess the effectiveness of Cimzia on the clinical response in children and adolescents with moderately-to-severely active pcJIA. The other objectives of the study were to further assess safety as well as efficacy and health outcomes.

Outcomes/endpoints

PK and immunogenicity variables

Primary PK and immunogenicity variables

Certolizumab pegol plasma concentrations and ADAb levels at Week 16 and Week 48 (Visits 8 and 13, respectively) were assessed and data were summarized.

Other PK and immunogenicity variables

Certolizumab pegol plasma concentrations and ADAb levels at other study timepoints.

PK and immunogenicity measurements

Blood samples were to be collected predose to determine plasma concentrations of Cimzia and ADAbs at Baseline (Week 0 [Visit 2]); Weeks 4, 12, 16, 24, 32, 40, and 48 (Visits 5, 7, 8, 10, 11, 12, and 13, respectively); and then every 24 weeks thereafter; the Early Discontinuation/End of Treatment (EOT) Visit; and the Final Visit 12 weeks after the last dose of IMP. In addition, blood samples were collected 5 to 7 days after dosing at Baseline (ie, at Week 1, Visit 3) and Week 16 (ie, return of study participant to clinic site at Week 17) to determine postdose plasma concentration.

Safety variables

Primary safety variable

The primary safety variables were the incidences of serious TEAEs and TEAEs leading to permanent withdrawal of IMP. Adverse events were solicited at every visit, recorded, and coded according to Medical Dictionary for Regulatory Activities (MedDRA®) criteria.

Other safety variables

The other safety variables were as follows:

• Incidences of TEAEs, TEAEs of interest, TEAEs by relatedness, TEAEs by severity, and TEAEs by duration of exposure.

• Clinical laboratory values (hematology, biochemistry, and urinalysis) at every visit except Weeks 1 and 2 (Visits 3 and 4) and Unscheduled Visits.

• Vital sign abnormalities at every visit.

• Assessments of study participant's developmental stages and growth (height, weight) to determine Tanner stages at Baseline (Week 0 [Visit 2]), every 24 weeks thereafter, and the Early Discontinuation/EOT Visit (weight at every visit through Final Visit). For study participants enrolled prior to Protocol Amendment 9, Tanner stage assessments were to be performed every 48 weeks following Protocol Amendment 8, and only for those study participants who had not reached Tanner stage V.

• Autoantibody (antinuclear antibodies [ANA] and anti-double-stranded DNA [anti-dsDNA] antibodies) concentrations at Baseline (Week 0 [Visit 2]) (testing for anti-dsDNA antibodies only if ANA was positive), Weeks 16 and 48 (Visits 8 and 13), and at the Early Discontinuation/EOT Visit

Efficacy and health outcomes variables

Secondary efficacy variable

Efficacy was assessed by the PedACR30, PedACR 50% (PedACR50), PedACR 70% (PedACR70), and PedACR 90% (PedACR90) response rates at Week 16 (Visit 8) as compared to Baseline.

Other efficacy and health outcomes variables

The other efficacy and health outcome variables were:

• PedACR30, PedACR50, PedACR70, and PedACR90 response rates at every visit except Week 16 (Visit 8) and Final Visit as compared to Baseline (see Section 4.6.1 for definition).

• Change from Baseline in number of joints with active arthritis at every visit except Final Visit.

• Change from Baseline in number of joints with limitation of range of motion at every visit except Final Visit.

• Change from Baseline in Physician's Global Assessment of Disease Activity (visual analog scale [VAS]) at every visit except Final Visit.

• Change from Baseline in CHAQ at every visit except Final Visit.

• Change from Baseline in Parent's Global Assessment of Overall Well-Being (VAS) at every visit except Final Visit.

• Ratio to Baseline in CRP at every visit except Final Visit.

• Change from Baseline in Juvenile Arthritis Disease Activity Score 71-joint (JADAS-71) at every visit except Final Visit.

• Change from Baseline in Parent's Assessment of Arthritis Pain (VAS) at every visit except Final Visit.

• Percentage of study participants with Clinically Inactive Disease (CID) at every post-Baseline visit except Final Visit.

• Percentage of study participants with clinical remission (CRM) at every post-Baseline visit from Week 24 onwards except Final Visit.

• Time (in days) to derived CID calculated from first dose of IMP.

• Time (in days) to derived CRM calculated from first dose of IMP.

• Change from Baseline (Week 0 [Visit 2]) in duration of morning stiffness at every visit except Final Visit.

• Change from Baseline in Faces Pain Scale-Revised (FPS-R) (child-reported, ages 5 to 11 years globally [ages 6 to 11 years in Russia]), daily during the first week of treatment; Weeks 4, 12, 16, 24 (Visits 5, 7, 8, and 10); and then every 8 weeks thereafter through the Early Discontinuation/EOT Visit. For study participants enrolled prior to Protocol Amendment 9, visit frequency changed to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8.

• Change from Baseline in JIA Pain VAS, daily during the first 7 days of the study (acute and standard versions); Weeks 4, 12, 16, and 24 (Visits 5, 7, 8 and 10); and then every 8 weeks thereafter through the Early Discontinuation/EOT Visit (standard version) for study participants ages 12 to 17 years.

• Change from Baseline in Fatigue Assessment Scale (FASCA) at every visit except Weeks 12 and 20 (Visits 7 and 9) and Final Visit.

• Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey responses at Baseline (Week 0 [Visit 2]), Week 4 (Visit 5), and every visit thereafter except Final Visit.

Sample size

Based upon the ICH guideline for the assessment of safety, the MAH planned to enroll a sufficient number of study participants to this study to have a minimum of 100 participants with at least 12 months continuous exposure to Cimzia. Assuming a dropout rate of approximately 20%, it was originally determined that 125 study participants would need to be enrolled. At the time of Protocol Amendment 5, 78 study participants had been enrolled on the Original Cimzia Dose, and it was planned to enroll a further 78 study participants on the Reduced Cimzia Dose, so that a comparable number of study participants on both doses could be analyzed. Thus, the total number of study participants planned to be enrolled was increased to 156 study participants. Assuming a Screening failure rate of 25%, it was planned to screen 195 study participants in total. With Protocol Amendment 9, an additional 30 study participants were planned to be enrolled on the Original Cimzia Dose with the aim to enroll at least 5 study participants in each weight range of 10kg to <20kg, 20kg to <40kg, and ≥40kg. Prior to the start of study conduct, simulations using the adult population PK model in pediatric study participants with pcJIA suggested that the planned sample size of 125 study participants would also be adequate for PK assessment purposes.

Randomisation and blinding (masking)

RA0043 was an open-label study with no randomization.

Statistical Methods

Categorical data were presented as summary tables. A missing category was included as applicable. Continuous variables were summarized with the mean, standard deviation, median, minimum, and maximum. For Cimzia plasma concentrations and CRP, the geometric mean and geometric coefficient of variation (CV) were presented. Mean, standard deviation, and median were displayed to 1 more decimal place than collected in the electronic Case Report Form. Minimum and maximum values were displayed to the same level of precision as collected in the electronic Case Report Form. Percentages were calculated using the number of study participants in the relevant population or subgroup as the denominator. Presentation of percentages were to 1 decimal place. Percentages were not presented if the frequency count was 0. No formal statistical hypothesis testing was performed. Ninety-five percent CIs for the percentage of responders were calculated using the exact binomial method.

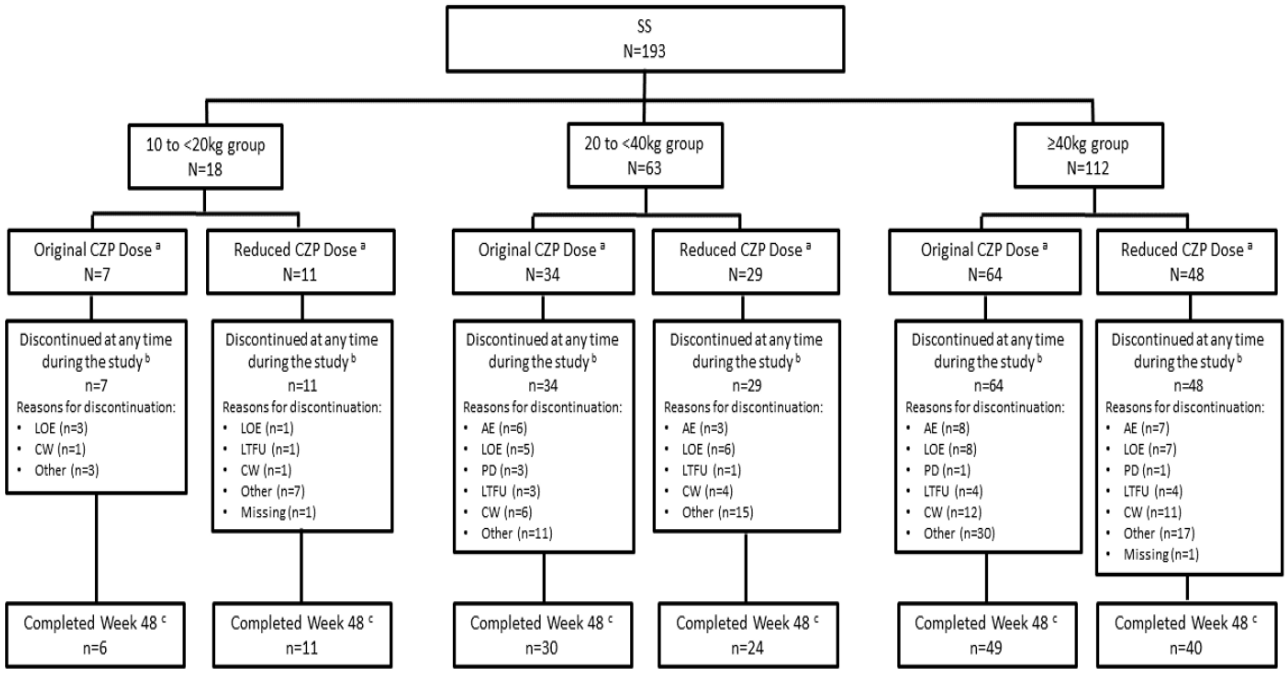
Results

Recruitment/Number analysed

A total of 227 study participants were screened during the study. A total of 34 (15.0%) of these study participants were screen failures. The most common reasons for screen failure were ineligibility and other (8.8% and 4.4% of study participants screened, respectively).

A total of 193 study participants were enrolled in the study, received at least 1 dose of Cimzia. Of these, 160 study participants (82.9%) completed at least Week 48 (Visit 13). As of the database lock date of 31 May 2024, all 193 study participants had discontinued from the study. The study participant disposition is presented in Figure 1.

Figure 1: Study 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 lock date of 31 May 2024 (included study participants who discontinued after Week 48 [Visit 13]).

[c] Completed at least Week 48 (Visit 13) as of the database lock date of 31 May 2024.

Note: Study completion was not defined in the protocol for RA0043. As of the database lock date of 31 May 2024, all 193 study participants in the SS had discontinued from the study.

Baseline data

Overall, study participants had a mean age of 11.9 years at Baseline (range: 3 to 17 years). Most study participants were female (67.4%), white (80.3%), and not of Hispanic or Latino ethnicity (71.5%). The mean BMI and BSA were 19.33kg/m^2 and 1.324m^2, respectively. The majority of study participants were from the US (68 study participants [35.2%]) and the Russian Federation (64 study participants [33.2%]). Most study participants had Baseline MTX use (139 study participants [72.0%]) and concomitant MTX use (148 study participants [76.7%]).

Table 2: Study participant demographics

Variable	Statistic	10 to <20kg N=18	20 to <40kg N=63	≥40kg N=112	Total N=193
	n	18	63	112	193
	Mean (SD)	5.4 (1.3)	9.1 (2.0)	14.5 (2.2)	11.9 (3.8)
Age (years)	Min, max	3, 8	5, 16	8, 17	3, 17
Age [a]					
2 to <6 years	n (%)	9 (50.0)	2 (3.2)	0	11 (5.7)
6 to <12 years	n (%)	9 (50.0)	53 (84.1)	13 (11.6)	75 (38.9)
12 to 17 years	n (%)	0	8 (12.7)	99 (88.4)	107 (55.4)
Age [b]					
24 months to <12 years	n (%)	18 (100)	55 (87.3)	13 (11.6)	86 (44.6)
12 to <18 years	n (%)	0	8 (12.7)	99 (88.4)	107 (55.4)
	n	18	63	112	193
	Mean (SD)	16.98 (2.00)	29.64 (5.15)	56.33 (13.65)	43.95 (18.48)
Weight (kg)	Min, max	12.3, 19.1	21.2, 38.6	40.0, 122.6	12.3, 122.6
	n	18	63	112	193
	Mean (SD)	108.81 (7.20)	133.18 (9.60)	160.93 (10.87)	147.01 (20.38)
Height (cm)	Min, max	92.5, 121.0	110.8, 153.6	133.8, 190.5	92.5, 190.5
	n	18	63	112	193
	Mean (SD)	14.35 (1.22)	16.68 (2.23)	21.62 (3.92)	19.33 (4.28)
BMI (kg/m^2)	Min, max	11.4, 16.3	13.5, 22.2	15.7, 38.2	11.4, 38.2

Variable	Statistic	10 to <20kg N=18	20 to <40kg N=63	≥40kg N=112	Total N=193
	n	18	63	112	193
	Mean (SD)	0.716 (0.063)	1.045 (0.120)	1.579 (0.219)	1.324 (0.362)
BSA (m^2)	Min, max	0.57, 0.80	0.81, 1.26	1.22, 2.47	0.57, 2.47
Gender					
Male	n (%)	7 (38.9)	20 (31.7)	36 (32.1)	63 (32.6)
Female	n (%)	11 (61.1)	43 (68.3)	76 (67.9)	130 (67.4)
Racial group					
American Indian/Alaskan Native	n (%)	0	1 (1.6)	4 (3.6)	5 (2.6)
Asian	n (%)	0	2 (3.2)	3 (2.7)	5 (2.6)
Black or African American	n (%)	0	0	6 (5.4)	6 (3.1)
Native Hawaiian or other Pacific Islander	n (%)	0	0	0	0
White	n (%)	17 (94.4)	53 (84.1)	85 (75.9)	155 (80.3)
Other/mixed	n (%)	1 (5.6)	7 (11.1)	14 (12.5)	22 (11.4)
Race					
White	n (%)	17 (94.4)	53 (84.1)	85 (75.9)	155 (80.3)
Nonwhite	n (%)	1 (5.6)	10 (15.9)	27 (24.1)	38 (19.7)
Ethnicity					
Hispanic or Latino	n (%)	10 (55.6)	18 (28.6)	27 (24.1)	55 (28.5)
Not Hispanic or Latino	n (%)	8 (44.4)	45 (71.4)	85 (75.9)	138 (71.5)
Country					
Argentina	n (%)	0	1 (1.6)	1 (0.9)	2 (1.0)
Brazil	n (%)	2 (11.1)	1 (1.6)	2 (1.8)	5 (2.6)
Canada	n (%)	1 (5.6)	3 (4.8)	11 (9.8)	15 (7.8)
Chile	n (%)	0	0	1 (0.9)	1 (0.5)
Mexico	n (%)	6 (33.3)	14 (22.2)	18 (16.1)	38 (19.7)
Russian Federation	n (%)	5 (27.8)	25 (39.7)	34 (30.4)	64 (33.2)
United States	n (%)	4 (22.2)	19 (30.2)	45 (40.2)	68 (35.2)
Baseline MTX use					
With	n (%)	13 (72.2)	52 (82.5)	74 (66.1)	139 (72.0)
Without	n (%)	5 (27.8)	11 (17.5)	38 (33.9)	54 (28.0)

Variable	Statistic	10 to <20kg N=18	20 to <40kg N=63	≥40kg N=112	Total N=193
Concomitant MTX use					
With	n (%)	13 (72.2)	53 (84.1)	82 (73.2)	148 (76.7)
Without	n (%)	5 (27.8)	10 (15.9)	30 (26.8)	45 (23.3)

BMI=body mass index; BSA=body surface area; CZP=certolizumab pegol; max=maximum; min=minimum; MTX=methotrexate; SD=standard deviation; SS=Safety Set

Note: Any CZP Dose covers the entire dosing period regardless of dose switching (see Section 6.1.1, Table 10-1, and Figure 3-2).

[a] Clinicaltrials.gov age categories that matched the age groups defined in the protocol.

[b] European Union Drug Regulating Authorities Clinical Trials age categories.

PK and immunogenicity results

The Geometric mean trough CZP plasma concentrations (95% CI) for each weight group at Week 12, Week 16, Week 24, Week 48, and Week 72 were as follows:

- For the 10 to <20kg weight group: 1.5066 (0.4265, 5.3217) µg/mL, 1.6166 (0.4720, 5.5368) µg/mL, 2.1473 (0.5394, 8.5479) µg/mL, 4.7404 (1.7596, 12.7710) µg/mL, and 6.5404 (1.8198, 22.8636) µg/mL, respectively
- For the 20 to <40kg weight group: 7.1480 (4.0691, 12.5568) µg/mL, 9.2277 (5.1453, 16.5491) µg/mL, 9.7804 (6.5912, 14.5126) µg/mL, 8.4459 (5.0002, 14.2661) µg/mL, and 7.5811 (4.1885, 13.7216) µg/mL, respectively
- For the ≥40kg weight group: 13.5071 (10.3684, 17.5961) µg/mL, 13.8928 (11.0030, 17.5416) µg/mL, 10.2119 (7.0742, 14.7413) µg/mL, 12.2987 (8.6950, 17.3692) µg/mL, and 11.7108 (7.9296, 17.2953) µg/mL, respectively

After Week 72, CZP plasma concentrations were overall sustained for the Original CZP Dose and the Reduced CZP Dose.

Based on the results of the immunogenicity assays, for the entire Treatment Period, most study participants were treatment-induced ADAb positive (95/105 study participants [90.5%] for the Original CZP Dose and 82/88 study participants [93.2%] for the Reduced CZP Dose).

The median ADAb titers persisted at a generally similar magnitude within each Dose group after Week 24 through Week 72. After Week 72, there were no clear trends in median ADAb titers for the Original CZP Dose and Reduced CZP Dose.

Scatterplots of CZP plasma concentration by overall ADAb titer classification for the entire Treatment Period for the Original CZP Dose and the Reduced CZP Dose are presented for the PK-PPS in Figure 8-9 and Figure 8-11, respectively.

CHMP comment:

The observed geometric mean CZP plasma concentrations were lower for the Reduced CZP Dose compared with the Original CZP Dose.

Most participants were treatment-induced ADAb positive, for original dose as well as for the reduced dose.

Efficacy results

Primary efficacy variable

No primary efficacy results are included because the primary variables in this study were PK, immunogenicity, and safety variables.

Secondary efficacy variables: PedACR30, PedACR50, PedACR70, and PedACR90 at Week 16 (Visit 8) compared to Baseline (Week 0 [Visit 2])

The Any Cimzia Dose contains all the efficacy data from all study participants treated with Cimzia during the study, regardless of dose-switching. The American College of Rheumatology Pediatric 30%, 50%, 70%, and 90% (PedACR30, 50, 70, 90) responses at Week 16 (Visit 8) compared to Baseline (Week 0 [Visit 2]) for the Any Cimzia Dose are presented for the full analysis set (using nonresponder imputation method) in the table below.

Table 3: PedACR30, PedACR50, PedACR70, and PedACR90 responses – Week 16 (Visit 8) compared to Baseline (Week 0 [Visit 2])

	Any CZP Dose Total N=193
PedACR30	
n	193
Frequency of response (%)	153 (79.3)
95% CI for percentage response	72.9, 84.8
PedACR50	
n	193
Frequency of response (%)	140 (72.5)
95% CI for percentage response	65.7, 78.7
PedACR70	
n	193
Frequency of response (%)	105 (54.4)
95% CI for percentage response	47.1, 61.6
PedACR90	
n	193
Frequency of response (%)	53 (27.5)
95% CI for percentage response	21.3, 34.3

CI=confidence interval; CZP=certolizumab pegol; FAS=Full Analysis Set; NRI=nonresponder imputation; PedACR=Pediatric American College of Rheumatology
Note: Percentages were calculated based on the total number of participants at Week 16 (Visit 8) in each group, n. 95% CI was calculated using Clopper-Pearson method.
Note: 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.
Note: Any CZP Dose covers the entire dosing period regardless of dose switching (see Section 6.1.1, Table 10-1, and Figure 3-2).

The majority of study participants were PedACR30 responders at Week 16 (Visit 8) (compared to Baseline [Week 0 (Visit 2)]) for the Any Cimzia Dose (79.3%).

The percentages of study participants who were PedACR50, PedACR70, and PedACR90 responders at Week 16 (Visit 8) (compared to Baseline [Week 0 (Visit 2)]) for the Any Cimzia Dose were 72.5%, 54.4%, and 27.5%, respectively.

By Baseline weight group

The majority of study participants were PedACR30 responders at Week 16 (Visit 8) (compared to Baseline [Week 0 (Visit 2)]) in all Baseline weight groups in the Any Cimzia Dose (range: 77.8% to 83.3%).

In general, the percentages of PedACR50, PedACR70, and PedACR90 responders at Week 16 (Visit 8) (compared to Baseline [Week 0 (Visit 2)]) were similar across the 2 higher Baseline weight groups (20 to <40kg and ≥40kg), respectively, for the Any Cimzia Dose. For the 10 to <20kg Baseline weight group, the PedACR50, PedACR70, and PedACR90 responses varied; however, the interpretation is limited due to the small number of study participants in this weight group for each Dose group (n=18).

By Baseline age group

The percentages of study participants who were PedACR30 responders at Week 16 (Visit 8) (compared to Baseline [Week 0 (Visit 2)]) were 72.7% for the 2 to <6 years age group, 82.7% for the 6 to <12 years age group, and 77.6% for the 12 to 17 years age group for the Any Cimzia Dose.

In general, the percentages of PedACR50, PedACR70, and PedACR90 responders at Week 16 (Visit 8) (compared to Baseline [Week 0 (Visit 2)]) were similar across the 2 older age groups (6 to <12 years and 12 to 17 years), respectively, for the Any Cimzia Dose. For the 2 to <6 years age group, the PedACR50, PedACR70, and PedACR90 responses varied; however, the interpretation is limited due to the small number of study participants in this age group for each Dose group (n=11).

CHMP comment:

The primary objective of study RA0043 was to evaluate the PK and safety, including the immunogenicity, of Cimzia administered subcutaneously in children and adolescents with moderately-to-severely active pcJIA. The clinical response was assessed as a secondary objective to provide information on the efficacy of Cimzia in the study population.

The majority of study participants were PedACR30 responders at Week 16 compared to baseline. The response was seen in all components of the PedACR response, indicating a clinical effect of the treatment. However, no comparator was included in the study, and no statistical hypothesis testing was performed.

Safety results

Extent of exposure

For the Any Cimzia Dose, the Original Cimzia Dose, and the Reduced Cimzia Dose, the mean totals of Cimzia received were 11,494.6mg, 5095.7mg, and 10,580.2mg, respectively, and the mean exposure durations were 4.336 years, 1.127 years, and 4.744 years, respectively. For the Any Cimzia Dose, the Original Cimzia Dose, and the Reduced Cimzia Dose, the mean study participant days at risk were 1608.2 days, 434.2 days, and 1722.7 days, respectively, and the total participant years at risk were and 849.8 years, 124.8 years, and 415.0 years, respectively.

The exposure duration and participant-time risk were higher in the Reduced Cimzia Dose as compared with the Original Cimzia Dose and the Any Cimzia Dose.

Adverse events

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

The Any Cimzia Dose included all TEAEs including those emerging after study participants switched doses.

Overall summary of TEAEs

For the Any Cimzia Dose, the incidences of TEAEs and related TEAEs (per Investigator assessment) were 95.3% (184 study participants) and 48.7% (94 study participants), respectively. In addition, the incidences of serious TEAEs, severe TEAEs, and study participant discontinuation due to TEAEs were

23.8% (46 study participants), 14.0% (27 study participants), and 12.4% (24 study participants), respectively. Three study participants (1.6%) had TEAEs leading to death in the Any Cimzia Dose.

Overall summary of TEAEs by Baseline weight group

For the Any Cimzia Dose, for the 10 to <20kg, 20 to <40kg, and the ≥40kg weight groups, the incidences of TEAEs were 88.9%, 96.8%, and 95.5%, respectively, and the incidences of related TEAEs (per Investigator assessment) were 38.9%, 49.2%, and 50.0%, respectively. The incidence of serious TEAEs was 27.8% in the 10 to <20kg weight group, and the incidence of serious TEAEs was higher in the 20 to <40kg weight group (31.7%) compared with the ≥40kg weight group (18.8%). The incidences of severe TEAEs and discontinuations due to TEAEs ranged from 5.6% to 19.0% and 0% to 14.3%, respectively. Given the number of study participants in the 10 to <20kg weight group (N=18), any noted differences in these results should be interpreted with caution. Three study participants in the ≥40kg weight group had TEAEs leading to death in the Any Cimzia Dose.

Most common TEAEs

For the Any Cimzia Dose, the 3 most commonly reported TEAEs (by incidence of preferred term [PT]) were nasopharyngitis (53 study participants [27.5%]), upper respiratory tract infection (48 study participants [24.9%]), and headache (39 study participants [20.2%]).

TEAEs by severity

For the Any Cimzia Dose, the majority of participants had TEAEs that were mild (89.6% [1709 events/ 2332 total events]) or moderate in intensity (66.8% [577 events/ 2332 total events]). The incidence of participants who had at least 1 TEAE that was severe in intensity was 14.0% (46 events/ 2332 total events).

The most common severe TEAEs (by incidence of PT) were juvenile idiopathic arthritis (5 study participants [2.6%]), anaemia (3 study participants [1.6%]), and abdominal pain and anxiety (2 study participants [1.0%] each). No other severe TEAEs were reported for >1 study participant in this dose.

TEAEs by relationship to Cimzia

For the Any Cimzia Dose, the incidence of TEAEs related to Cimzia was 48.7%. The most commonly reported TEAEs related to Cimzia (by incidence of PT) were injection site pain (17 study participants [8.8%]), juvenile idiopathic arthritis (14 study participants [7.3%]), and upper respiratory tract infection (12 study participants [6.2%]).

Most common serious TEAEs

For the Any Cimzia Dose, the incidence of serious TEAEs was 23.8% (46 study participants). The most common serious TEAEs (by incidence of PT) were pneumonia (7 study participants [3.6%]), anaemia (3 study participants [1.6%]), and abdominal pain, vomiting, pyrexia, sepsis, juvenile idiopathic arthritis, and pregnancy on contraceptive (2 study participants [1.0%] each); no other serious TEAEs were reported for >1 study participants in this dose. Serious TEAEs were most commonly reported in the system organ class of Infection and infestations (22 study participants [11.4%]), Gastrointestinal disorders (7 study participants [3.6%]), Injury, poisoning, and procedural complications, Pregnancy, puerperium, and perinatal conditions, and Blood and lymphatic system disorders (4 study participants [2.1%] each).

AE of special interest

No cases of potential Hy's Law were reported during the study. Up to the database lock (DBL) date of 31 May 2024, there were 2 suspected hepatic events reported.

Deaths

A total of 3 study participants in the Any Cimzia Dose died prior to the DBL date for the final CSR of 31 May 2024. Of those, 2 deaths were deemed related to Cimzia (per investigator assessment). One was in a female that experienced septic shock and tuberculosis liver and the other was in a male that experienced disseminated tuberculosis. The third death was deemed unrelated (road traffic accident).

CHMP comment:

Although it is of concern that there were 3 deaths in the study, the 2 cases possibly related to Cimzia treatment were related to infections (septic shock and tuberculosis). These risks are considered sufficiently covered by the product information.

Clinical laboratory evaluation, vital sign measurements, and physical examination findings

There were no meaningful trends in changes in clinical laboratory parameters or vital signs during the study.

CHMP comment:

Treatment with Cimzia across a range of doses was well tolerated in children and adolescents with moderately to severe active pcJIA. It can be agreed with the MAH that the safety results for the study participants were consistent with the established safety profile of TNFα inhibitors. No new safety signals emerged.

2.3.3. Discussion on clinical aspects

RA0043 was a Phase 3, multicenter, open-label study to assess the PK, immunogenicity, safety, and efficacy of Cimzia in children and adolescents with moderately-to-severely active polyarticular-course juvenile idiopathic arthritis (pcJIA).

A total of 193 study participants were enrolled in the study, received at least 1 dose of Cimzia. Of these, 160 study participants (82.9%) completed at least Week 48 (Visit 13). Of the 193 study participants, 18, 63, and 112 were enrolled in the 10 to <20kg, 20 to <40kg, and ≥40kg weight groups, respectively.

Throughout the study, Cimzia dosing was a fixed dose based on weight and given every 2 weeks (Q2W), with the exception of the lowest weight group on the Reduced Cimzia Dose, who received the maintenance dose every 4 weeks (Q4W).

At the onset, study participants were to receive a fixed-dose Cimzia 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, referred to as Original Cimzia Dose. An interim population PK analysis of the first 34 pediatric study participants, conducted in Jun 2013, suggested that while observed Cimzia plasma concentrations remained in the adult range, they were at the upper end of the distribution. A decision was made to reduce the loading and maintenance doses by 50% for ongoing and newly enrolled participants (referred to as the Reduced Cimzia Dose). The Cimzia dose was not reduced due to any safety findings during the study.

The primary objective of study RA0043 was to evaluate the PK and safety, including the immunogenicity, of Cimzia administered subcutaneously in children and adolescents with moderately-to-severely active pcJIA. The clinical response was assessed as a secondary objective to provide

information on the efficacy of Cimzia in the study population. The majority of study participants were PedACR30 responders at Week 16 compared to baseline. The response was seen in all components of the PedACR response, indicating a clinical effect of the treatment. However, no comparator was included in the study, and no statistical hypothesis testing was performed.

Regarding safety, among all Cimzia-treated patients the incidence of TEAEs and serious TEAEs was 95.3% and 23.8%, respectively. The 3 most commonly reported TEAEs were nasopharyngitis (27.5%), upper respiratory tract infection (24.9%), and headache (20.2%). The most common severe TEAEs were juvenile idiopathic arthritis (2.6%), anaemia (1.6%), and abdominal pain and anxiety (1.0%).

Three study participants (1.6%) had TEAEs leading to death. Of those, 2 deaths were deemed related to Cimzia (per investigator assessment). One was in a female that experienced septic shock and tuberculosis liver and the other was in a male that experienced disseminated tuberculosis. The third death was deemed unrelated (road traffic accident). Although it is of concern that there were 3 deaths in the study, the 2 cases possibly related to Cimzia treatment were related to infections (septic shock and tuberculosis). These risks are considered sufficiently covered by the product information.

Considering that the statement in the SmPC section 4.2 (*"The safety and efficacy of Cimzia in children and adolescents below age 18 years have not yet been established. No data are available.")* is no longer correct, the MAH is requested to submit a variation to update section 4.2 (or provide a justification for not doing so) and include a brief summary of the main results from study RA0043 in the SmPC section 5.1 and 5.2. If paediatric data are to be included in the SmPC, the MAH is also asked to consider whether any particular warnings regarding possible risks associated with pegylation are to be included.

3. CHMP overall conclusion and recommendation

Treatment with Cimzia across a range of doses was well tolerated in children and adolescents with moderately to severe active pcJIA. It can be agreed with the MAH that the safety results for the study participants were consistent with the established safety profile of TNFα inhibitors. No new safety signals evoked.

Considering that the statement in the SmPC section 4.2 (*"The safety and efficacy of Cimzia in children and adolescents below age 18 years have not yet been established. No data are available.")* is no longer correct, the MAH is requested to submit a variation to update section 4.2 (or provide a justification for not doing so) and include a brief summary of the main results from study RA0043 in the SmPC section 5.1 and 5.2. If paediatric data are to be included in the SmPC, the MAH is also asked to consider whether any particular warnings regarding possible risks associated with pegylated products in the paediatric population are to be included.

☒ Fulfilled:

In view of the available data regarding the paediatric population in the phase 3 study (RA0043) with Cimzia, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and *no later than 60 days after the receipt* of these conclusions.