Amsterdam, 25 July 2024
EMA/CHMP/330518/2024
Committee for Medicinal Products for Human Use (CHMP)

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/P46/040

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 May 2024	27 May 2024	☐
☐	CHMP Rapporteur Assessment Report	01 July 2024	20 Jun 2024	☐
☐	CHMP members comments	15 July 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	18 July 2024	n/a	☐
☒	CHMP adoption of conclusions:	25 July 2024	25 July 2024	☐

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1. Introduction

On 13 May 2024, the MAH submitted a completed paediatric study for Cimzia, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Certolizumab pegol is a humanized antigen-binding fragment conjugated to polyethylene glycol with specificity for human tumor necrosis factor α (TNFα). Certolizumab pegol is approved in the EU since 2009 for the treatment of several inflammatory diseases, such as axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis), plaque psoriasis, psoriatic arthritis, and rheumatoid arthritis.

Outside EU (US and some other countries) Certolizumab pegol is also approved for treatment of Crohn's disease. In the EU, the marketing application for treatment of moderate to severe Crohn's disease patients was refused by the Committee for Medicinal Products for Human Use in Mar 2008 following re-examination of an initial negative opinion in Nov 2007.

In the context of the CD approval in the US, as per the Paediatric Research Equity Act, the Food and Drug Administration (FDA) requested the MAH to conduct a study in paediatric patients: C87035, A Phase 2, Open-label, Multicenter Study to Assess the Safety and Efficacy of Certolizumab Pegol in Children and Adolescents with Active Crohn's Disease (NURTURE Study). C87035 was designed to collect data on the safety, efficacy, and pharmacokinetics of Cimzia in children and adolescents with active CD. In April 2012, enrolment was terminated following data review and discussion with the FDA, and the Article 46 was subsequently submitted in the EU on 18 Jun 2013.

CR0012 Study was a Phase 2b, open-label, multicenter follow-up study in children and adolescents with moderately to severely active CD who completed C87035 or were terminated from C87035 when the study was stopped by UCB. The extension study was conducted to assess the long-term safety and tolerability in children and adolescents with CD receiving Cimzia.

The MAH recently noticed that the Article 46 submission for this Cimzia paediatric study CR0012 was missed. This study was completed (LPLV) on 21 Nov 2017 and the CSR should therefore have been submitted to the EMA by 21 May 2018 as per Article 46 regulation. Following email communication with EMA the MAH committed to submitting the final study report.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CR0012 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Cimzia is not approved for paediatric patients in the EU. For adults, a 200 mg prefilled syringe/prefilled pen/dose-dispenser cartridge is available. In study CR0012, the 200 mg pre-filled syringe was used.

	CZP dose (mg) injections	
Treatment group	**High Dose Group**	**Low Dose Group**
Dose frequency	**Q4W**	**Q4W**
Study participant weight		
20 to <40kg (44 to <88lbs)	1x1mL PFS/200mg	1x0.5mL PFS/100mg
≥40kg (≥88lbs)	2x1mL PFS/400mg	1x1mL PFS/200mg

CZP=certolizumab pegol; PFS=prefilled syringe; Q4W=every 4 weeks

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CR0012, An Open-Label, Multicenter Study to Assess the Safety of Certolizumab Pegol in Children and Adolescents with Active Crohn's Disease Who Completed C87035 or Were Terminated from C87035 When the Study was Stopped by UCB

2.3.2. Clinical study CR0012

Description

CR0012 was a Phase 2b, open-label, multicenter follow-up study in children and adolescents with moderately to severely active CD who completed C87035 or were terminated from C87035 when the study was stopped by UCB. The study was conducted to assess the long-term safety and tolerability of CZP.

Methods

Study participants

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

1. Written Informed Consent form was signed and dated by the subject or by the parent(s) or legally acceptable representative. The Consent form or a specific Assent form, where required, was to be signed and dated by minors.
2. Subject/parent(s)/legally acceptable representative was considered reliable and capable of adhering to the protocol, visit schedule, or medication intake according to the judgment of the Investigator.
3. Subject completed the C87035 study (Week 62 Visit) or was terminated from C87035 when the study was stopped by UCB and completed all assessments required for Week 62/Visit 23 at the time of termination.
4. Subject’s current or recent regimen of concomitant medication(s) for CD was to be stable through the study period.

Treatments

The following treatment was administered.

Table 1. Doses of CZP in CR0012

	CZP dose (mg) injections	
Treatment group	**High Dose Group**	**Low Dose Group**
Dose frequency	**Q4W**	**Q4W**
Study participant weight		
20 to <40kg (44 to <88lbs)	1x1mL PFS/200mg	1x0.5mL PFS/100mg
≥40kg (≥88lbs)	2x1mL PFS/400mg	1x1mL PFS/200mg

CZP=certolizumab pegol; PFS=prefilled syringe; Q4W=every 4 weeks

Objective(s)

The primary objective of this open-label, multicenter study was to assess the long-term safety of CZP in study participants who completed C87035 or were terminated from C87035 when the study was stopped by UCB. Due to the small number of study participants who enrolled in the study (16 study participants) and the decreasing sample size over time, no conclusions regarding disease activity can be made.

Data collected from visits after Week 38 are provided in tables and listings, but not presented in text. At Week 38, 11 study participants remained in the study, and 2 study participants continued CR0012 for more than 200 weeks.

Pharmacokinetics (PK) was listed as a secondary objective.

Outcomes/endpoints

The safety variables included in the study were:

- Adverse events (AEs)
- Laboratory parameters (hematology, biochemistry, urinalysis)
- Vital signs
- Autoantibodies (antinuclear antibody [ANA] and anti-double-stranded deoxyribonucleic acid [dsDNA] antibody)

The study also included PK and efficacy endpoints. The primary efficacy variable was the proportion of subjects in clinical remission where clinical remission was defined as a Pediatric Crohn's Disease Activity Index (PCDAI) score ≤10.

Blood samples for PK characterization was to be collected approximately every 12 weeks and included pre-dose (trough) samples.

Sample size

A total of 16 subjects participated in this study. Due to the nature of the study, no formal sample size estimation was performed.

Randomisation and blinding (masking)

The study was an open-label follow-up study and no randomisation was performed.

Statistical Methods

Descriptive statistics were displayed to provide an overview of the study results.

Results

Participant flow

Table 2. Disposition and discontinuation reasons

Disposition	CZP Low Dose N=4 n (%)	CZP High Dose N=12 n (%)	All CZP Doses N=16 n (%)
Started study	4 (100)	12 (100)	16 (100)
Completed study	3 (75.0)	3 (25.0)	6 (37.5)
Discontinued	1 (25.0)	9 (75.0)	10 (62.5)
Primary reason for discontinuation			
Adverse event	0	3 (25.0)	3 (18.8)
Lack of efficacy	0	2 (16.7)	2 (12.5)
Protocol violation	0	0	0
Lost to follow-up	0	0	0
Consent withdrawn	0	2 (16.7)	2 (12.5)
Other	1 (25.0)	2 (16.7)	3 (18.8)
Started reinduction period in C87035 or CR0012	0	8 (66.7)	8 (50.0)
Completed reinduction period in C87035 or CR0012	0	8 (66.7)	8 (50.0)

CZP=certolizumab pegol; Q4W=every 4 weeks; SS=Safety Set
Note: Completed study was defined as receiving CZP Q4W until the subject reached the age of 18 years or until CZP was approved for use in the US by pediatric patients with Crohn's disease.
Note: If a subject had not been previously reinduced in C87035, the subject was eligible for 1 reinduction due to the loss of response in CR0012.
Note: Six subjects had CZP reinduced in C87035 and 2 subjects had CZP reinduced in CR0012.
Data source: Table 1.3

Baseline data

Table 3. Patient demographics

Variable Statistic	CZP Low Dose N=4	CZP High Dose N=12	All CZP Doses N=16
Age (years)			
Mean (SD)	13.5 (2.4)	13.9 (2.9)	13.8 (2.7)
Median (min, max) [a]	13.5 (11, 16)	14.0 (10, 18)	14.0 (10, 18)
Age [b], n (%)			
6 to <12 years	1 (25.0)	3 (25.0)	4 (25.0)
12 to <18 years	3 (75.0)	8 (66.7)	11 (68.8)
18 to <65 years [a]	0	1 (8.3)	1 (6.3)
Gender, n (%)			
Male	2 (50.0)	6 (50.0)	8 (50.0)
Female	2 (50.0)	6 (50.0)	8 (50.0)
Weight (kg)			
Mean (SD)	57.38 (25.95)	48.98 (11.59)	51.08 (15.73)
Median (min, max)	54.45 (31.1, 89.5)	48.95 (30.9, 76.4)	48.95 (30.9, 89.5)
Height (cm)			
Mean (SD)	157.88 (16.70)	159.06 (14.32)	158.76 (14.37)
Median (min, max)	156.80 (139.4, 178.5)	163.20 (132.6, 177.8)	162.60 (132.6, 178.5)
BMI (kg/m^2)			
Mean (SD)	21.98 (5.59)	19.16 (2.29)	19.86 (3.42)
Median (min, max)	21.90 (16.0, 28.1)	19.10 (15.4, 24.2)	19.10 (15.4, 28.1)

Number analysed

Table 4. Analysis sets

Analysis set	CZP Low Dose N=4 n (%)	CZP High Dose N=12 n (%)	All CZP Doses N=16 n (%)
AS	4 (100)	12 (100)	16 (100)
SS	4 (100)	12 (100)	16 (100)
ITT	4 (100)	12 (100)	16 (100)

AS=All Subjects Set; CZP=certolizumab pegol; ITT=Intention-to-Treat Set; SS=Safety Set
Data source: Table 1.2

Efficacy results

The primary efficacy variable was the proportion of subjects in clinical remission (clinical remission was defined as a PCDAI score ≤10). Summaries of PCDAI scores by visit for the ITT Population are provided below.

Table 5. Summary of Clinical Remission and Clinical Response Rates by Visit Analysis Set: ITT Population

Week Number	CZP Low Dose N=4	CZP High Dose N=12	All CZP Doses N=16
Week 0 (C87035)			
n	4	12	16
Clinical Remission n (%)	0	0	0
95% CI			
Clinical Response n (%)	0	0	0
95% CI			
Week 14			
n	4	11	15
Clinical Remission n (%)	4(100)	8 (72.7)	12 (80.0)
95% CI		[46.4, 99.0]	[59.8, 100.0]
Clinical Response n (%)	4(100)	10 (90.9)	14 (93.3)
95% CI		[73.9, 100.0]	[80.7, 100.0]
Week 26			
n	3	9	12
Clinical Remission n (%)	2 (66.7)	6 (66.7)	8 (66.7)
95% CI	[13.3, 100.0]	[35.9, 97.5]	[40.0, 93.3]
Clinical Response n (%)	2 (66.7)	8 (88.9)	10 (83.3)
95% CI	[13.3, 100.0]	[68.4, 100.0]	[62.2, 100.0]
Week 38			
n	3	6	9
Clinical Remission n (%)	2 (66.7)	3 (50.0)	5 (55.6)
95% CI	[13.3, 100.0]	[10.0, 90.0]	[23.1, 88.0]
Clinical Response n (%)	3(100)	5 (83.3)	8 (88.9)
95% CI		[53.5, 100.0]	[68.4, 100.0]

At Week 38, 5 subjects had an increase in Tanner stage over Baseline, 6 subjects maintained a Baseline Tanner stage, and 5 subjects had missing Tanner stages at Week 38. No subjects had a decrease in Tanner stage at Week 38 compared with Baseline. These results suggest that the paediatric subjects are not developmentally regressing during the study.

Safety results

A summary of the incidence of TEAEs for the SS is presented below.

Table 6. Incidence of TEAEs

Category	CZP Low Dose N=4 n (%) [#]	CZP High Dose N=10 n (%) [#]	CZP Reinduction (400mg) N=2 n (%) [#]	All CZP Doses N=16 n (%) [#]
Any TEAE	2 (50.0) [5]	6 (60.0) [67]	2 (100) [10]	10 (62.5) [82]
Serious TEAEs	0	4 (40.0) [5]	1 (50.0) [2]	5 (31.3) [7]
Subject discontinuations due to TEAEs	0	3 (30.0) [5]	0	3 (18.8) [5]
Permanent withdrawal of study medication due to TEAEs	0	2 (20.0) [3]	0	2 (12.5) [3]
TEAEs requiring dose change	0	0	1 (50.0) [1]	1 (6.3) [1]
Drug-related TEAEs	0	2 (20.0) [8]	0	2 (12.5) [8]
Severe TEAEs	0	1 (10.0) [1]	0	1 (6.3) [1]
All deaths (AEs leading to death)	0	0	0	0
Deaths (TEAEs leading to death)	0	0	0	0

AE=adverse event; CZP=certolizumab pegol; TEAE=treatment-emergent adverse event; SS=Safety Set
Note: n=number of subjects reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: Drug-related TEAEs were those with relationship of possible, probable, highly probable, or missing.
Note: If a subject was reinduced in CR0012, that subject and all TEAEs for that subject were included in the CZP Reinduction Group.
Data source: Table 7.1

A summary of the most common TEAEs is provided below.

Table 7. Incidence of TEAEs reported by ≥2 subjects in the All CZP Dose Group

MedDRA (Version 20.1) SOC PT	CZP Low Dose N=4 n (%)	CZP High Dose N=10 n (%)	CZP Reinduction (400mg) N=2 n (%)	All CZP Doses N=16 n (%)
Any TEAE	2 (50.0)	6 (60.0)	2 (100)	10 (62.5)
Gastrointestinal disorders	1 (25.0)	5 (50.0)	2 (100)	8 (50.0)
Abdominal pain upper	0	4 (40.0)	0	4 (25.0)
Crohn's disease	0	1 (10.0)	1 (50.0)	2 (12.5)
Nausea	0	2 (20.0)	0	2 (12.5)
Stomatitis	0	1 (10.0)	1 (50.0)	2 (12.5)
Infections and infestations	0	4 (40.0)	1 (50.0)	5 (31.3)
Nasopharyngitis	0	2 (20.0)	0	2 (12.5)
Musculoskeletal and connective tissue disorders	0	2 (20.0)	0	2 (12.5)
Pain in extremity	0	2 (20.0)	0	2 (12.5)
Nervous system disorders	1 (25.0)	1 (10.0)	0	2 (12.5)
Dizziness	1 (25.0)	1 (10.0)	0	2 (12.5)
Respiratory, thoracic and mediastinal disorders	1 (25.0)	1 (10.0)	0	2 (12.5)
Cough	1 (25.0)	1 (10.0)	0	2 (12.5)

One of 10 subjects in the CZP High Dose Group reported a severe TEAE of an exacerbation of Crohn's disease that was also considered serious. Overall, 5 subjects reported SAEs, including 4 subjects in the CZP High Dose Group and 1 subject in the CZP Reinduction Group. The most common SAE reported was an exacerbation of Crohn's disease (1 subject each in the CZP High Dose Group and the CZP Reinduction Group). In the CZP High Dose Group, SAEs of small intestinal obstruction, gastritis viral, pancreatitis viral, and suicide attempt were reported in 1 subject each and in the CZP Reinduction Group 1 subject reported an SAE of anal abscess. The majority of SAEs were moderate or mild in intensity, not or unlikely to be related to study medication, and were resolved or resolving by the end of the study. An overview of treatment-emergent SAEs is shown below.

Table 8. Treatment-emergent SAEs

Treatment group	Preferred term	TEAE duration (days)/ TEAE onset date (relative day)	Intensity/ relationship to study medication	Action taken with study medication	SAE led to study discontinuation
CZP Reinduction	Crohn's disease	6/+37	Moderate/ not related	Not applicable	No
	Anal abscess	3/+24	Moderate/ not related	Not applicable	No
CZP High Dose	Small intestinal obstruction	10/+11	Moderate/ unlikely related	Study medication withdrawn	Yes
	Gastritis viral	3/+5	Mild/ unlikely related	Not applicable	No
CZP High Dose	Pancreatitis viral	36/19	Mild/ not related	Dose not changed	No
CZP High Dose	Suicide attempt	--/+38	Mild/ not related	Not applicable	No
CZP High Dose	Crohn's disease	2/+12	Severe/ possibly related	Not applicable	Yes

All TEAEs leading to discontinuation from the study were reported in the CZP High Dose Group (3 subjects): abdominal pain upper and TEAE of small intestinal obstruction; abdominal tenderness; and exacerbation of Crohn's disease.

Pharmacokinetics results

PK data were available from 16 patients with 4 study participants in the CZP Low Dose Group and 12 study participants in the CZP High Dose Group.

At Weeks 14, 26, and 38 of CR0012, geometric mean CZP concentrations ranged from 3.32µg/mL to 2.25µg/mL and 5.47µg/mL to 4.73µg/mL for the CZP Low Dose Group and the CZP High Dose Group, respectively.

2.3.3. Discussion on clinical aspects

Cimzia is not approved for treatment of Crohn's disease in the EU.

In the context of the CD approval in the US, FDA requested the MAH to conduct a study in paediatric patients: C87035, A Phase 2, Open-label, Multicenter Study to Assess the Safety and Efficacy of Certolizumab Pegol in Children and Adolescents with Active Crohn's Disease (NURTURE Study). C87035 was designed to collect data on the safety, efficacy, and pharmacokinetics of Cimzia in children and adolescents with active CD. In April 2012, enrolment was terminated following data review and discussion with the FDA, and the Article 46 was subsequently submitted in the EU on 18 Jun 2013.

CR0012 Study was a Phase 2b, open-label, multicenter follow-up study in children and adolescents with moderately to severely active CD who completed C87035 or were terminated from C87035 when the study was stopped by UCB. The extension study was conducted to assess the long-term safety and tolerability in children and adolescents with CD receiving Cimzia.

A total of 16 paediatric patients (8 male, 8 female) were included in the study, whereof 6 completed the study. The mean age was 13.8 years, ranging from 10 to 18 years. Treatment-emergent adverse events were reported in 10/16 patients (62.5%) and serious treatment-emergent adverse events were reported in 5/16 patients (31.3%). TEAEs were most commonly reported in the SOCs of Gastrointestinal disorders (8 subjects) and Infections and infestations (5 subjects). Overall, the most common TEAEs (reported by ≥2 subjects), by PT, were abdominal pain upper (4 subjects) and exacerbation of Crohn's disease, nausea, stomatitis, nasopharyngitis, pain in extremity, dizziness, and cough (2 subjects each). There were no deaths in the study.

The MAH concludes that the overall safety profile in this paediatric population with CD was similar to that observed previously in adults with CD, and consistent with that expected in subjects with CD receiving anti-TNF-α therapy. No new safety signals were identified with long-term use. Due to the small number of subjects who enrolled in the study (16) and the decreasing sample size over time, no conclusions regarding disease activity can be made.

This is agreed with.

The presentation of the sparse PK data is acceptable given the current procedure. However, the data were limited, and no firm conclusions can be drawn.

3. CHMP overall conclusion and recommendation

The observed safety profile in paediatric patients with Crohn's disease included in the current study (n=16) was similar to that observed previously in adults with CD, and consistent with that expected in subjects with CD receiving anti-TNF-α therapy. No new safety signals were identified. Due to the small sample size, no efficacy or PK conclusions can be drawn.

☒ Fulfilled:

No regulatory action required.