06 July 2023
EMA/390341/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Simponi

International non-proprietary name: golimumab

Procedure No. EMEA/H/C/000992/II/0113

Note

Variation 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	15 Mar 2023	15 Mar 2023	☐
☐	CHMP Rapporteur Assessment Report	17 Apr 2023	17 Apr 2023	☐
☐	PRAC Rapporteur Assessment Report	24 Apr 2023	17 Apr 2023	☐
☐	PRAC members comments	28 Apr 2023	n/a	☐
☐	CHMP members comments	02 May 2023	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	03 May 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	04 May 2023	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	10 May 2023	10 May 2023	☐
☐	Start of written procedure	10 May 2023	10 May 2023	☐
☐	Request for supplementary information	12 May 2023	12 May 2023	☐
☐	Submission of MAH responses	07 June 2023	07 June 2023	☐
☐	Restart of procedure	08 June 2023	08 June 2023	☐
☐	CHMP Rapporteur Assessment Report	21 June 2023	19 June 2023	☐
☐	CHMP members comments	26 June 2023	26 June 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	29 June 2023	n/a	☐
☐	Start of written procedure	04 July 2023	04 July 2023	☐
☒	opinion	06 July 2023	06 July 2023	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen Biologics B.V. submitted to the European Medicines Agency on 28 February 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study CNTO148UCO1001 (PURSUIT PEDS PK) listed as a category 3 study in the RMP. This is a phase 1b open-label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFα antibody, in pediatric subjects with moderately to severely active ulcerative colitis. The RMP version 24.1 has also been submitted.

The requested variation proposed amendments to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

This variation concerns the submission of the final report from study CNTO148UCO1001, a Phase 1b open-label study to assess the safety and PK of subcutaneously administered golimumab in paediatric ulcerous colitis. The study is listed as a category 3 study in the Risk Management Plan (RMP) and the requested variation propose amendments to the RMP but no update to the PI.

Golimumab is a fully human monoclonal antibody that binds to human TNFα and neutralizes TNFα bioactivity. It was first approved for treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis in 2009 and for other inflammatory diseases after that, including juvenile idiopathic arthritis. In 2013 it was approved for treatment of adults with moderately to severely active UC and is currently being explored as a treatment for paediatric patients with moderately to severely active UC.

In addition to the completed Phase 1b open-label CNTO148UCO1001 study assessed in this variation the paediatric UC programme also includes an ongoing Phase 3 randomized, open-label study to assess the efficacy, safety, and pharmacokinetics of golimumab treatment in subjects aged 2 to 17 years. Data on the Phase 3 study are not yet available.

CNTO148UCO1001 was a Phase 1b, multicenter, open-label study to assess the PK and safety of golimumab treatment in paediatric subjects 2 through 17 years of age with moderately to severely active UC. Subjects should have failed conventional treatment but be naïve to anti-TNFα agents.

Thirty-five patients were included and around 29% of the patients were between 2-11 years old and around 43% of the patients had a weight <45 kg (including 5 patients with a weight<30kg), fulfilling the intended number of patients initially planned by the MAH.

The initial dose (induction dose) was 200 mg week 0 and 100 mg week 2 for patients >45 kg, in line with the dose for adult patients. For patients <45 kg, the dose was based on their body surface area (90mg/m^2 week 0 and 45mg/m^2 week 2). The patients who achieved a response at week 6 were able to continue to the study extension phase, with a maintenance dose of 100 mg Q4W for children >45mg and 45 mg/m2 for children <45 kg (max 100 mg). It is noted that this maintenance dose is the highest dose prescribed for adults (in adult UC it is recommended for patients with an inadequate

response to induction therapy or adults > 80kg), however all subjects who entered the study extension had the option to decrease their dose to golimumab 50 mg or 22.5 mg/m^2 at Week 14 or thereafter at the discretion of the investigator. Two subjects had their dose decreases, one at a single occasion by mistake, the other lowered the dose from 100 mg to 50 mg at week 146.

Of the 35 subjects enrolled, a total of 20 subjects (57.1%) entered into the study extension at Week 14. The most common reasons for subjects to not continue in the study extension were unsatisfactory therapeutic effect (28.6%) and AEs (8.6%). Of the patients entering the study extension, 9/20 (45.0%) subjects discontinued study agent through Week 126, mainly because of unsatisfactory therapeutic response (6 patients) and AEs (3 patients). Although efficacy was not the main topic for this study and data are based on open label treatment with no control group it is noted that at week 6, the proportion of patients achieving clinical response, clinical remission and mucosal healing based on the Mayo score were around 60%, 43% and 54% and thus no less than seen in adult population at this timepoint. In addition, 23% of the patients achieved complete mucosal healing. There were no signs of a lesser effect in the subgroup of younger patients or patients with lower weight (<45 kg) however the data are based on small numbers and no firm conclusion can be made.

Regarding the pharmacokinetics, some concerns were identified related to the bioanalysis and the immunogenicity analyses. Since this variation concerns the submission of the final report from study CNTO148UCO1001, and no SmPC update is proposed, the issues identified are not further pursued. However, if a future application includes the PK results from this study, the missing documentation should be provided and assessed in that application.

The serum golimumab concentrations appeared to be relatively comparable between pediatrics with UC with a body weight ≥45 kg and adults with UC when compared within the same body weight categories. There seemed to be a trend towards lower mean serum concentration in pediatrics weighing < 45 kg (who received the BSA-adjusted dose regimen) as compared to those weighing ≥ 45 kg and compared to the reference adults UC population (who received the flat fixed dose regimen).

Overall, based on the limited data in the pediatrics, these results should be interpreted with caution. However, there are indications that a higher BSA-adjusted dose regimen may be needed for the <45 kg pediatric subgroup. A higher dose has been implemented in the ongoing Phase 3 study (CNTO148UCO3003).

Regarding safety, the average duration of follow-up was 115.6 weeks, with an average exposure of 27.1 administrations of golimumab. Adverse events were very common and 94.3% reported 1 or more AEs during the entire study. The most frequently reported SOCs were Gastrointestinal disorders (82.9%), Infections and infestations (54.3%), and General disorders (42.9%). The most frequent AEs were colitis ulcerative, (62.9%), headache (34.3), abdominal pain (25.7%), upper respiratory tract infection, anemia and nausea. The distribution and type of AEs were similar as in the adult population; however, the frequency of events was higher in the paediatric UC population. This was especially seen in the incidence of infections, where the incidence of infections per 100 subject-years of follow-up was 121.23. Since small children are more prone to infectious disease this is not unsuspected. A similar incidence was seen in the JiA population. There were no deaths during the study. Serious adverse events (SAEs) were however seen in 16 (45.7%) patients and were mainly associated with disease progression. Most of the SAEs were assessed as having no relation to the treatment.

Markedly abnormal changes in hematology and chemistry laboratory values were uncommon, however one subject had 1 event of markedly abnormal elevation in alkaline phosphatase. Upon request, the MAH provided additional information regarding this subject and the fact that alkaline phosphatase was elevated already at baseline, not associated with any other liver function test elevation, fluctuating

during the study time (8-years) and normalizing at the end of the study, despite still on treatment, make the association with Simponi treatment unlikely.

To conclude, the overall safety profile in this small pediatric UC study was consistent with the known safety profile of golimumab with no new safety concerns identified. However, since the phase 3 study in the pediatric UC study is still ongoing it is anticipated that the safety information from this study is incorporated in the assessment of the overall safety when the final result from that study is submitted.

An updated RMP was submitted with this application, removing this study as category 3 study from the additional pharmacovigilance plan. In addition, the MAH has included dose recommendation for adult UC patients <80 kg with inadequate response after induction treatment to align with the updated SmPC approved in EMEA/H/C/000992/II/0079. This is acceptable.

The benefit-risk balance of Simponi remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study CNTO148UCO1001 (PURSUIT PEDS PK) listed as a category 3 study in the RMP. This is a phase 1b open-label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFα antibody, in pediatric subjects with moderately to severely active ulcerative colitis. The RMP version 26.1 has also been submitted.

☒is recommended for approval.

Amendments to the marketing authorisation

The variation requires amendments to the Risk Management Plan.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Study CNTO148UCO1001 was a Phase 1b open label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab in paediatric subjects aged 2 to 17 years with moderately to severely active ulcerative colitis (UC). Thirty-five (35) patients were included and around 29% of the patients were between 2-11 years old and around 43% of the patients had a weight <45 kg (including 5 patients with a weight<30kg).

The serum golimumab concentrations appeared to be relatively comparable between paediatrics with

UC with a body weight ⩾45 kg and adults with UC when compared within the same body weight categories. There seemed to be a trend towards lower mean serum concentration in paediatrics weighing < 45 kg (who received the BSA-adjusted dose regimen) as compared to those weighing ≥ 45 kg and compared to the reference adults UC population (who received the flat fixed dose regimen).

The overall safety profile in this small paediatric UC study was consistent with the known safety profile of golimumab with no new safety concerns identified.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Golimumab is a fully human monoclonal antibody with an IgG1 heavy chain isotype (G1m[z] allotype) and a kappa light chain isotype. Golimumab binds to human TNFα with high affinity and specificity and neutralizes TNFα bioactivity. Elevated TNFα levels have been associated with multiple immune-mediated diseases, including UC. These observations led to clinical programs evaluating golimumab in subjects with moderately to severely active UC, which led to the first approval globally on 20 September 2013 of SIMPONI for this indication in adults. Golimumab is currently being explored as a treatment for pediatric patients with moderately to severely active UC.

The development program for golimumab in pediatric UC consists of a completed Phase 1b open-label study to assess the safety and PK of subcutaneously administered golimumab in subjects aged 2 to 17 years (CNTO148UCO1001) and an ongoing Phase 3 randomized, open-label study to assess the efficacy, safety, and pharmacokinetics of golimumab treatment in subjects aged 2 to 17 years (CNTO148UCO3003). Data on this Phase 3 study are not yet available.

This variation concerns the submission of the final report from study CNTO148UCO1001 listed as a category 3 study in the RMP. The Risk Management Plan (RMP) version 24.1 has also been submitted. The requested variation proposed amendments to the RMP.

6. Clinical Pharmacology aspects

The PK and/or PD of golimumab were studied in subjects with moderately to severely active UC in 1 Phase 1b study (in pediatric subjects), 1 Phase 2/3 induction study (in adult subjects), and 1 Phase 3 maintenance study (in adult subjects) (**Table 1**).

Table 1: Overview of Completed Studies in Pediatric and Adult Subjects With UC

Study ID and Title	Age and Body Weight Range	Dose Regimen	Number of Subjects Treated	PK Sampling Scheme[a]
CNTO148UCO1001 A Phase 1b Open-Label Study to Assess the Safety and Pharmacokinetics of Subcutaneously Administered Golimumab, a Human anti-TNFα Antibody, in Pediatric Subjects With Moderately to Severely Active Ulcerative Colitis	6 to 17 years; 19.7 to 134.0 kg	Subjects with body weight <45 kg: 90 mg/m^2 at Week 0 and 45 mg/m^2 at Week 2, and 45 mg/m^2 q4w starting at Week 6 among Week 6 responders Subjects with body weight ≥45 kg: 200 mg at Week 0 and 100 mg at Week 2, and 100 mg q4w starting at Week 6 among Week 6 responders	35	Sparse
C0524T17 (induction) A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis	18 to 78 years; 33 to 149.7 kg	100 mg → 50 mg 200 mg → 100 mg 400 mg → 200 mg placebo → placebo Week 0 and Week 2 dose administration	1064	Sparse
C0524T18 (maintenance) A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis	18 to 79 years; 33 to 150 kg	50 mg 100 mg placebo q4w among golimumab induction responders at Week 6	1228	Sparse

[a] Intensive sampling schemes enable determination of PK parameters using a nonmodel-based approach (ie, non-compartmental analysis). Sparse sampling schemes require a model-based approach to determine PK parameters.

6.1. Methods – analysis of data submitted

CNTO148UCO1001 was a Phase 1b, multicenter, open-label study to assess the safety and PK of golimumab treatment in pediatric subjects aged 2-17 years with moderately to severely active UC. The primary outcome of this study was to assess the PK of golimumab. Major secondary outcomes included safety and efficacy.

During the PK portion of the study (Weeks 0-14), subjects received SC golimumab at weeks 0 and 2 (**Table 2**). Subjects in clinical response at Week 6 were eligible to receive open-label maintenance therapy with golimumab (at Week 6 and Week 10) and to enter the study extension at Week 14. For detailed information of the study design, see section *7. Clinical Efficacy aspects/Methods-analysis of submitted data*. The dose regimens were anticipated to deliver golimumab exposure in pediatric subjects comparable to those observed in the reference adult UC population (200 mg → 100 mg treatment group in the golimumab adult studies).

Table 2: Golimumab SC Dose Regimens by Body Weight; Pharmacokinetic Portion of the Study

Table 1:	Golimumab SC Dose Regimens by Body Weight; Pharmacokinetic Portion of the Study		
Body Weight	**Week 0**	**Week 2**	**Subjects in clinical response at Week 6: Week 6 and Week 10**
<45 kg	90 mg/m^2 (up to a maximum of 200 mg)	45 mg/m^2 (up to a maximum of 100 mg)	45 mg/m^2 (up to a maximum of 100 mg)
≥45 kg	200 mg	100 mg	100 mg

A summary of the demographics at baseline is given in **Table 3**.

Table 3: Summary of demographics at baseline by golimumab SC dose regimen; Treated subjects (Study CNTO148UCO1001

	Golimumab SC dose regimen	
	90 mg/m^2→45 mg/m^2	200 mg →100 mg
Treated subjects	15	20
Sex		
N	15	20
Male	7 (46.7%)	10 (50.0%)
Female	8 (53.3%)	10 (50.0%)
Age (yrs)		
N	15	20
Mean (SD)	10.3 (2.28)	15.8 (0.89)
Median	10.0	16.0
IQ range	(9.0; 12.0)	(15.0; 16.5)
Range	(6; 14)	(14; 17)
Age categories (yrs)		
N	15	20
2-11	10 (66.7%)	0
12-17	5 (33.3%)	20 (100.0%)
Weight (kg)		
N	15	20
Mean (SD)	34.06 (7.160)	65.01 (21.257)
Median	34.30	57.55
IQ range	(28.90; 41.50)	(54.00; 68.15)
Range	(19.7; 43.3)	(45.5; 134.0)
Weight categories (kg)		
N	15	20
<45	15 (100.0%)	0
<30	5 (33.3%)	0
≥ 45	0	20 (100.0%)
Height (cm)		
N	15	20
Mean (SD)	143.00 (12.696)	168.58 (9.871)
Median	144.00	167.60
IQ range	(136.00; 157.00)	(164.35; 176.50)
Range	(113.4; 158.6)	(150.0; 186.0)

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Sampling times for PK and immunogenicity assessments

Pre-dose blood samples were taken on days 1 (Week 0), 15 (Week 2), 29 (Week 4), 43 (Week 6), 99 (Week 14) and at the final visit (for subjects not entering study extension) for analysis of golimumab in serum. A PK blood sample was also withdrawn on Day 4.

Blood samples for analysis of antibodies to golimumab were withdrawn on Days 1 (Week 0), 43 (Week 6) and 99 (Week 14), including the final visit for subjects not entering the extension (final visit occurs 16 weeks after the last administration of study agent).

During the study extension (> Week 14), samples for determinations of ADAs and golimumab were taken every three months between weeks 18 and 54 and thereafter every sixth months between

weeks 54 and 102. Samples were also withdrawn at week 110 and thereafter every sixth months and at the final visit.

Bioanalysis

Serum golimumab concentrations were determined using a validated electrochemiluminescent immunoassay (ECLIA) method on the Meso Scale Discovery® (MSD) platform (validation report CP2008V-043). The lowest quantifiable concentration in a sample for MSD ECLIA was 0.03905 µg/mL at a minimum required dilution of 1:5.

A validated drug-tolerant Enzyme Immunoassays (EIA) method was used to detect antibodies to golimumab in the presence of golimumab (validation report CP2012V-037).

A validated ECLIA method was used to determine neutralizing antibodies in subjects who were positive for anti-drug antibodies (ADAs) (validation report CP2015V-001).

Pharmacokinetic analyses

Serum golimumab concentrations over time were evaluated. Population PK analyses were performed using PK data collected through Week 14. PK data of golimumab from other studies, such as data from adult subjects with UC and data from pediatric subjects with JIA were also used in the population PK analysis. The population PK analyses will be provided in a separate technical report and is not reported here.

6.2. Results

Serum golimumab concentrations – through Week 14

Peak serum golimumab concentrations were observed on Day 4 (mean: 13.9 µg/mL). Serum golimumab concentrations through Week 6 are summarized in **Table 5**. All subjects had detectable concentrations.

Table 4: Summary of Serum Golimumab Concentrations (micrograms/mL) Through Week 6; Treated Subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Baseline	
N	34
Mean (SD)	0.00 (0.000)
Median	0.00
IQ range	(0.00; 0.00)
Range	(0.0; 0.0)
Day 4	
N	34
Mean (SD)	13.86 (5.091)
Median	13.17
IQ range	(9.70; 16.61)
Range	(4.6; 27.8)
Week 2	
N	31
Mean (SD)	6.46 (3.077)
Median	5.72
IQ range	(3.80; 9.17)
Range	(2.0; 12.3)
Week 4	
N	31
Mean (SD)	6.51 (3.375)
Median	7.61
IQ range	(3.22; 9.51)
Range	(1.6; 12.4)
Week 6	
N	31
Mean (SD)	2.56 (1.657)
Median	2.64
IQ range	(0.92; 3.83)
Range	(0.2; 5.3)

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In pediatric subjects who were in clinical response to golimumab at Week 6 and therefore received doses of golimumab at Weeks 6 and 10, mean (SD) serum golimumab concentration at Week 14 (steady-state) was 2.09 (1.72) µg/mL (n=19). One subject had plasma concentrations below the LOQ.

Serum Golimumab Concentrations by Baseline Age

Median (and mean) serum golimumab concentrations over time in subjects 2 to 11 years were generally lower than those in the 12 to 17 years age subgroup. At Week 6, the mean (SD) serum golimumab concentrations were 1.80 (1.86) µg/mL (n=8) and 2.83 (1.54) µg/mL (n=23) among subjects 2 to 11 years of age and 12 to 17 years of age, respectively. Of note, all subjects who were in the 2 to 11 years of age group had body weight <45 kg; hence they received the 90 mg/m^2 → 45 mg/m^2 induction regimen. The sample size in the younger age group was relatively small (n=10) and may not allow definitive conclusions.

Serum Golimumab Concentrations by Baseline Body Weight/Golimumab Dose Regimen

Serum golimumab concentrations through Week 6 were compared across the 2 baseline body weight/golimumab dose regimen subgroups (ie, <45 kg [90 mg/m^2 → 45 mg/m^2] and ≥45 kg [200 mg → 100 mg]). Median (and mean) serum golimumab concentrations over time in the <45 kg body weight subgroup were generally lower compared with subjects in the ≥45 kg body weight subgroup (**Table 4**). The relatively lower concentration observed in the <45 kg subgroup did not impact efficacy.

Table 5: Summary of Serum Golimumab Concentrations (micrograms/mL) Through Week 6 by Golimumab SC Dose Regimen; Treated Subjects (Study CNTO148UCO1001)

	Golimumab SC dose regimen	
	90 mg/m^2→45 mg/m^2	200 mg →100 mg
	<45 kg	≥45 kg
Baseline		
N	14	20
Mean (SD)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00
IQ range	(0.00; 0.00)	(0.00; 0.00)
Range	(0.0; 0.0)	(0.0; 0.0)
Day 4		
N	14	20
Mean (SD)	12.86 (4.674)	14.55 (5.368)
Median	12.32	14.13
IQ range	(8.82; 15.05)	(10.70; 17.51)
Range	(5.6; 21.6)	(4.6; 27.8)
Week 2		
N	14	17
Mean (SD)	4.66 (2.399)	7.94 (2.814)
Median	3.92	8.60
IQ range	(2.87; 5.66)	(5.72; 9.18)
Range	(2.0; 10.0)	(2.2; 12.3)
Week 4		
N	12	19
Mean (SD)	4.48 (3.313)	7.79 (2.791)
Median	3.30	8.60
IQ range	(2.04; 5.93)	(6.53; 9.72)
Range	(1.6; 12.4)	(1.7; 11.4)
Week 6		
N	12	19
Mean (SD)	1.53 (1.551)	3.21 (1.400)
Median	1.06	3.44
IQ range	(0.52; 1.48)	(2.44; 3.97)
Range	(0.2; 5.3)	(0.6; 5.0)

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Serum Golimumab Concentrations by Baseline Immunomodulator Status

The median (and mean) serum golimumab concentrations over time were generally comparable between subjects who received golimumab in combination with immunomodulators (ie, 6-MP/AZA or MTX) and those who were not receiving immunomodulators, except for the Week 6 visit. At Week 6, mean (SD) serum golimumab concentration was slightly higher in subjects who received immunomodulators 2.79 (1.55) µg/mL (n=18) versus 2.25 (1.82) µg/mL (n=13), respectively.

Serum golimumab concentrations – from Week 14 Through Week 126

No samples were planned to be collected at Week 126. Among subjects who entered the study extension, median and mean serum trough golimumab concentration values from Week 14 through Week 102 were generally consistent ranging from 1.18-1.54 µg/mL and 1.47-2.02 µg/mL, respectively. At each sampling occasion, the number of subjects varied between 7 and 20. The mean trough concentration at Week 110 was higher than expected 3.87 µg/mL (n=6). The reason for this discrepancy is unknown and might be attributed to variability given the small sample size. Most patients had detectable drug levels (above the LLOQ) through week 110.

Serum golimumab concentrations – After Week 126

Based on the limited number of subjects with available data from Week 110 through Week 326 (no concentration data were available after Week 326), ranging from 2 to 8 subjects, median and mean serum trough golimumab concentration values were generally consistent over time ranging from 2.01 µg/mL to 3.74 µg/mL and from 2.52 µg/mL to 4.34 µg/mL, respectively. All subjects with available data had serum golimumab concentrations above the limit of quantification

Comparison of Golimumab Concentrations between Pediatric and Adult UC Subjects

Through Week 6 in the induction period, serum golimumab concentrations observed in the overall pediatric UC population were generally comparable to those observed in the reference adult UC population from study C0524T17 (**Figure 1**).

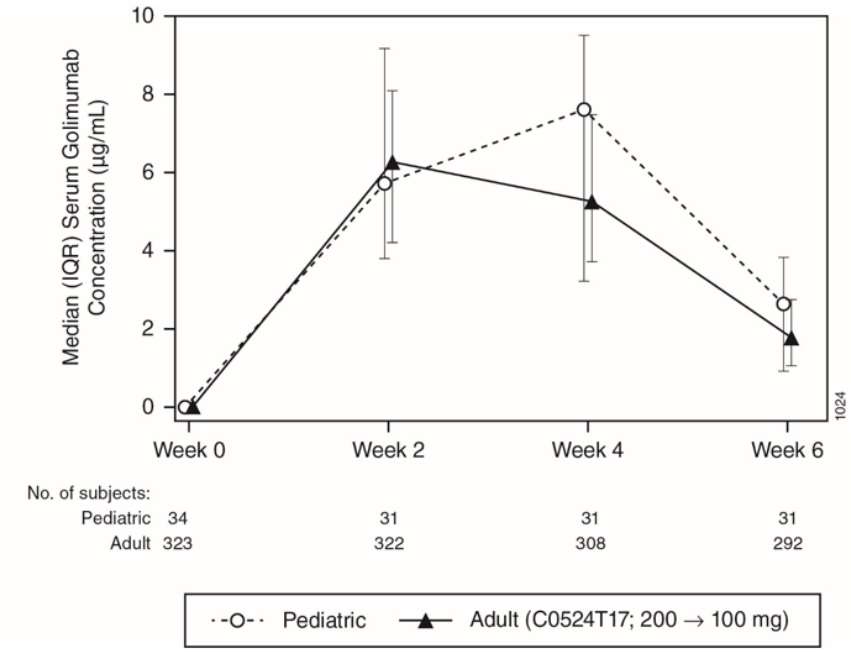


Figure 1: Line Plot of Pediatric Vs Adult Median Serum Golimumab Concentrations (micrograms/mL) Through Week 6; Treated Subjects (Study CNTO148UCO1001)

At Week 14, during the maintenance period, the median (mean) serum golimumab concentration in the overall pediatric UC population (1.39 µg/mL [2.02 µg/mL]) was comparable to that in the reference adult UC population (1.44 µg/mL [1.68 µg/mL]). Although limited PK data were available for the pediatric population after Week 14, serum trough golimumab concentrations observed in the long-term extension after Week 14 in pediatric subjects were comparable to those in the corresponding adult UC population.

PK Subgroup Analysis by Subject Weight

Serum golimumab concentrations in the <45 kg body weight subgroup who received the BSA-adjusted golimumab induction dose regimen (90 → 45 mg/m^2) appeared lower compared to the reference adult population who received the 200 mg → 100 mg induction regimen (**Figure 2**).

Serum golimumab concentrations in the ≥45 kg pediatric body weight subgroup who received the 200 → 100 mg induction dose regimen seemed higher when compared with the reference adult population who also received the 200 mg → 100 mg induction regimen (**Figure 2**). The median body weight in the adults and the pediatrics were 72.1 kg and 57.6 kg, respectively. The serum golimumab

concentrations seemed similar between pediatric subjects with UC with body weight ≥45 kg and adult subjects with UC when compared within the same body weight categories (**Figure *3***).

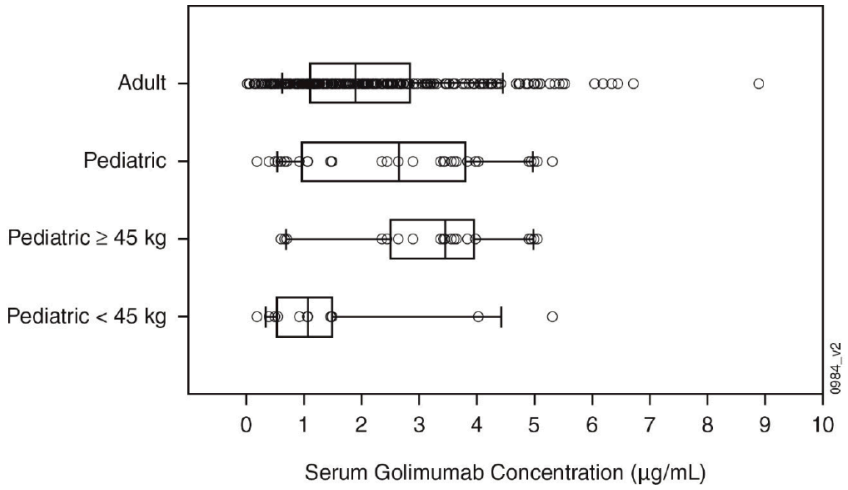


Figure 2: Serum Golimumab Concentrations at Week 6 in the Adult and Pediatric Ulcerative Colitis Populations

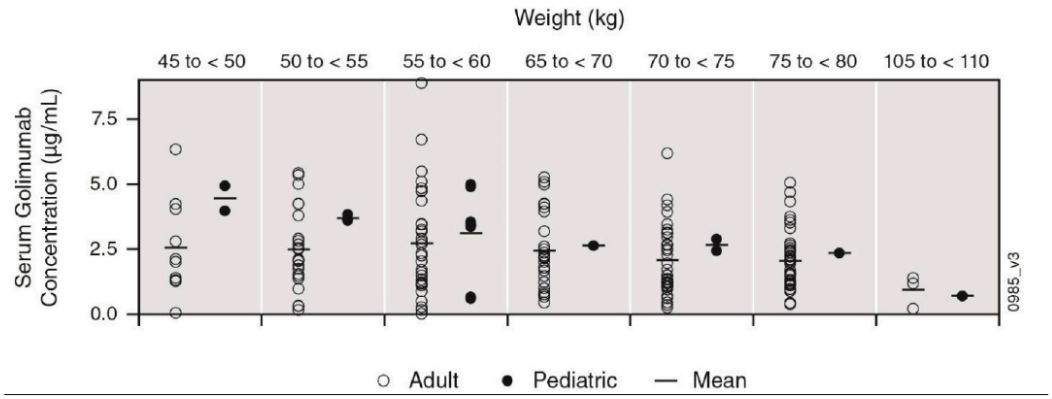


Figure 3: Body Weight-Matched Comparison of Serum Golimumab Concentrations Between Adult and Pediatric Subjects With Ulcerative Colitis (Study CNTO148UCO1001)

Immunogenicity

Through Week 14

Of 32 golimumab-treated pediatric subjects with appropriate samples, 2 (6.3%) subjects were positive for antibodies to golimumab through Week 6 using the drug-tolerant EIA. One additional pediatric subject tested positive for antibodies to golimumab through Week 14 with a titer of 1:96. All 3 subjects were also positive for NAb.

From Week 14 Through Week 126

Of 20 golimumab-treated subjects with appropriate samples, 5 (25%) subjects were positive for antibodies to golimumab through Week 126 with titers less than 1 in 96. One (20%) subject was positive for neutralizing antibodies.

After Week 126

Of the 11 subjects in the study extension after Week 126 with appropriate samples, 3 (27.3%) subjects were positive for antibodies to golimumab through the final visit, with peak titers ranging from 1:6 to 1:96. Two of these 3 subjects (66.7%) were positive for NAbs.

Comparison of Antibodies to Golimumab Between Pediatric and Adult Subjects

At Week 6, 6.3% (2 of 32) of pediatric subjects were positive for antibodies to golimumab compared to 4.3% (14 of 328) of adult subjects. The incidence of antibodies to golimumab was 28.6% (10 of 35) through Week 434/final visit of the pediatric UC study compared to 26.0% (286 of 1102) through Week 228 for the adult UC study.

6.3. Discussion

The Applicant has performed a Phase 1b study to assess the safety and PK of golimumab treatment in pediatric subjects aged 2-17 years with moderately to severely active UC. If the children weighed ≥45 kg 200 and 100 mg of golimumab were given on Weeks 0 and 2, respectively, followed 100 mg once every fourth week, starting at Week 6. If the children weighed ‹45 kg, 90 mg/m^2 (up to a maximum of 200 mg) and 45 mg/m^2 (up to a maximum of 100 mg) of golimumab were given on Weeks 0 and 2, respectively, followed 45 mg/m^2 (up to maximum of 100 mg) once every fourth week, starting at Week 6. At week 14 and thereafter, subjects had the option to decrease the dose to 50 mg or 22.5 mg/m^2 at the discretion of the investigator. A single dose increases back to 100 mg or 45 mg/m^2 was permitted based on the subject's UC disease activity.

Validated methods were used to determine golimumab in serum and ADAs and the occurrence of NAb. It is noted that limited information has been provided for some of these analyses, for instance incurred sample reproducibility and parallelism were investigated, but no information could be found in the documentation, the method validation report for the NAb method, CP2015V-001, is missing, documentation showing that the PK samples and the immunogenicity samples (ADAs and NAbs) were analysed within the time frame for the long-term stability is also missing. Since this variation concerns the submission of the final report from study CNTO148UCO1001, and no SmPC update is proposed, these issues are not further pursued. However, if a future application includes the PK results from this study, the missing documentation should be provided and assessed in that application.

Peak serum golimumab concentration was observed on Day 4 (mean (SD), 13.9 (5.09) µg/mL). The serum concentrations seemed relatively comparable between Weeks 14 and 102 (mean range: 1.5-2.0 µg/mL) and tended to be slightly higher from Week 110 onwards (mean range: 2.5-4.3 µg/mL). However, after Week 110 there was only a limited number of subjects with PK samples (n=2-8), and the interindividual variability was large. It is unclear how many subjects that had a decrease in the dose to 50 mg or 22.5 mg/m^2. This should be clarified by the MAH since this may have an impact on the interpretation of the results **(OC).**

The serum golimumab concentrations appeared to be relatively comparable between pediatrics with UC with a body weight ≥45 kg and adults with UC when compared within the same body weight categories. To be noted, only a few children were included in each body weight category, and therefore no major conclusions can be drawn. There seemed to be a trend towards lower mean serum concentration in pediatrics weighing < 45 kg (who received the BSA-adjusted dose regimen) as compared to those weighing ≥ 45 kg and compared to the reference adults UC population (who received the flat fixed dose regimen).

Overall, based on the limited data in the pediatrics, these results should be interpreted with caution. However, there are indications that a higher BSA-adjusted dose regimen may be needed for the <45

kg pediatric subgroup. Despite this trend towards a lower exposure, no impact on the efficacy was noted. A higher dose has been implemented in the ongoing Phase 3 study (CNTO148UCO3003).

The immunogenicity profile of golimumab seemed similar between pediatric and adult subjects with UC.

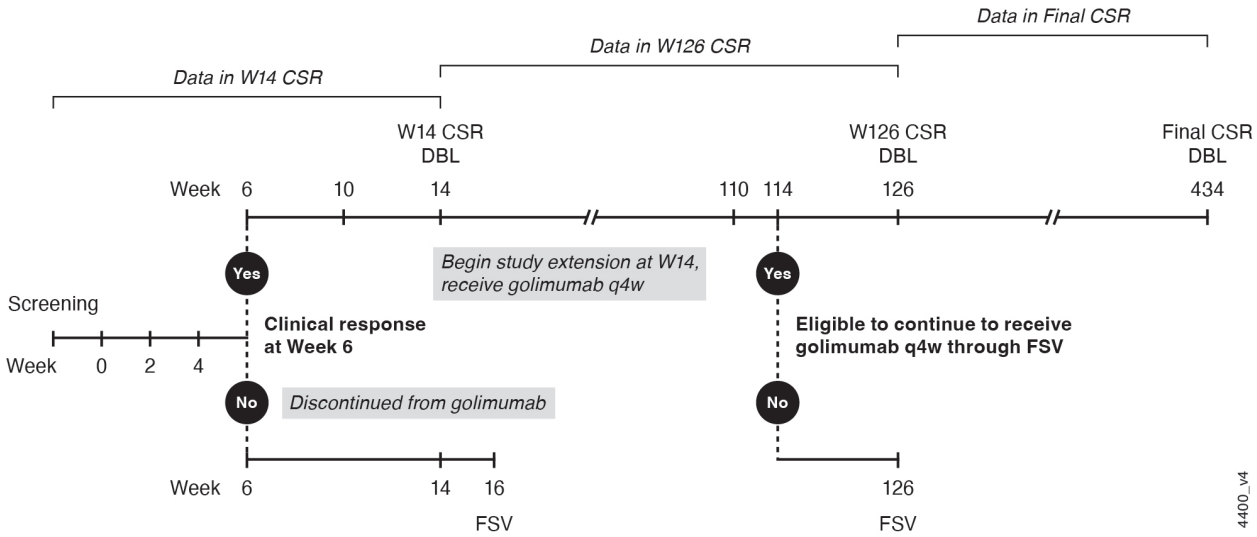
7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

CNTO148UCO1001 (hereafter referred to as UCO1001) was a Phase 1b, multicenter, open-label study to assess the PK and safety of golimumab treatment in paediatric subjects 2 through 17 years of age with moderately to severely active UC, defined as a baseline Mayo score of 6 through 12, inclusive, with endoscopy sub-score of ≥2. Subjects who demonstrated an inadequate response to, failed to tolerate, or had a medical contraindication to conventional therapies (ie, IV or oral corticosteroids or the immunomodulators AZA or 6-MP), and were naïve to anti-TNFα agents were eligible for study participation. The study was to enroll at least 30 subjects, with a goal of enrolling at least 10 subjects with body weight <45 kg, including at least 4 subjects with body weight <30 kg.

The following concomitant medications for UC were allowed in this study: 5-ASAs, corticosteroids (including budesonide), and immunomodulators (ie, 6-MP, AZA, MTX).

Figure 4: Study design for CNTO148UCO1001



During the PK portion of the study (Week 0 through Week 14), subjects received SC golimumab at Week 0 and Week 2.

Subjects in clinical response at Week 6 were eligible to receive open-label maintenance therapy with golimumab (at Week 6 and Week 10) and to enter the study extension at Week 14.

Subjects who were not in clinical response at Week 6 were withdrawn from further study agent administration but returned for protocol-specified procedures and evaluations up to and including the Week 14 visit. In addition, these subjects had a final visit 16 weeks following the last administration of study agent.

During the first portion of the study extension (Week 14 through Week 126), subjects received SC golimumab q4w starting at Week 14 based on body weight (see clin pharm section). All subjects who

entered the study extension had the option to decrease their dose to golimumab 50 mg or 22.5 mg/m^2 at Week 14 or thereafter at the discretion of the investigator. A single dose increased back to 100 mg or 45 mg/m^2 was permitted based on the investigator's assessment of an increase in a subject's UC disease activity; subjects remained on the increased 100 mg or 45 mg/m^2 dose for the remainder of the study extension. Subjects in the study extension continued to receive golimumab q4w through Week 110. At Week 114, subjects who, in the opinion of the investigator, may benefit from continued treatment were eligible to continue to receive golimumab q4w through the final visit. Subjects who did not receive study agent after Week 110 had a follow-up safety visit at Week 126.

During the study extension, a DBL was performed at Week 126 and the results were presented in the UCO1001 126W CSR. The second portion of the study extension continued after Week 126 for the subjects who were eligible at Week 114 to continue to receive golimumab q4w. The study extension was intended to continue until marketing authorization was obtained for golimumab in the treatment of pediatric UC in their country, or until a decision had been made not to pursue an indication in pediatric UC, whichever occurred first. However, all subjects discontinued study agent and terminated study participation by Week 434, at which point the final DBL occurred.

The primary outcome of this study was to assess the PK of golimumab. Major secondary outcomes included safety through Week 6 and Week 126, as well as clinical response, clinical remission, and mucosal healing, all at Week 6, and PUCAI remission at Week 54 and Week 110.

The efficacy endpoint definitions are as follows:
- Clinical response: a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.
- Clinical remission as measured by the Mayo score: a Mayo score ≤ 2 points, with no individual subscore > 1.
- Clinical remission as measured by the PUCAI score: a PUCAI score < 10.
- Mucosal healing: an endoscopy subscore of the Mayo score of 0 or 1.

Rapporteur assessment:

The study design is adequate and the criteria for active moderate to severe disease acceptable. Although not the primary focus, some efficacy endpoints were defined and evaluated at week 6, 54 and 110.

7.2. Results

Of the 35 subjects enrolled at Week 0, a total of 20 subjects (57.1%) were in clinical response at Week 6 and entered into the study extension at Week 14. Of the 20 subjects who entered into the study extension at Week 14, 11 subjects (55.0%) continued in the study extension after Week 126. All subjects discontinued study agent and terminated study participation by Week 434, at which point the final DBL occurred.

Fifteen of the 35 enrolled subjects (42.9%) discontinued study agent through Week 14 (PK Portion). The most common reasons for subjects to not continue in the study extension (Week 14 through Week 126) were unsatisfactory therapeutic effect (10 subjects [28.6%]) and AEs (3 subjects [8.6%]). Nine (45.0%) of the 20 subjects who were in clinical response at Week 6 and entered into the study extension discontinued study agent through Week 126. Of these 9 subjects, 6 subjects (30.0%)

discontinued due to unsatisfactory therapeutic response and 3 subjects (15.0%) discontinued due to AEs.

Table 6: Summary of UC demographics, disease characteristics, and concomitant medications at baseline; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Sex	
Male	17 (48.6%)
Female	18 (51.4%)
Race	
White	30 (85.7%)
Black or African American	1 (2.9%)
Other	3 (8.7%)
Not reported	1 (2.9%)
Age (yrs)	
Median	15.0
2-11	10 (28.6%)
12-17	25 (71.4%)
Weight (kg)	
Median	50.60
<45	15 (42.9%)
<30	5 (14.3%)
≥ 45	20 (57.1%)
Height (cm)	
Median	158.00
UC disease duration (yrs)	
Median	1.22
Baseline CRP concentrations (mg/L)	
Median	2.65
Extent of disease	
Limited to left side of colon	10 (28.6%)
Extensive	25 (71.4%)
Baseline Mayo score	
Median	8.0
Severity of UC disease	
Moderate disease (Mayo score >= 6 to <= 10)	30 (85.7%)
Severe disease (Mayo score > 10)	5 (14.3%)
Baseline PUCAI score	
Median	45.0
Subjects with 1 or more concomitant medications	30 (85.7%)
Corticosteroids (parenteral or oral)[a]	12 (34.3%)
Corticosteroids (budesonide)[b]	1 (2.9%)
Corticosteroids (rectal)[a]	1 (2.9%)
Immunomodulatory agents	20 (57.1%)
6-MP/AZA	18 (51.4%)
Methotrexate	2 (5.7%)
Aminosalicylates	23 (65.7%)

[a] Excluding budesonide
[b] Including oral or rectal

Efficacy Results Through Week 14

Summaries of efficacy were based on subjects who received at least 1 administration of study agent.

Subjects who had any of the following events through Week 6 were considered to be treatment failures from the time of event onward:

- Had a colectomy (partial or full) or ostomy
- Discontinued study agent due to unsatisfactory therapeutic effect or an AE of worsening UC

- Had a prespecified prohibited medication change

For all clinical endpoints through Week 6, treatment failure rules were applied. For dichotomous endpoints, subjects who had a treatment failure were considered as not achieving the respective endpoint. For continuous endpoints, subjects who had a treatment failure had their baseline values carried forward from the time of the treatment failure.

For clinical endpoints after Week 6, no treatment failure rules were applied.

For all analyses, subjects with insufficient data for binary endpoints were considered to not have achieved their respective endpoint; for subjects with insufficient data for continuous endpoints, the last available value was carried forward. These data handling rules were applied for all efficacy endpoints.

Efficacy Outcomes Through Week 6

At Week 6, the proportion of treated subjects in **clinical response** as measured by the Mayo score was 60.0%.

At Week 6, the proportions of subjects in **clinical remission** as measured by the Mayo score and by the PUCAI score were 42.9% and 34.3%, respectively

At Week 6, 19 subjects (54.3%) achieved **mucosal healing** (improvement in the endoscopic appearance of the mucosa), based on a Mayo endoscopy subscore of 0 or 1 (indicating normal or inactive disease, or mild disease). Eight subjects (22.9%) achieved complete mucosal healing, based on a Mayo endoscopy subscore of 0 (indicating normal or inactive disease) at Week 6.

An improvement in clinical and endoscopic disease activity was observed based on reduction in the full and partial Mayo scores from baseline to Week 6. The median reduction in the full Mayo score from baseline at Week 6 was 4.0. Improvement from baseline was observed at Week 2 for the partial Mayo score (the median reduction from baseline was 3.0). At Week 6, the median reduction from baseline remained the same for the partial Mayo score. Improvement in clinical and endoscopic disease activity was also reflected in the 4 Mayo subscores at Week 6.

Reductions in the PUCAI score were evident at Week 2, when the median reduction from baseline in the PUCAI score was 25.0 (a decrease in the PUCAI score of 20 points from baseline is considered a minimally clinically important change; Turner 2007). This decrease in the median PUCAI score remained through Week 6.

Of the 35 treated subjects, 12 subjects were taking concomitant corticosteroids (excluding budesonide) at baseline. The median average daily corticosteroid dose was 0.62 mg/kg/day at baseline. Through Week 6, the median average daily corticosteroid (P.Eq) dose decreased on average by one-third in these subjects. The median dose at Week 6 was 0.16 mg/kg/day.

The median (mean) CRP concentration at baseline was 2.65 mg/L (10.05 mg/L) for treated subjects. The median (mean) change from baseline at Week 6 was -0.59 mg/L (-4.73 mg/L). Among 16 subjects with abnormal CRP at baseline, 9 subjects (56.3%) achieved normalization of CRP (≤3 mg/L) at Week 6

According to the MAH, the proportions of subjects in clinical response and clinical remission were generally similar across demographic, baseline disease characteristic, and baseline concomitant medication subgroups. Some numerical differences were observed in some subgroups (ie, region and extent of disease) and may be due to the small sample size, which limits interpretation of these subgroup analyses.

Other Efficacy Outcomes After Week 6 Through Week 14

Efficacy outcomes among responders to golimumab at Week 6 who continued q4w maintenance treatment at Weeks 6 and 10 were evaluated through Week 14 using the PUCAI score. Of the 21 treated subjects in clinical response at Week 6, 12 (57.1%) subjects were in clinical remission at Week 6, Week 10, and Week 14, respectively

Rapporteur assessment:

Included patients had a moderate to severe active UC, with a median Mayo score of 8 and median PUCAI score of 45. Around 29% of the patients were between 2-11 years old and around 43% of the patients had a weight <45 kg.

Of the 35 subjects enrolled, a total of 20 subjects (57.1%) entered into the study extension at Week 14. The most common reasons for subjects to not continue in the study extension were unsatisfactory therapeutic effect (10 subjects [28.6%]) and AEs (3 subjects [8.6%]). Only patients with a clinical response at week 6 were allowed to enter the study extension.

Of the patients entering the study extension, 9/20 (45.0%) subjects discontinued study agent through Week 126. Of these, 6 subjects (30.0%) discontinued due to unsatisfactory therapeutic response and 3 subjects (15.0%) discontinued due to AEs. All subjects discontinued study agent and terminated study participation by Week 434, at which point the final DBL occurred.

At week 6, the proportion of patients achieving clinical response, clinical remission and mucosal healing based on the Mayo score were around 60%, 43% and 54%. This is in line with the results seen in the adult population, although it is acknowledged that a direct comparison is not possible and paediatric data are based on OL treatment. Remission according to PUCAI was achieved in 34.3% of the subjects. In addition, 23% of the patients achieved complete mucosal healing. There were no signs of a lesser effect in the subgroup of younger patients or patients with lower weight (<45 kg) however these results are based on a low number of patients so no firm conclusion can be made.

Efficacy Results After Week 14 Through Week 126

Summaries of efficacy were based on subjects who were clinical responders at Week 6 and entered the study extension at Week 14 who received at least 1 administration of study agent in the study extension through Week 126. Treatment failure rules were not applied. For all analyses, subjects with insufficient data for binary endpoints were considered to not have achieved their respective endpoint; for subjects with insufficient data for continuous endpoints, the last available value was carried forward.

Through Week 110, 45.0%, 55.0%, and 50.0% of subjects were in clinical remission (as measured by the PUCAI) at Week 30, Week 54, and Week 110, respectively.

According to the MAH, post-hoc subgroup analyses by body weight (<45 kg, ≥45 kg), age (2 to 11, 12 to 17 years of age), and steroid use at the beginning of the study extension (receiving, not receiving) showed results consistent with the overall rate at each timepoint for clinical remission

The median baseline PUCAI score was 45.0 for subjects in the study extension. At Week 14, the median reduction from baseline was 30 for subjects in the study extension, which was maintained through Week 126.

Additional post-hoc analyses of these 20 subjects who entered the study extension show that through Week 110, 55.0%, 60.0%, and 50.0% of subjects had a clinically meaningful change (defined as a decrease of ≥20 points from Week 0) in the PUCAI score at Week 30, Week 54, and Week 110, respectively. The subgroup efficacy outcomes for the subjects with clinically meaningful change in the

PUCAI score were generally consistent with those of the overall population. However, according to the MAH a trend towards better efficacy outcomes for the subjects with clinically meaningful change in the PUCAI score was observed in the younger age subgroup (2 to 11 years of age) compared with the older age subgroup (12 to 17 years of age) and in the lower body weight subgroup (<45 kg) compared with the higher body weight subgroup (≥45 kg). According to the MAH, interpretation is limited due to the small sample size.

After Week 126

The intent of the efficacy analyses in the study extension after Week 126 was to assess maintenance of clinical benefit from Week 126. Summaries of efficacy were based on subjects who continued in the study extension after Week 126 and who received at least 1 administration of study agent in the study extension at Week 126. Treatment failure rules were not applied. Analyses are based on observed data (ie, no missing data rules were applied), and each subject's data were only included up until the point that the subject withdrew from the study.

Efficacy Analyses

The median PUCAI score at study extension baseline (Week 110) was 0.0. Starting at Week 134 (the first efficacy measurement after the study extension baseline), the median change from the study extension baseline was 0.0, which was maintained throughout the study extension for subjects remaining in the study extension.

Rapporteur assessment:

Twenty patients continued treatment beyond week 14. At week 54 and week 110, 55.0% and 50% of the patients were in clinical remission (as measured by the PUCAI). Eleven patients continued the study beyond week 126. Data are limited to make any firm conclusion regarding efficacy.

7.3. Discussion

CNTO148UCO1001 was a Phase 1b, multicenter, open-label study to assess the PK and safety of golimumab treatment in paediatric subjects 2 through 17 years of age with moderately to severely active UC. Subjects should have failed conventional treatment but be naïve to anti-TNFα agents.

Included patients had a moderate to severe active UC, with a median Mayo score of 8 and median PUCAI score of 45. Thirty-five patients were included and around 29% of the patients were between 2-11 years old and around 43% of the patients had a weight <45 kg (including 5 patients with a weight<30kg), fulfilling the intended number of patients initially planned by the MAH.

The initial dose (induction dose) was 200 mg week 0 and 100 mg week 2 for patients >45 kg, in line with the dose for adult patients. For patients <45 kg, the dose was based on their body surface area (90mg/m^2 week 0 and 45mg/m^2 week2). The patients who achieved a response at week 6 were able to continue to the study extension phase, with a maintenance dose of 100 mg Q4W for children >45mg and 45 mg/m2 for children <45 kg (max 100 mg). It is noted that this maintenance dose is the highest dose prescribed for adults (in adult UC it is recommended for initially non responders and adults >80 kg), however all subjects who entered the study extension had the option to decrease their dose to golimumab 50 mg or 22.5 mg/m^2 at Week 14 or thereafter at the discretion of the investigator. As stated in the clin pharm section it is however unclear how many patients that received a reduced dose and this has to be clarified.

Of the 35 subjects enrolled, a total of 20 subjects (57.1%) entered into the study extension at Week 14. The most common reasons for subjects to not continue in the study extension were unsatisfactory therapeutic effect (10 subjects [28.6%]) and AEs (3 subjects [8.6%]).

Of the patients entering the study extension, 9/20 (45.0%) subjects discontinued study agent through Week 126. Of these, 6 subjects (30.0%) discontinued due to unsatisfactory therapeutic response and 3 subjects (15.0%) discontinued due to AEs.

At week 6, the proportion of patients achieving clinical response, clinical remission and mucosal healing based on the Mayo score were around 60%, 43% and 54%. This is in line with the results seen in the adult population, although it is acknowledged that a direct comparison is not possible and paediatric data are based on OL treatment. Remission according to PUCAI was achieved in 34.3% of the subjects. In addition, 23% of the patients achieved complete mucosal healing. There were no signs of a lesser effect in the subgroup of younger patients or patients with lower weight (<45 kg) however these results are based on a low number of patients so no firm conclusion can be made.

Twenty patients continued treatment beyond week 14. At week 54 and week 110, 55.0% and 50% of the patients were in clinical remission (as measured by the PUCAI). Eleven patients continued the study beyond week 126. Data are limited to make any firm conclusion regarding efficacy.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

Study design is presented in the previous sections. Safety was evaluated based on the following: AEs, Injection-site reactions, Clinical laboratory tests (hematology and serum chemistry), TB evaluation with reflex testing on suspicion of infection, ANA and anti-dsDNA antibody testing, Physical examination including skin examinations, Vital sign measurements, Urine pregnancy tests for females of childbearing potential.

Analyses to assess the number of subjects reporting events and the number of events per hundred subject-years of follow-up in golimumab-treated subjects in the UCO1001 study are presented for the following study periods:

- From Week 0 through the final visit
- From Week 0 through Week 14·
- From Week 14 through Week 126·
- From Week 126 through the final visit.

From Week 0 through Week 14, analysis also included a presentation of AEs from Week 0 to Week 6 (ie, the induction period for golimumab studies in UC).

8.2. Results

Overall Extent of Exposure

All 35 subjects received a dose of golimumab at Week 0 and all but 1 subject received a dose of golimumab at Week 2. During the study extension through Week 126, 20 subjects received a total of 375 total injections with an average of 18.8 SC administrations of golimumab and a median of 2.1 years of follow-up. During the study extension after Week 126, 11 subjects received a total of 467

total injections with an average of 41.9 SC administrations of golimumab and a median of 3.2 years of follow-up. The last exposure to golimumab took place at Week 434.

The average duration of follow-up was 115.6 weeks, with an average exposure of 27.1 administrations of golimumab.

Adverse events

Table 7: Overall summary of treatment-emergent adverse events from Week 0 through Final Safety Visit; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Avg duration of follow-up (weeks)	115.6
Avg exposure (number of administrations)	27.1
Subjects who died	0
Subjects who discontinued study agent because of 1 or more adverse events	6 (17.1%)
Subjects with 1 or more:	
Adverse events	33 (94.3%)
Serious adverse events	16 (45.7%)
Infections[a]	23 (65.7%)
Serious infections[a]	1 (2.9%)
Neoplasms (malignant)	0
Injection-site reactions[b]	7 (20.0%)

[a] Infection as assessed by the investigator.
[b] Injection-site reactions as assessed by the investigator.

Common Adverse Events

Of the 35 treated subjects, 94.3% reported 1 or more AEs during the entire study. The most frequently reported SOCs were Gastrointestinal disorders (82.9%), Infections and infestations (54.3%), and General disorders (42.9%). When adjusted for follow-up, the incidence of AEs per 100 subject-years of follow-up was 643.54. Adverse events (reported in at least 10% of subjects) during the study (from Week 0 through final visit) are presented in the table below:

Table 8: Number of subjects with 1 or more treatment-emergent adverse events (in at least 10% of subjects) from Week 0 through Final Safety Visit by MedDRA preferred term; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Avg duration of follow up (weeks)	115.6
Avg exposure (number of administrations)	27.1
Number of subjects with 1 or more treatment-emergent adverse events	33 (94.3%)
Preferred term	
Colitis ulcerative	22 (62.9%)
Headache	12 (34.3%)
Abdominal pain	9 (25.7%)
Upper respiratory tract infection	8 (22.9%)
Anaemia	7 (20.0%)
Fatigue	7 (20.0%)
Nausea	7 (20.0%)
Diarrhoea	6 (17.1%)
Cough	5 (14.3%)
Injection site pain	5 (14.3%)
Nasopharyngitis	5 (14.3%)
Acne	4 (11.4%)
Decreased appetite	4 (11.4%)
Injection site erythema	4 (11.4%)
Musculoskeletal chest pain	4 (11.4%)
Oropharyngeal pain	4 (11.4%)
Pharyngitis	4 (11.4%)

Reasonably-related adverse events

A reasonably related AE is an AE that was classified by the investigator as "possibly," "probably," or "very likely" related to study agent or was of unknown relationship to study agent. Sixteen (45.7%) of 35 treated subjects reported 1 or more reasonably-related AEs during the entire study. When adjusted for follow-up, the incidence of reasonably-related AEs per 100 subject-years of follow-up was 171.52.

The most frequently reported SOCs were General disorders and administration site conditions (8 [22.9%] subjects) and Gastrointestinal disorders (7 [20.0%] subjects). The most frequently reported reasonably-related AEs by preferred term were injection-site pain (5 [14.3%] subjects) and injection-site erythema (4 [11.4%] subjects).

Week 0 Through Week 14

Of the 35 subjects treated, 85.7% reported 1 or more AEs through Week 6. The average duration of follow-up was 5.8 weeks, with an average exposure of 2 administrations of golimumab. The most frequently reported SOCs were Gastrointestinal disorders (48.6%), General disorders and administration site conditions (28.6%), and Nervous system disorders (28.6%). The most common AEs included colitis ulcerative (22.9%), headache (22.9%), abdominal pain (14.3%), injection site pain (14.3%), and fatigue (11.4%). Through Week 14, 94.3% of treated subjects reported 1 or more AEs, with an average duration of follow-up of 13.1 weeks and an average exposure of 3.2 administrations of golimumab. The most frequently reported AEs were similar to those reported through Week 6: colitis ulcerative (37.1%), headache (25.7%), abdominal pain (25.7%), nausea (17.1%), fatigue (14.3%) and injection site pain (14.3%).

Reasonably-related adverse events

Eleven (31.4%) of 35 treated subjects reported 1 or more reasonably-related AEs through Week 6. The most frequently reported SOCs were General disorders and administration site conditions (6 [17.1%] subjects), Gastrointestinal disorders (3 [8.6%] subjects), and Skin and subcutaneous tissue disorders (3 [8.6%] subjects). The most frequently reported reasonably-related AEs were injection site pain (5 [14.3%] subjects) and injection site erythema (3 [8.6%] subjects). According to the MAH the pattern of reasonably-related AEs reported through Week 14 was consistent with those observed through Week 6.

Week 14 Through Week 126

Of the 20 treated subjects, 95.0% reported 1 or more AEs from Week 14 through Week 126. The average duration of follow-up was 79.1 weeks, with an average exposure of 18.8 administrations of golimumab. The most frequently reported SOCs were Gastrointestinal disorders (85.0%), Infections and infestations (55.0%), and Respiratory, thoracic and mediastinal disorders (45.0%). The most frequently reported AEs by preferred term were colitis ulcerative (50.0%); headache (35.0%); abdominal pain and upper respiratory tract infection (25.0% each); and diarrhea, fatigue, and nausea (20.0% each).According to the MAH, from Week 14 through Week 126, the safety profile of golimumab was generally consistent with that observed through Week 14.

Reasonably-related adverse events

Ten (50.0%) of 20 treated subjects reported 1 or more reasonably-related AEs from Week 14 through Week 126. The most frequently reported SOCs were Gastrointestinal disorders (5 [25.0%] subjects), General disorders and administration site conditions (4 [20.0%] subjects), and Infections and infestations (3 [15.0%] subjects). The most frequently reported reasonably-related AEs by preferred term were colitis ulcerative (3 [15.0%] subjects), abdominal pain (2 [10.0%] subjects), injection site irritation (2 [10.0%] subjects) and injection site pain (2 [10.0%] subjects).

Week 126 Through Final Visit

Of the 11 treated subjects, 90.9% reported 1 or more AEs during the study extension after Week 126. The average duration of follow-up was 176.6 weeks, with an average exposure of 41.9 administrations of golimumab. The most frequently reported SOCs were Infections and infestations (10 [90.9%] subjects) and Gastrointestinal disorders (5 [45.5%] subjects). The most frequently reported AEs by preferred term were upper respiratory tract infection (5 [45.5%] subjects) and cough (4 [36.4%] subjects).

Reasonably-related adverse events

Four (36.4%) of 11 treated subjects reported 1 or more reasonably-related AEs during the study extension after Week 126. The most frequently reported SOCs were Infections and infestations (3 [27.3%] subjects) and General disorders and administration site conditions (2 [18.2%] subjects). The most frequently reported reasonably-related AE by preferred term was injection-site irritation (2 [18.2%] subjects).

Rapporteur assessment:

The average duration of follow-up was 115.6 weeks, with an average exposure of 27.1 administrations of golimumab. Adverse events were very common and 94.3% reported 1 or more AEs during the entire study. The most frequently reported SOCs were Gastrointestinal disorders (82.9%), Infections and infestations (54.3%), and General disorders (42.9%). The most frequent AEs were colitis ulcerative, (62.9%), headache (34.3), abdominal pain (25.7%), upper respiratory tract infection (22.9%), anaemia (20%)and nausea (20%). The distribution and type of AEs were similar as in the adult population; however, the frequency of events were higher in the paediatric UC population. This is not unexpected, and the same finding was seen in the JiA population when compared with RA population.

Deaths

No deaths were reported during the entire study (from Week 0 through the final visit).

Other Serious Adverse Events

Week 0 Through Final Visit

Table 9: Number of subjects with 1 or more treatment-emergent serious adverse events from Week 0 through Final Safety Visit by MedDRA system-organ class and preferred term; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Avg duration of follow up (weeks)	115.6
Avg exposure (number of administrations)	27.1
Subjects with 1 or more serious adverse events	16 (45.7%)
System-organ class/preferred term	
Gastrointestinal disorders	14 (40.0%)
Colitis ulcerative	13 (37.1%)
Abdominal pain	1 (2.9%)
Pancreatitis acute	1 (2.9%)
Blood and lymphatic system disorders	1 (2.9%)
Iron deficiency anaemia	1 (2.9%)
Hepatobiliary disorders	1 (2.9%)
Cholangitis sclerosing	1 (2.9%)
Infections and infestations	1 (2.9%)
Respiratory tract infection	1 (2.9%)
Urinary tract infection	1 (2.9%)
Injury, poisoning and procedural complications	1 (2.9%)
Forearm fracture	1 (2.9%)
Metabolism and nutrition disorders	1 (2.9%)
Decreased appetite	1 (2.9%)

Week 0 Through Week 14

Through Week 6, 7 (20.0%) subjects reported a total of 8 SAEs. The most frequently reported SAE was colitis ulcerative, reported by 7 (20.0%) subjects. One subject with colitis ulcerative also reported an SAE of abdominal pain. The pattern of SAEs reported through Week 14 was similar to those reported through Week 6. An additional 4 subjects reported 5 SAEs, for a total of 11 subjects reporting 13 SAEs through Week 14. The 5 SAEs reported between Week 6 and Week 14 were colitis ulcerative (3 subjects), acute pancreatitis (1 subject), and iron deficiency anemia (1 subject).

Week 14 Through Week 126

From Week 14 through Week 126, 5 (25.0%) subjects reported a total of 8 SAEs. The most frequently reported SAE was colitis ulcerative, reported by 3 (15.0%) subjects. One of these subjects discontinued golimumab due to the SAE of colitis ulcerative. The other SAEs reported were decreased appetite, cholangitis sclerosing, respiratory tract infection, urinary tract infection, and forearm fracture.

Two subjects reported more than 1 SAE each. One of these subjects reported concurrent respiratory tract and urinary tract infections as well as a forearm fracture. Another subject reported decreased appetite and an ulcerative colitis flare, each during different study visits.

One subject with previously noted elevated liver enzymes and a history of sclerosing cholangitis had worsening primary sclerosing cholangitis during the study extension that was not considered related to the study drug by the investigator. The subject was hospitalized, which was reported as an SAE. A liver biopsy and magnetic resonance cholangiopancreatography scan were consistent with primary sclerosing cholangitis. The subject was treated and discharged from the hospital the next day. Elevated liver enzymes above the ULN were reported, but no markedly abnormal AST, ALT, or bilirubin values were observed. Golimumab treatment was not interrupted due to the SAE of sclerosing cholangitis.

Week 126 Through Final Visit

No SAEs were reported during the study extension after Week 126

Rapporteur assessment:

There were no deaths during the study. Serious adverse events (SAEs) were seen in 16 (45.7%) patients and were mainly associated with disease progression (colitis ulcerative, 13 patients). Other SAEs occurring (abdominal pain, acute pancreatitis, iron deficit anaemia, sclerosing cholangitis, respiratory tract infection, urinary tract infection, forearm fracture and decreased appetite) were only seen in one patient each, however two patients had multiple SAEs (one patient had respiratory tract and urinary tract infections as well as a forearm fracture and one patient had decreased appetite and an ulcerative colitis flare). It is noted that the patient with sclerosing cholangitis also had a history of this disease, thus a relapse. According to the MAH, none of the SAEs were assessed as being related to the study drug and for the majority of the cases, this could be agreed on based on the narratives provided by the MAH. No new safety concerns were evoked based on this information.

Discontinuation of Study Agent due to Adverse Events

A summary of AEs leading to discontinuation of study agent from Week 0 to final visit is presented in the table below. Six subjects (17.1%) discontinued study agent due to AEs during the entire study: 5 due to colitis ulcerative (4 of which were SAEs) and 1 due to diarrhea hemorrhagic. When adjusted for follow-up, the incidence of AEs leading to discontinuation per 100 subject-years of follow-up was 7.74.

Table 10: Number of subjects who discontinued study agent because of 1 or more adverse events from Week 0 through Final Safety Visit by MedDRA system-organ class and preferred term; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Avg duration of follow up (weeks)	115.6
Avg exposure (number of administrations)	27.1
Subjects who discontinued study agent because of 1 or more adverse events	6 (17.1%)
System-organ class/preferred term	
Gastrointestinal disorders	6 (17.1%)
Colitis ulcerative	5 (14.3%)
Diarrhoea haemorrhagic	1 (2.9%)

Week 0 Through Week 14

Two subjects (5.7%) discontinued study agent due to AEs through Week 6, both due to SAEs of colitis ulcerative. Through Week 14, 1 additional subject discontinued study agent due to an SAE of colitis ulcerative, for a total of 3 (8.6%) subjects discontinuing study due to an AE (all SAEs).

Week 14 Through Week 126

Three subjects (15.0%) discontinued study agent due to AEs from Week 14 through Week 126. Two subjects discontinued due to AEs of colitis ulcerative, 1 of which was an SAE. One subject also discontinued due to diarrhea hemorrhagic.

Week 126 Through Final Visit

No subjects discontinued study agent due to AEs during the study extension after Week 126

Rapporteur assessment:

During the entire study, 6 patients discontinued study medication due to an AE, all which also could be related to disease worsening (5 due to colitis ulcerative and 1 due to diarrhea hemorrhagic). This does not evoke any further concern.

Infections

Week 0 Through Final Visit

No opportunistic infections or TB were reported during the study. From Week 0 through final visit, 23 (65.7%) subjects reported infections, with upper respiratory tract infection the most frequently reported infection (8 [22.9%] subjects. When adjusted for follow-up, the incidence of infections per 100 subject-years of follow-up was 121.23. One subject reported 2 simultaneous serious infections, 1 event each of respiratory tract infection and urinary tract infection.

Week 0 Through Week 14

No serious infections or infections of interest (opportunistic infection, TB) were reported through Week 14. Through Week 6, 9 (25.7%) subjects reported infections, with pharyngitis the most frequently reported infection (3 [8.6%] subjects). Four (11.4%) subjects reported an infection requiring oral or parenteral antimicrobial treatment through Week 6. According to the MAH, the patterns of infections reported through Week 14 were similar to those reported through Week 6. A total of 13 (37.1%) subjects reported infections through Week 14. Pharyngitis was reported by 3 subjects (8.6%), and Clostridium difficile colitis, Clostridium difficile infection, nasopharyngitis, and upper respiratory tract infection were reported by 2 subjects each (5.7%). Seven (20.0%) subjects reported an infection requiring oral or parenteral antimicrobial treatment through Week 14.

Week 14 Through Week 126

No opportunistic infections or TB were reported from Week 14 through Week 126. From Week 14 through Week 126, 15 (75.0%) subjects reported infections, with upper respiratory tract infection the most frequently reported infection (5 [25.0%] subjects). One subject reported 2 treatment-emergent serious infections on the same date, 1 event each of respiratory tract infection and urinary tract infection. Eleven (55.0%) subjects reported an infection requiring oral or parenteral antimicrobial treatment from Week 14 through Week 126.

Week 126 Through Final Visit

No opportunistic infections or TB were reported during the study extension after Week 126. During the study extension after Week 126, 9 (81.8%) subjects reported infections, with upper respiratory tract infection the most frequently reported infection (5 [45.5%] subjects). No serious infections were reported during the study extension after Week 126. Four (36.4%) subjects reported an infection requiring oral or parenteral antimicrobial treatment during the study extension after Week 126. One (9.1%) subject reported a COVID-19 infection during the study extension after Week 126.

Malignancy

No malignancies were reported during the entire study (from Week 0 through the Final Safety Visit).

Injection-site Reactions

Week 0 Through Final Visit

Summary of treatment-emergent injection-site reactions from Week 0 to final visit is presented in the table below: The number of injections that resulted in an injection-site reaction was 70/984 (7.1%). A total of 7 (20.0%) subjects reported 1 or more injection-site reactions. When adjusted for follow-up, the incidence of injection-site reactions per 100 subject-years of follow-up was 99.30. No subject discontinued study agent administrations as a result of an injection-site reaction.

Table 11: Number of subjects with 1 or more treatment-emergent injection-site reactions from Week 0 through Final Safety Visit by MedDRA system-organ class and preferred term; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Avg number of administrations	27.1
Total number of injections	984
Injections with injection-site reactions	70 (7.1%)
Subjects with 1 or more injection-site reactions[a]	7 (20.0%)
System-organ class/preferred term	
General disorders and administration site conditions	5 (14.3%)
Injection site pain	5 (14.3%)
Injection site erythema	4 (11.4%)
Injection site irritation	2 (5.7%)
Injection site induration	1 (2.9%)
Injection site pruritus	1 (2.9%)
Injection site swelling	1 (2.9%)
Skin and subcutaneous tissue disorders	2 (5.7%)
Erythema	2 (5.7%)
Pruritus	1 (2.9%)

Week 0 Through Week 14

The number of injections that resulted in an injection-site reaction was 19/96 (19.8%). A total of 6 (17.1%) subjects reported 1 or more injection-site reactions, all of which were mild. The most commonly reported were injection-site pain (14.3%) and injection-site erythema (8.6%). No subject discontinued study agent administrations as a result of an injection-site reaction from Week 0 through Week 14. According to the MAH, the pattern and incidence of injection-site reactions reported through Week 14 was similar to that reported through Week 6.

Week 14 Through Week 126

The number of injections that resulted in an injection-site reaction was 21/375 (5.6%). A total of 4 (20.0%) subjects reported 1 or more injection-site reactions, all of which were non-serious and mild. The most commonly reported were injection-site irritation (2 [10.0%] subjects) and injection-site pain (2 [10.0%] subjects). Of the 21 injections that resulted in injection-site reactions, 18 were self-administered injections and 3 were administered by a healthcare professional. No subject discontinued study agent administration as a result of an injection-site reaction from Week 14 through Week 126. One subject reported an injection-site reaction at 15 separate visits during the study extension. Of the 15 injections that resulted in injection-site reactions for this subject, 2 injections were administered by a healthcare professional at the study site. According to the MAH, the incidence of injection-site reactions through Week 126 was consistent with findings through Week 14.

Week 126 Through Final Visit

The number of injections that resulted in an injection-site reaction was 37/467 (7.9%). A total of 2 (18.2%) subjects reported 1 or more injection-site reactions with the preferred terms injection-site irritation (2 [18.2%] subjects) and injection-site swelling (1 [9.1%] subject). All of the injection-site reactions were non-serious and mild. No subject discontinued study agent administration as a result of an injection-site reaction from Week 126 through the final visit. Of the 37 injections that resulted in injection-site reactions, 36 were self-administered injections, 1 injection was administered by a caregiver, and 0 injections were administered by a healthcare professional at the study site. Of the 2 subjects who reported 1 or more injection-site reactions, 1 subject reported an injection-site reaction at 8 separate visits and the other subject reported an injection-site reaction at 29 separate visits during the study extension after Week 126.

Possible Anaphylactic Reactions and Serum-Sickness Like Reactions

No possible anaphylactic or serum-sickness like reactions were identified during the entire study (from Week 0 through the final visit), including among subjects who were tested positive for antibodies to golimumab.

Adverse Drug Reactions

Based on review of golimumab safety data from study CNTO148UCO1001, the MAH states that no new ADRs have been identified and the safety profile in pediatric subjects in CNTO148UCO1001 is considered similar to that seen in adults with UC.

Rapporteur assessment:

No malignancy, opportunistic infections or TB were reported during the study. Infections were common, 23 (65.7%) subjects reported infections during the entire study, with upper respiratory tract infection the most frequently reported infection. When adjusted for follow-up, the incidence of infections per 100 subject-years of follow-up was 121.23. This was higher than noted in the adult UC studies, but in line with the results seen in JiA. Information regarding infection is already included in the SmPC and no updates are needed. A total of 7 (20.0%) subjects reported 1 or more injection-site reactions. No subject discontinued study agent administrations as a result of an injection-site reaction and no possible anaphylactic or serum-sickness like reactions were identified during the entire study.

CLINICAL LABORATORY EVALUATIONS

Hematology

Through Week 6, 5 of 30 (16.7%) subjects reported markedly abnormal decreases in absolute lymphocytes. This did not occur in more than 1 subject on more than 1 occasion. Through Week 14, 5 of 34 (14.7%) subjects reported markedly abnormal decreases in absolute lymphocytes, with 2 subjects reporting more than 1 event. All other reports of markedly abnormal hematology were single events.

From Week 14 through Week 126, 4 (20.0%) subjects had markedly abnormal decreases in absolute lymphocytes on more than 1 occasion, and 1 (5.0%) subject had markedly abnormal decreases in absolute neutrophils on more than 1 occasion. According to the MAH, these events are consistent with the safety profile of golimumab seen in adult UC golimumab studies. During the study extension after Week 126, there were no subjects who had markedly abnormal changes in hematology.

Chemistry

Among all treated subjects, markedly abnormal changes in chemistry laboratory values were uncommon through Week 6. No markedly abnormal changes in chemistry laboratory values were reported in more than 1 subject on more than 1 occasion through Week 6 or through Week 14. One subject had 2 events of markedly abnormal decreases in albumin during the study extension through Week 126. One subject had 1 event of markedly abnormal elevation in alkaline phosphatase during the study extension after Week 126. There were no other markedly abnormal clinical chemistry values during the study extension after Week 126.

Vital signs, physical findings, and other observation related to safety

Vital Signs and Physical Examination Findings

No SAEs were reported for changes in vital signs or physical examination findings.

Antibodies to Golimumab and Possible Reactions to Study Agent

According to the MAH, the number of subjects with antibodies to golimumab was too small (10 out of 35) to draw conclusions on the relationship between antibody formation and injection-site reactions.

Week 0 Through Final Visit

From Week 0 through the final visit, 3 of 10 subjects who tested positive for antibodies had an injection-site reaction.

Week 0 Through Week 14

One of 3 (33.3%) antibody-positive subjects through Week 14 reported a non-serious injection-site reaction. The antibody-positive subject reported injection site erythema, injection site pain and injection site pruritus on Day 16 that was considered an injection-site reaction; the subject had a golimumab antibody titer of 1:12 on Day 45 and 1:24 on Day 94. This subject was not in clinical response at Week 6.

Week 14 Through Week 126

The highest titer reported among any of these subjects was 1:96. Two of 5 (40.0%) antibody-positive subjects between Week 14 and Week 126 reported injection-site reactions and most were mild; none were serious. The most commonly reported injection-site reactions were injection-site pain and injection site irritation.

Week 126 Through Final Visit

Of the 3 subjects who were positive for antibodies to golimumab between Week 126 and the final visit using drug-tolerant EIA, 1 subject had injection-site irritation which was of mild intensity. The highest antibody titer in this subject was 1:48.

Antinuclear Antibodies and Anti-dsDNA Antibodies

A summary of ANA test results using a ≥ 1:160 titer for positivity in subjects who were negative at Week 0 and developed a positive result through the final visit is presented in the table below:

	Golimumab		
	Week 0 through Week 14	Week 14 through Week 126	Week 126 through Final Safety Visit
Treated subjects	35	20	11
Subjects evaluated	31	18	10
Subjects ANA negative at Week 0[a]	26 (83.9%)	16 (88.9%)	10 (100.0%)
Subjects ANA positive at any time[b]	1 (3.8%)	0	1 (10.0%)

[a] Denominator is number of subjects evaluated (had data at both Week 0 and at least one postbaseline visit).
[b] Denominator is number of subjects ANA negative at Week 0.

Subjects who were positive (≥1:160) for ANA at any time postbaseline were evaluated for anti-dsDNA antibodies. From Week 0 through Week 14, the 3 subjects who were positive for ANA at any time postbaseline, irrespective of their baseline status were evaluated for anti-dsDNA. All 3 subjects were negative for anti-dsDNA at baseline.

From Week 14 through Week 126, two subjects positive for ANA postbaseline were evaluated for anti-dsDNA antibodies. Both subjects were negative for anti-dsDNA antibodies at baseline and no subject was positive for anti-dsDNA antibodies at any time.

From Week 126 through final visit, the 1 subject positive for ANA postbaseline was negative for anti-dsDNA antibodies at Week 110 and throughout the study extension after Week 126

Safety in special groups and situations

Table 12: Overall summary of treatment-emergent adverse events from Week 0 through Final Safety Visit by age; Treated subjects (Study CNTO148UCO1001)

	Age (yrs)	
	2-11	12-17
Treated subjects	10	25
Avg duration of follow-up (weeks)	131.4	109.3
Avg exposure (number of administrations)	31.5	25.4
Subjects who died	0	0
Subjects who discontinued study agent because of 1 or more adverse events	3 (30.0%)	3 (12.0%)
Subjects with 1 or more:		
Adverse events	10 (100.0%)	23 (92.0%)
Serious adverse events	8 (80.0%)	8 (32.0%)
Infections[a]	7 (70.0%)	16 (64.0%)
Serious infections[a]	1 (10.0%)	0
Neoplasms (malignant)	0	0
Injection-site reactions[b]	0	7 (28.0%)

[a] Infection as assessed by the investigator.
[b] Injection-site reactions as assessed by the investigator.

Table 13: Overall summary of treatment-emergent adverse events from Week 0 through Final Safety Visit by weight; Treated subjects (Study CNTO148UCO1001)

	Weight (kg)			
	<45			
	<30	30-<45	Combined	>=45
Treated subjects	5	10	15	20
Avg duration of follow-up (weeks)	77.4	152.6	127.6	106.6
Avg exposure (number of administrations)	18.2	36.2	30.2	24.8
Subjects who died	0	0	0	0
Subjects who discontinued study agent because of 1 or more adverse events	3 (60.0%)	1 (10.0%)	4 (26.7%)	2 (10.0%)
Subjects with 1 or more:				
Adverse events	5 (100.0%)	10 (100.0%)	15 (100.0%)	18 (90.0%)
Serious adverse events	5 (100.0%)	6 (60.0%)	11 (73.3%)	5 (25.0%)
Infections[a]	3 (60.0%)	7 (70.0%)	10 (66.7%)	13 (65.0%)
Serious infections[a]	0	1 (10.0%)	1 (6.7%)	0
Neoplasms (malignant)	0	0	0	0
Injection-site reactions[b]	0	1 (10.0%)	1 (6.7%)	6 (30.0%)

[a] Infection as assessed by the investigator.
[b] Injection-site reactions as assessed by the investigator.

Rapporteur assessment:

Markedly abnormal changes in hematology and chemistry laboratory values were uncommon, however one subject had 1 event of markedly abnormal elevation in alkaline phosphatase. Upon request, the MAH provided additional information regarding this subject: The patient had elevated alkaline phosphatase already at the beginning of the study that fluctuated during the 8 years the patient participated in the study. Only one event was > 500 U/L (at week 186) and elevated values were not associated with elevations in alanine transaminase, aspartate transaminase, or total bilirubin. Although no explanation regarding the elevated alkaline phosphatase is provided in the case narrative, the values were normalized during the end of the study when the patient were still on treatment. An association with Simponi-treatment seems unlikely.

Both leukopenia and anaemia are listed as common ADRs in the SmPC 4.8 and cases of pancytopenia has been reported and are described in 4.4 and 4.8. In addition, elevated liver enzymes (AST, ALT) are listed as common ADR and hepatic disorder is listed as uncommon in 4.8.

It is agreed with the MAH that the number of subjects with antibodies to golimumab was too small (10 out of 35) to draw conclusions on the relationship between antibody formation and injection-site

reactions. From Week 0 through the final visit, 3 of 10 subjects who tested positive for antibodies had an injection-site reaction.

It is noted that a greater proportion of patients in the younger subgroup and patients with lower weight reported more SAEs, however the interpretation is limited by the small sample size.

To conclude, the overall safety profile through the final visit was consistent with that observed through Week 14 and through Week 126 and with the known safety profile of golimumab with no new safety concerns identified.

8.3. Discussion

The average duration of follow-up was 115.6 weeks, with an average exposure of 27.1 administrations of golimumab. Adverse events were common and 94.3% reported 1 or more AEs during the entire study. The most frequently reported SOCs were Gastrointestinal disorders (82.9%), Infections and infestations (54.3%), and General disorders (42.9%). The most frequent AEs were colitis ulcerative, (62.9%), headache (34.3), abdominal pain (25.7%), upper respiratory tract infection (22.9%), anaemia (20%)and nausea (20%). The distribution and type of AEs were similar as in the adult population; however, the frequency of events were higher in the paediatric UC population. This is not unexpected, and the same finding was seen in the JiA population when compared with RA population.

There were no deaths during the study. Serious adverse events (SAEs) were seen in 16 (45.7%) patients and were mainly associated with disease progression (colitis ulcerative, 13 patients). Other SAEs occurring (abdominal pain, acute pancreatitis, iron deficit anaemia, sclerosing cholangitis, respiratory tract infection, urinary tract infection, forearm fracture and decreased appetite) were only seen in one patient each, however two patients had multiple SAEs (one patient had respiratory tract and urinary tract infections as well as a forearm fracture and one patient had decreased appetite and an ulcerative colitis flare). It is noted that the patient with sclerosing cholangitis also had a history of this disease, thus a relapse. According to the MAH, none of the SAEs were assessed as being related to the study drug and for the majority of the cases, this could be agreed on based on the narratives provided by the MAH. No new safety concerns were evoked based on this information.

During the entire study, 6 patients discontinued study medication due to an AE, all which also could be related to disease worsening (5 due to colitis ulcerative and 1 due to diarrhoea haemorrhagic). This does not evoke any further concern. No malignancy, opportunistic infections or TB were reported during the study. Infections were common, 23 (65.7%) subjects reported infections during the entire study, with upper respiratory tract infection the most frequently reported infection. When adjusted for follow-up, the incidence of infections per 100 subject-years of follow-up was 121.23. This was higher than noted in the adult UC studies, but in line with the results seen in JiA. Information regarding infection is already included in the SmPC and no updates are needed. A total of 7 (20.0%) subjects reported 1 or more injection-site reactions. No subject discontinued study agent administrations as a result of an injection-site reaction and no possible anaphylactic or serum-sickness like reactions were identified during the entire study.

Markedly abnormal changes in hematology and chemistry laboratory values were uncommon, however one subject had 1 event of markedly abnormal elevation in alkaline phosphatase. Upon request, the MAH provided additional information regarding this subject and the fact that alkaline phosphatase was elevated already at baseline, not associated with any other liver function test elevation, fluctuating during the study time (8-years) and normalizing at the end of the study, despite still on treatment, make the association with Simponi treatment unlikely.

It is noted that a greater proportion of patients in the younger subgroup and patients with lower weight reported more SAEs, however the interpretation is limited by the small sample size.

To conclude, the overall safety profile through the final visit was consistent with that observed through Week 14 and through Week 126 and with the known safety profile of golimumab with no new safety concerns identified.

9. PRAC advice

N/A

10. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Version Number	24.1
Rationale for submitting an updated RMP	Completion of the final report for category 3 additional pharmacovigilance activity CNTO148UCO1001.
Summary of significant changes in this RMP	Product(s) Overview: Aligned with updated SmPC (EMEA/H/C/000992/II/0079) to include dosage recommendation for patients treated for ulcerative colitis who have body weight <80 kg and an inadequate response after Week 2. Pharmacovigilance Plan: Removed CNTO148UCO1001 as a category 3 additional pharmacovigilance activity.

Two other RMPs are currently under evaluation:

RMP Version Number	Submitted on	Procedure Number
23.2	20 December 2022	EMEA/H/C/000992/II/0111
23.3	21 December 2022	EMEA/H/C/000992/II/0112

Rapporteur assessment:

An updated RMP was submitted with this application, removing this study as category 3 study from the additional pharmacovigilance plan. In addition, the MAH has included dose recommendation for adult UC patients <80 kg with inadequate response after induction treatment to align with the updated SmPC approved in EMEA/H/C/000992/II/0079. This is acceptable.

Two other RMP version is currently under evaluation during this process, thus the MAH has color-marked the changes that are referring to this variation. There is however one section in the RMP referring to this variation but no explanation for the change is provided by the MAH (see extract

below). The change is not mentioned in the EMEA/H/C/000992/II/0112. However, the changes seem not to evoke any concerns and do not contradict the text regarding this topic in the SmPC. Thus, also this change is acceptable.

that of endogenous IgG antibodies. It is expected that human infants born to golimumab-treated mothers will have golimumab in their serum at birth and that TNF will be inhibited until the serum concentration falls below a pharmacologically relevant level. ~~The relevance of this to the infants is unknown.~~

Golimumab may be secreted in small amounts in breast milk. ~~However, this is unlikely to contribute to significant infant systemic exposure because IgG antibodies are degraded in the gastrointestinal tract and are not absorbed across the gut.~~

10.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

11. Request for supplementary information

11.1. Major objections

N/A

11.2. Other concerns

Clinical aspects

Pharmacokinetics

1. It is unclear how many subjects that had a decrease in the dose to 50 mg or 22.5 mg/m^2. This should be clarified by the MAH since this may have an impact on the interpretation of the results.

Safety

2. one subject had 1 event of markedly abnormal elevation in alkaline phosphatase. No further information regarding this case is provided and the MAH is asked to provide a narrative if possible**.**

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

None

12.2. Other concerns

Clinical aspects

Question 1
It is unclear how many subjects that had a decrease in the dose to 50 mg or 22.5 mg/m^2. This should be clarified by the MAH since this may have an impact on the interpretation of the results.

Summary of the MAH's response
A total of 2 subjects out of 35 had dose decreases from 100 mg to 50 mg. No subjects had a dose decrease to 22.5 mg/m2. One subject had a single dose decrease from 100 mg to 50 mg. This decrease was a self-administration mistake by the subject. There were no AEs related to this dose decrease, and the dose was increased back to 100 mg at the next visit. A second subject had a dose decrease from 100 mg to 50 mg at Week 146 per protocol which allowed a dose decrease in the long-term extension at the discretion of the investigator. After this protocol-allowed dose decrease, there was a single dose increase to 100 mg at Week 230 which appeared to be an error. After the single 100 mg dose administered at Week 230, the subject received 50 mg from Week 146 through the end of study participation at Week 394. These dose decreases, which occurred in only 2 subjects, had no impact on the interpretation of the results.

Assessment of the MAH's response
Only two subjects had dose decreases, one on a single occasion by mistake the other from 100 mg to 50 mg from week 146. It is agreed with the Applicant that this does not affect any conclusions drawn from the study.

Conclusion

Issue resolved

Question 2

One subject had 1 event of markedly abnormal elevation in alkaline phosphatase. No further information regarding this case is provided and the MAH is asked to provide a narrative if possible**.**

Summary of the MAH's response

There was one subject with a markedly abnormal elevation of alkaline phosphatase during the study extension. The subject had an elevated value at screening (247 U/L; normal range: 31 to 110 U/L).

The subject had consistently elevated alkaline phosphatase values over the next 8 years in the study, varying between almost 2x the ULN to a single value 5x the ULN (590 U/L at Week 186) which met the markedly abnormal definition (% increase ≥100 U/L and value >500 U/L). The alkaline phosphatase levels normalized near the end of study participation (from available laboratory results at Week 374 and Week 398). The subject's elevated alkaline phosphatase levels were without clinical consequence and were not associated with elevations in alanine transaminase, aspartate transaminase, or total bilirubin. This subject has an extensive narrative in the final CSR detailing the SAEs (concomitant urinary tract infection, respiratory tract infection, and forearm fracture) and an AE leading to study drug discontinuation (ulcerative colitis flare; Week 398) in the study.

Assessment of the MAH's response

The patient had elevated alkaline phosphatase already at the beginning of the study that fluctuated during the 8 years the patient participated in the study. Only one event was > 500 U/L (at week 186) and elevated values were not associated with elevations in alanine transaminase, aspartate transaminase, or total bilirubin. Although no explanation regarding the elevated alkaline phosphatase is provided in the case narrative, the values were normalized during the end of the study when the patient were still on treatment. An association with Simponi-treatment seems unlikely.

Conclusion

Issue resolved