11 December 2025
EMA/8289/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Simponi

International non-proprietary name: golimumab

Procedure No. EMEA/H/C/000992/II/0121

Note

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

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List of abbreviations

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADR	adverse drug reaction
AE	adverse event
AS	ankylosing spondylitis
AUCW0-6	area under the concentration-time curve from Week 0 to 6
AUCW50-54	area under the concentration-time curve from Week 50 to 54
AZA	azathioprine
BSA	body surface area
CI	confidence interval
CL/F	apparent clearance
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
DEVELOP	prospective, observational study of the long-term safety and clinical status of pediatric patients <17 years of age with IBD
ECLIA	electrochemiluminescence immunoassay
EIA	enzyme immunoassay
E-R	exposure-response
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GI	gastrointestinal
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
Ig	immunoglobulin
IV	intravenous(ly)
IWRS	Interactive Web Response System
mAb	monoclonal antibody
MSD	meso scale discovery
MTX	methotrexate
NK	natural killer
nr-AxSpA	nonradiographic axial spondyloarthritis
PBRER	Periodic Benefit Risk Evaluation Report

PFS	prefilled syringe
PFS-U	prefilled syringe-UltraSafe
PFS-V	prefilled syringe-Varioject
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
PT	preferred term
PUCAI	Pediatric Ulcerative Colitis Activity Index
PURSUIT	program of ulcerative colitis research studies utilizing an investigational treatment
PsA	psoriatic arthritis
q4w	every 4 weeks
QoL	quality of life
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SCS	Summary of Clinical Safety
SmPC	summary of product characteristics
SOC	system organ class
T16	C0524T16 Phase 2/3 IV induction study in adults
T17	C0524T17 Phase 2/3 SC induction study in adults
T18	C0524T18 Phase 3 SC maintenance study in adults
TB	tuberculosis
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
UCO1001	CNTO148UCO1001 Phase 1b SC study in participants aged 2 to <18 years
UCO3003	CNTO148UCO3003 Phase 3 SC study in participants aged 2 to <18 years
US	United States
V/F	apparent volume of distribution
WT	weight

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen Biologics B.V. submitted to the European Medicines Agency on 19 December 2024 an application for a variation. During the procedure, the marketing authorisation was transferred to Jassen Cilag International N.V.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA, IIIB

Extension of indication to include treatment of paediatric ulcerative colitis, based on results from study CNTO148UCO3003; this is a phase 3 randomised, open-label study to assess the efficacy, safety, and pharmacokinetics of golimumab treatment, a human anti-TNFα monoclonal antibody, administered subcutaneously in paediatric participants with moderately to severely active ulcerative colitis. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. Version 28.1 of the RMP has also been submitted. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is updated in accordance with the latest EMA excipients guideline and aligned with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0421/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0421/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0421/2022.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 28 January 2016 (EMEA/H/SA/463/4/2015/PED/II) and 12 November 2020 (EMEA/H/SA/463/4/FU/1/2020/PED/II).

The Scientific Advice pertained to clinical aspects and paediatric development of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	19 December 2024
Start of procedure:	26 January 2025
CHMP Rapporteur Assessment Report	21 March 2025
PRAC Rapporteur Assessment Report	21 March 2025
PRAC Outcome	10 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 April 2025
Request for supplementary information (RSI)	25 April 2025
CHMP Rapporteur Assessment Report	16 September 2025
PRAC Rapporteur Assessment Report	16 September 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	02 October 2025
CHMP members comments	06 October 2025
Updated CHMP Rapporteur Assessment Report	09 October 2025
2nd Request for supplementary information (RSI)	16 October 2025
PRAC Rapporteur Assessment Report	17 November 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	26 November 2025
PRAC Outcome	27 November 2025
CHMP members comments	01 December 2025
Updated CHMP Rapporteur Assessment Report	05 December 2025
Opinion	11 December 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH initially applied for the following indication:

Paediatric ulcerative colitis (pUC)

Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients 2 years of age and older who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Clinical presentation, diagnosis

Ulcerative colitis (UC) is an inflammatory disorder which involves the surface mucosa, crypt epithelium, and submucosa of the colon (Ordás 2012[1]; Stenson 2000[2]). Clinically, patients with UC suffer from diarrhoea, rectal bleeding, weight loss, abdominal pain, fever, and may also display prominent extra intestinal manifestations, most commonly arthritis (Ordás 2012; Stenson 2000). Paediatric UC is similar to adult UC in terms of demographics, clinical features, pathophysiology, and response to treatment (Kelsen 2008[3]; Sauer 2009[4]; Stefanska 2017[5]; Turner 2011[6]).

UC is a chronic gastrointestinal (GI) inflammatory disorder characterised by a life-long chronic course of remissions and exacerbations. While the peak occurrence of paediatric UC is in late adolescence, all ages can be affected, and 4% of paediatric IBD patients are diagnosed in early (age <5 years) childhood (Kelsen 2008). Children aged 2 to 6 years account for approximately 10% of paediatric UC (Herrinton 2007[7], Loftus 2007[8]).

[1] Ordas I (2012), Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380(9853):1606-1619
[2] Stenson WF (2000). Inflammatory bowel disease. In: Goldman l, Bennett, JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders Co; 2000;722-729
[3] Kelsen J (2008), Baldassano RN. Inflammatory bowel disease: the difference between children and adults. Inflamm Bowel Dis. 2008;14Suppl2:S9-11
[4] Sauer CG (2009), Kugathasan S. Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD. Gastroenterol Clin North Am. 2009;38(4):611-628
[5] Stefanska AM (2017), Distlerova D, Musaus J, et al. Extrapolation in the development of paediatric medicines: examples from approvals for biological treatments for paediatric chronic immune-mediated inflammatory diseases. Arch Dis Child. 2017;102(10):952-957
[6] Turner D (2011), Griffiths AM. Acute severe ulcerative colitis in children: a systematic review. Inflamm Bowel Dis. 2011;17(1):440-449
[7] Herrinton LJ (2007), Liu L, Lafata JE et al. Estimation of the period and prevalence of IBD among nine health plans using computerized diagnoses and outpatient pharmacy dispensing. Inflamm Bowel Dis. 2007;13:451-461. PMID: 17219403 DOI: 10.1002/ibd.20021
[8] Loftus EV, Jr. Objective measures of disease activity: alternative to symptom indices, Rev gastroenterol Disorder 2007; 7:(suppl 2 S47):506-13

Management

Treatment of paediatric UC generally follows the same treatment paradigms that are used to treat adult UC (Sauer 2009; Turner 2011). Although there are multiple therapies in several distinct drug classes approved to treat adult UC, approved pharmacologic treatment options are limited for paediatric patients with UC, especially for those who have failed to respond to or tolerate conventional therapy (5-ASA, corticosteroids, or immunomodulators).

Currently, there are 2 approved biologics for children from 6 years of age with UC: infliximab, which is given every 8 weeks during maintenance by IV infusion, and adalimumab, which is given every 2 weeks during maintenance by SC injection While infliximab and adalimumab are generally safe and well tolerated in the paediatric UC population, less than half of paediatric UC patients achieve sustained clinical remission on infliximab or adalimumab (Croft 2021[9]; Hyams 2012a[10]; Hyams 2012b[11]). Additionally, secondary loss of response to infliximab after an initial response occurs in 20% to 40% of all IBD patients after 1 year of therapy (Ben-Horin 2014[12]; Bolia 2018[13]).

Without an effective pharmacologic treatment, the only alternative is colectomy which is associated with notable morbidity (Turner 2009[14], Uchida 2010[15]). As such, there is a need for additional treatment options for paediatric patients with moderately to severely active UC.

2.1.2. About the product

Golimumab is a human mAb with an IgG 1 heavy chain isotype (G1m allotype) and a kappa light chain isotype. Golimumab binds with high affinity to both soluble and transmembrane forms of the tumour necrosis factor alpha (TNFα) and inhibits TNFα bioactivity. Golimumab is classified according to the Anatomical Therapeutic Chemical Classification System as a TNFα inhibitor (ATC code: L04AB06).

Golimumab for SC administration is approved globally for the treatment of adults with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondylarthritis, and UC. Additionally, golimumab is approved globally in the treatment of children with polyarticular juvenile idiopathic arthritis (SC or IV administration).

Simponi is available as solution for injection in prefilled syringes (50 mg and 100 mg) and prefilled pens (45 mg/0.45 ml, 50 mg and 100 mg). In this application, the MAH requested approval only for the 45 mg/0.45 mL pre-filled pen intended for paediatric patients and for the 50 mg and 100 mg prefilled syringes.

[9] Croft NM (2021), Faubion WA Jr, Kugathasn S, et al. (2021). Efficacy and safety of adalimumab in paediatric patients with moderate-to-severe ulcerative colitis (ENVISION I): a randomised, controlled, phase 3 study. Lancet Gastroenterol Hepatol 2021; 6: 616–627
[10] Hyams J (2012a), Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10:391-399
[11] Hyams JS (2012b), Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterol. 2012;143(2):365-374
[12] Ben-Horin S (2014), Kopyloy U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmun Rev. 2014;13(1):24-30
[13] Bolia R (2018), Rosenbaum J, Schildkraut V, et al. Secondary Loss of Response to Infliximab in Pediatric Crohn Disease: Does It Matter How and When We Start? J Pediatr Gastroenterol Nutr. 2018;66(4):637-640
[14] Turner D (2009). Severe Acute Ulcerative Colitis: The Pediatric Perspective. Dig Dis. 2009;27(3):322-326. PMID: 19786759 DOI: 10.1159/000228568
[15] Uchida K (2010), Araki T, Inoue M, et al. Poor Catch-up Growth After Proctocolectomy in pediatric patients with ulcerative colitis receiving prolonged steroid therapy. Pediatr Surg Int. 2010;26(4):373-377. PMID: 20182750 DOI: 10.1007/s00383-010-2577-6

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received Scientific Advice on two occasions for the phase 3 study, CNTO148UCO3003 (see also section 1.1.).

On 28 January 2016, the MAH received Scientific Advice (EMA/CHMP/SAWP/33895/2016) on the following:

- The results (pharmacokinetics [PK] efficacy and safety) of the PK study CNTO148UCO1001 through the week 14 database lock.
- The scientific rationale for pursing an extrapolation-based approach and the details of the MAH's extrapolation plan for seeking a paediatric UC indication.
- The clinical development plan to support the dose selected for paediatric patients with body weight <45 kg.

On the 12 November 2020, the MAH received Scientific Advice (EMA/CHMP/SAWP/580825/2020) on the following:

- Acceptability to remove the infliximab arm from the ongoing CNTO148UCO3003 study in paediatric UC.

The Simponi UC PIP included the following studies to be completed:

- Study 1 (Quality): Development of an age-appropriate paediatric presentation
- Study 2 (Clinical): A multicentre, open-label study to assess the PK and safety of golimumab in patients from 2 to less than 18 years old with moderately to severely active UC (CNTO148UCO1001).
- Study 4 (Clinical): Randomised, open label golimumab study in paediatric patients from 2 to less than 18 years with moderately to severely active UC (CNTO148UCO3003)
- Study 5 (Modelling and simulation): Population PK modelling and simulation study
- Study 6 (Modelling and simulation): Exposure-response modelling and simulation study
- Study 7 (Modelling and simulation): Analysis of internal and literature data to support the assumptions of similarity of disease, treatment effects, and exposure-response relationship between paediatric and adult subjects with UC

2.1.4. General comments on compliance with GCP

The MAH states that all studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH did not submit any environmental risk assessment (ERA) studies in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) which states that proteins are unlikely to result in significant risk to the environment. This is agreed by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

This variation comprised the clinical study reports from two studies, one phase 3 study (CNTO148UCO3003, completed through week 54, study extension ongoing at time of assessment) and one supportive phase 1 study (CNTO148UCO1001, completed). Study CNTO148UCO1001 was assessed in a previous variation (EMEA/H/C/000992/II/0113).

The phase 3 study is a, multicentre, randomised, open label golimumab study (CNTO148UCO3003 (PURSUIT 2)) designed to enrol paediatric participants aged 2 to <18 years with moderately to severely active UC defined as a baseline full Mayo score of 6 through 12, inclusive, with an endoscopy sub score of ≥2.

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Type						
Study ID EudraCT Number First Patient First Visit / Completion date (day Month year) Study Status	**Countries/ Territories: Number of Centers**	**Phase Study Description/Design, Study Population, Primary Objective(s)**	**Total Number of Subjects**	**Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment**	**Number of Subjects Treated (by Treatment Group)**	**Type of Study Report Issue Date Document ID Number**
CNTO148UCO3003 PURSUIT2 Ongoing Week 54 Synopsis 2023-507142-83 20 December 2018 / 11 April 2024	BEL, BRA, ESP, FRA, ISR, ITA, KOR, POL, USA: 27	Phase 3 Randomised, open-label multicenter study Paediatric participants aged 2 to 17 years (at the time of the first administration of study intervention at Week 0) with moderately to severely active UC, defined as a baseline Mayo score of 6 through 12, inclusive, with an endoscopy subscore of ≥2 To evaluate the efficacy of golimumab in inducing clinical remission as assessed by the Mayo score, in paediatric participants with moderately to severely active ulcerative colitis (UC). To evaluate the safety profile of golimumab, in paediatric participants with moderately to severely active UC	Planned: 70 Enrolled: 84 Randomised: 58 Non-randomised: 26	<u>Golimumab:</u> Supplied as a sterile liquid for SC injection in single use PFS-U or PFP-V. Each PFS-U contains either 100 mg (in 1 mL liquid) or 50 mg (in 0.5 mL liquid) of golimumab, with each 0.1 mL of liquid containing 10 mg of golimumab. The PFP-V for paediatric use can deliver a dose between 10 and 45 mg in 5 mg increments. <u>Infliximab:</u> Supplied in a 20 mL disposable glass vial and administered as an IV infusion **Golimumab treatment arm (Group 1)**: Week 0 through Week 6 (Short Term Phase): Participants received dose regimens of SC golimumab at Week 0 and Week 2 based on body weight. • Participants with body weight <45 kg received BSA adjusted induction doses of 120 mg/m^2 (up to a mas of 22 mg) at Week 0 and 60 mg/m^2 (up to a max of 100 mg) at Week 2 • Body weight ≥45 kg received 200 mg at Week 0 and 100 mg at Week 2 **Week 6 through Week 54 (Long Term Phase):** Participants in the golimumab arm continued to receive golimumab q4w through Week 50. For participants not in clinical response at Week 6, additional doses were given,	Golimumab: 69 Infliximab: 15	Full CSR (Week54) 30 October 2024 EDMS-RIM-1232235

Study Type						
Study ID EudraCT Number First Patient First Visit / Completion date (day Month year) Study Status	**Countries/ Territories: Number of Centers**	**Phase Study Description/Design, Study Population, Primary Objective(s)**	**Total Number of Subjects**	**Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment**	**Number of Subjects Treated (by Treatment Group)**	**Type of Study Report Issue Date Document ID Number**
				followed by a response assessment at Week 14, to determine if these participants continued with golimumab q4w through Week 50. **Week 54 through end of study:** Participants who benefited from golimumab continued to receive SC golimumab q4w starting at Week 54 until marketing authorization is obtained for golimumab for the treatment of paediatric patients with UC, the participant turns 18 and has access to commercially available golimumab, or until a decision is made not to pursue an indication in this paediatric UC population, whichever occurs first. **Infliximab treatment arm (Group 2);** Participants (≥30 kg only) were administered 5 mg/kg IV at Weeks 0 and 2. For those in clinical response, administration continued with 5 mg/kg starting at Week 6 continuing q8w through Week 50 For those not in clinical response, a step-wise dose escalation was permitted to a max of 10 mg/kg (capped at 1gm) at an interval of q4w through Week 54.		
CNTO148UCO1001 PURSUIT PEDS PK Synopsis 2012-004366-18 25 September 2013 /	AUT, CAN, DEU, FRA, ISR, POL, USA: 20	Phase 1b Open label multicenter study	Screened: 56 Enrolled:35	<u>Golimumab:</u> Supplied as a sterile liquid for SC injection in single-use prefilled syringes.	Body Wt <45 kg: 15	Full CSR (Final) 16 February 2023 EDMS-RIM-822732 16 February 2023

Study Type						
Study ID EudraCT Number First Patient First Visit / Completion date (day Month year) Study Status	**Countries/ Territories: Number of Centers**	**Phase Study Description/Design, Study Population, Primary Objective(s)**	**Total Number of Subjects**	**Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment**	**Number of Subjects Treated (by Treatment Group)**	**Type of Study Report Issue Date Document ID Number**
01 September 2022 Completed		Paediatric participants aged 2 to 17 years with moderately to severely active ulcerative colitis (UC) To evaluate the pharmacokinetics (PK) and safety of golimumab in paediatric subjects aged 2 through 17 years with moderately to severely active ulcerative colitis		Each single-use prefilled syringe contained either 50 mg (in 0.5 mL of liquid) or 100 mg (in 1 mL of liquid) golimumab **Week 0 through Week 14 (PK Phase):** Participants received dose regimens of SC golimumab at Week 0 and Week 2 based on body weight: • Body weight <45 kg received 90 mg/m^2 at Week 0 and 45 mg/m^2 at Week 2 • Body weight ≥45 kg received 200 mg at Week 0 and 100 mg at Week 2 Participants not in clinical response at Week 6 were withdrawn from further golimumab administration. Participants in clinical response at Week 6, received maintenance therapy SC based on body weight: • Body weight <45 kg received 45mg/m^2 at Week 6 and Week 10 • Body weight ≥45 kg received 100 mg at Week 6 and Week 10 These participants were eligible to enter the study extension at Week 14. **Week 14 through Week 110 (end of study):** Participants who entered the study extension were dosed q4w SC based on body weight: • Participants with body weight <45 kg had option to decrease their golimumab SC dose to 22.5 mg/m^2 up to a maximum of 50 mg or continued to receive 45 mg/m^2 up to a max of 100 mg q4w through Week 110	Body Wt ≥45 kg: 20	Full CSR (Week 126) EDMS-ERI-141311916 14 November 2017 Full CSR (Week 14) EDMS-ERI-114482237 26 May 2016

Study Type						
Study ID EudraCT Number First Patient First Visit / Completion date (day Month year) Study Status	**Countries/ Territories: Number of Centers**	**Phase Study Description/Design, Study Population, Primary Objective(s)**	**Total Number of Subjects**	**Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment**	**Number of Subjects Treated (by Treatment Group)**	**Type of Study Report Issue Date Document ID Number**
				• Participants with body weight ≥45 kg had option to decrease their golimumab SC dose to 50 mg or to continue to receive 100 mg 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 under the protocol until marketing authorization is obtained for golimumab in the treatment of paediatric UC in that country, or until a decision has been made not to pursue an indication in paediatric UC, whichever occurs first.		

2.3.2. Pharmacokinetics

Similarity of pharmacology

The pharmacology of golimumab is similar in adults and children. Unlike small-molecule drugs, mAbs are not metabolised by hepatic cytochrome P450 enzymes. Thus, age-related changes in hepatic phase I and phase II metabolism are not likely to affect golimumab elimination and impairment of hepatic or renal functions may have a negligible effect on metabolism and clearance. As a mAb, golimumab is metabolised by the same catabolic pathways as endogenous immunoglobulins and is typically broken down into small peptides and amino acids through proteolysis. A common pathway shared by endogenous IgG and mAbs is non-specific Fc receptor mediated catabolism. FcRn is a salvage protein that protects IgG from catabolism. It binds to IgG in the acidic conditions of endosomes and recycles back to the extracellular surface (Ryman 2017). In the body, vascular endothelial cells make up the capillary walls and therefore, have extensive access to mAb in plasma. Golimumab is distributed predominantly within the vascular compartment. Therefore, age-related changes in body composition (ie, water and lipid composition) are not expected to affect distribution of golimumab.

Pharmacokinetics in clinical trials

The PK and pharmacodynamic properties of golimumab were studied in participants with moderately to severely active UC in two phase 2/3 induction studies and one phase 3 maintenance study in adults, which supported initial approval in UC and one phase 1b study and one phase 3 study in paediatric participants (Table 1).

Table 1: Overview of Completed Studies in Paediatric and Adult Participants With UC

Study ID and Title	Age and WT Range	Dose Regimen	Number of Participants Treated	PK Sampling Scheme[a]
UCO1001 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 UC	6 to 17 years; 19.7 to 134.0 kg	Participants with WT <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[b] Participants with WT ≥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
UCO3003 A Phase 3 Randomized, Open-label Study to Assess the Efficacy, Safety, and Pharmacokinetics of Golimumab Treatment, a Human anti-TNFα Monoclonal Antibody, Administered Subcutaneously in Pediatric Participants with Moderately to Severely Active UC	4 to 17 years; 16.0 to 107.0 kg	Participants with WT <45 kg: 120 mg/m^2 at Week 0 and 60 mg/m^2 at Week 2, and 60 mg/m^2 q4w starting at Week 6 among Week 6 responders[b] Participants with WT ≥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	69	Sparse

Study ID and Title	Age and WT Range	Dose Regimen	Number of Participants Treated	PK Sampling Scheme[a]
T17 (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 UC	18 to 78 years; 33.0 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
T16 (induction) A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Intravenously, in Subjects with Moderately to Severely Active UC	19 to 79 years; 35.0 to 150.0 kg	1 mg/kg 2 mg/kg 4 mg/kg Placebo Week 0 administration	290	Sparse
T18 (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 UC	18 to 79 years; 33.0 to 150.0 kg	50 mg 100 mg Placebo q4w Among golimumab induction responders at Week 6	1228	Sparse

Key: ID=identification; PK=pharmacokinetic(s); q4w=every 4 weeks; TNFα=tumor necrosis factor alpha; UC=ulcerative colitis; WT=weight.

Note:

[a] Intensive sampling schemes enable determination of PK parameters using noncompartmental analysis. Sparse sampling schemes require a model-based approach to determine PK parameters.

[b] Participants with body weight <45 kg received BSA asjusted induction doses up to a maximum of 200 mg at Week 0 and up to a maximum of 100 mg at week 2, Week 6 and q4w thereafter.

Methods

Bioanalysis

Serum golimumab concentrations were determined using a validated electrochemiluminescent-based immunoassay (ECLIA) method on the Meso Scale Discovery (MSD) platform.

A validated drug-tolerant enzyme immunoassay (EIA) method was used to detect antibodies to golimumab.

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

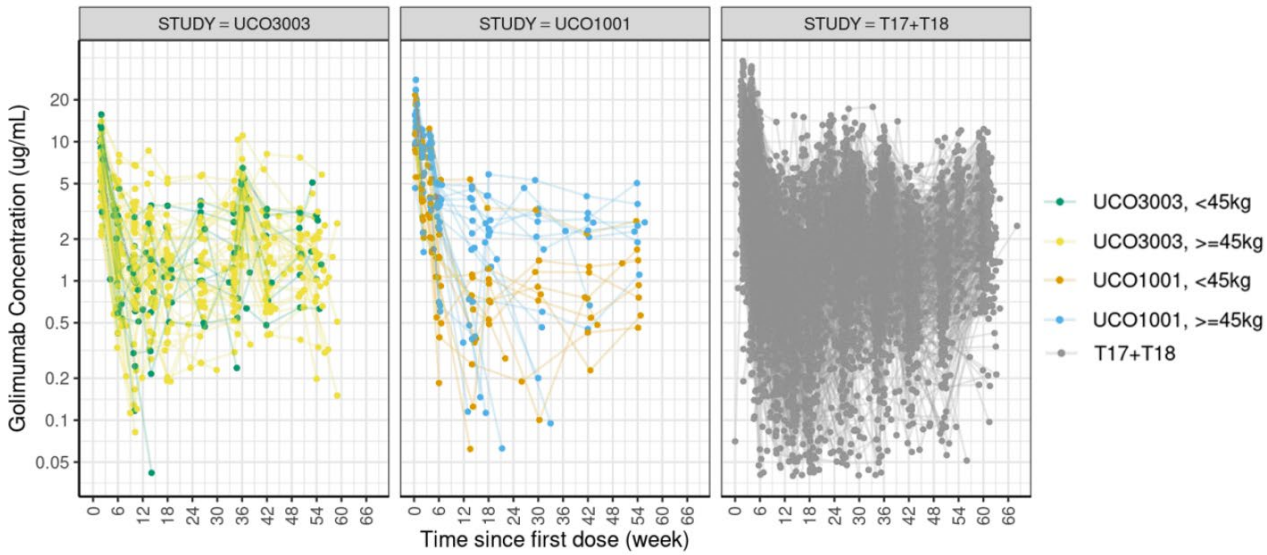
Population PK Analysis

The objectives of the popPK analysis were as follows:

- To characterise golimumab PK following SC administration of golimumab in the paediatric UC population.
- To assess and support the proposed alternative dose regimens for paediatric UC patients by matching golimumab exposures between paediatric and adult UC patients, based on PK simulations.

A popPK analysis was performed using golimumab concentration data from the paediatric studies UCO3003 (data up to week 54) and UCO1001 (data up to week 54), and the adult studies T17 (data up to week 6) and T18 (data up to week 54). Participants who received at least 1 dose of golimumab and had at least 1 valid golimumab serum concentration with associated sampling time and dosage records were included in the popPK analysis. Serum golimumab concentration-time data were analysed using nonlinear mixed effect modeling methods as implemented in NONMEM in a validated environment.

The final dataset included a total of 9,052 (paediatric: 789, adult: 8,263) measurable serum golimumab concentrations from 1,064 (paediatric: 104, adult: 960) participants with UC, visualised in Figure 1. Samples below quantification limit were excluded from the analysis which counted for approximately 4% of the total amount of paediatric PK samples.



Notes: Individual concentration-time data were plotted using colored dots connected by lines. Data from all dose regimens including the final dataset for popPK analysis were plotted. Identified outlier data were not plotted. T17+T18 group includes data in the induction phase (Week 0-6) from Study T17 and data in the maintenance phase (Week 6 and thereafter) from Study T18.

Figure 1: Individual Serum Golimumab Concentration-time Data in Studies UCO3003, UCO1001, T17, and T18

Key demographics are summarised in Table 2, 19 (18.3%) and 201 (20.9%) of the paediatric and adult patients, respectively, had a record of an immune response positive (IRP).

Table 2: Summary of key demographics in the PopPK analysis dataset

Study Number		Pediatric UC			Adult UC
		CNTO148UCO3003	CNTO148UCO1001	Total	C0524T17/T18
N		69	35	104	960
Baseline age (years)	Mean (SD)	13.4 (3.30)	13.4 (3.21)	13.4 (3.25)	40.2 (13.3)
	Median	14.0	15.0	15.0	38.5
	Range	(4.00; 17.0)	(6.00; 17.0)	(4.00; 17.0)	(18.0; 78.0)
Baseline weight (kg)	Mean (SD)	52.4 (17.5)	51.7 (22.7)	52.2 (19.3)	73.8 (17.7)
	Median	51.2	50.6	50.9	72.1
	Range	(16.4; 107)	(19.7; 134)	(16.4; 134)	(33.0; 150)
Baseline body-surface area (m^2)	Mean (SD)	1.51 (0.326)	1.49 (0.378)	1.50 (0.343)	1.86 (0.253)
	Median	1.52	1.52	1.52	1.85
	Range	(0.69; 2.38)	(0.79; 2.63)	(0.69; 2.63)	(1.17; 2.75)
Baseline albumin (g/dL)	Mean (SD)	4.45 (0.388)	3.96 (0.467)	4.31 (0.465)	4.19 (0.434)
	Median	4.50	4.00	4.40	4.20
	Range	(2.90; 5.20)	(3.10; 4.70)	(2.90; 5.20)	(2.50; 5.30)

The popPK model of golimumab for UC had been originally developed based on the adult UC studies including Studies T17 and T18 to support the filing of the UC indication for adult patients, which was subsequently updated to include the paediatric phase 1b study UCO1001 to support dose selection for the paediatric phase 3 study UCO3003. In the current popPK analysis, parameters of the previous popPK model were re-estimated using the data from the adult studies (T17 and T18, 8,263 golimumab concentrations from 960 participants) to incorporate allometric scaling with the fixed standard exponent values for WT effect on clearance and volume of distribution, and to remove one of the covariates (concomitant methotrexate therapy) which was not relevant to the UC population. Subsequently, this refined popPK model was applied to the data from the paediatric studies (UCO3003 and UCO1001), which consisted of 789 golimumab concentrations from 104 paediatric participants. The analysis of the paediatric data was performed using the MAXEVAL=0 option in NONMEM, which allows for empirical Bayesian estimation without re-estimating the population parameters. The popPK model parameters used for the paediatric analysis are reported in Table 3.

Table 3 Parameter Estimates of the Final Refined PopPK Model Following SC Administration of Golimumab in Adult UC Participants (Studies T17 and T18)

Parameters, unit	Estimate	RSE (%)	Shrinkage (%)
CL/F (L/day)[a]	0.948	1.61	--
CL/F-Baseline WT	0.750 FIX	--	--
CL/F-Baseline ALB	-1.14	8.54	--
CL/F-IRP	0.185	15.1	--
V/F (L)[b]	13.5	1.77	--
V/F-Baseline WT	1.00 FIX	--	--
k_a (day^{-1})	0.943	10.4	--
IIV of CL/F (%CV)	32.4	3.84	8.61
IIV of V/F (%CV)	28.7	9.67	32.7
Correlation between IIV of CL/F and V/F	0.484	--	--
Proportional residual error (%)	27.4	2.77	--
Additive residual error (µg/mL)	0.121	15.8	--

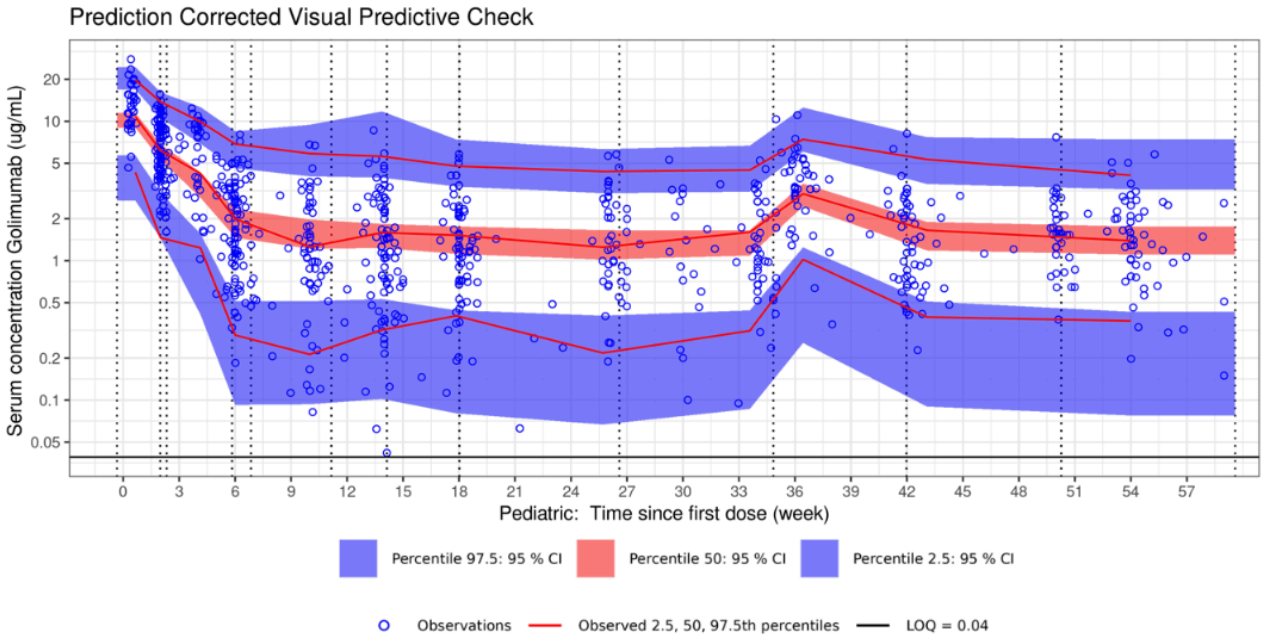
Key: ALB=albumin (g/dL); CL/F=apparent clearance; CV=coefficient of variation ($\sqrt{\exp(variance)-1}\times 100\%$); exp=exponential; IIV=interindividual variability; IRP=immune response (antibodies to golimumab) positive (YES=1/NO=0); k_a=first-order absorption rate constant; popPK=population pharmacokinetics; RSE=relative standard error; SC=subcutaneous; UC=ulcerative colitis; V/F=apparent volume of distribution; WT=weight (kg).

Notes:

[a] $CL/F\ (L/day) = 0.948 \times \left(\frac{WT}{70}\right)^{0.75} \times \left(\frac{ALB}{4.2}\right)^{-1.14} \times (1 + 0.185 \times IRP)$

[b] $V/F\ (L) = 13.5 \times \left(\frac{WT}{70}\right)^{1}$

The model fit and predictive performance of the refined model on the adult and paediatric data was confirmed by the diagnostic plots including goodness-of-fit plots and prediction-corrected visual predictive check (pcVPC). The pcVPCs for the paediatric data are shown in Figure 2, Figure 3, and Figure 4.



CI=confidence interval; LOQ=(lower) limit of quantification.
Notes: Blue open circles and red solid lines indicate the observed data and the 2.5, 50, and 97.5th percentile lines. Blue and red ribbons indicate 95% CI of the 2.5, 50, and 97.5th percentiles of the simulated data. Vertical dotted lines indicate time bins used to calculate the percentiles. A total of 500 simulation replicates were generated to obtain the CIs.

Figure 2: Prediction-Corrected Visual Predictive Check (Studies UCO3003 and UCO1001)

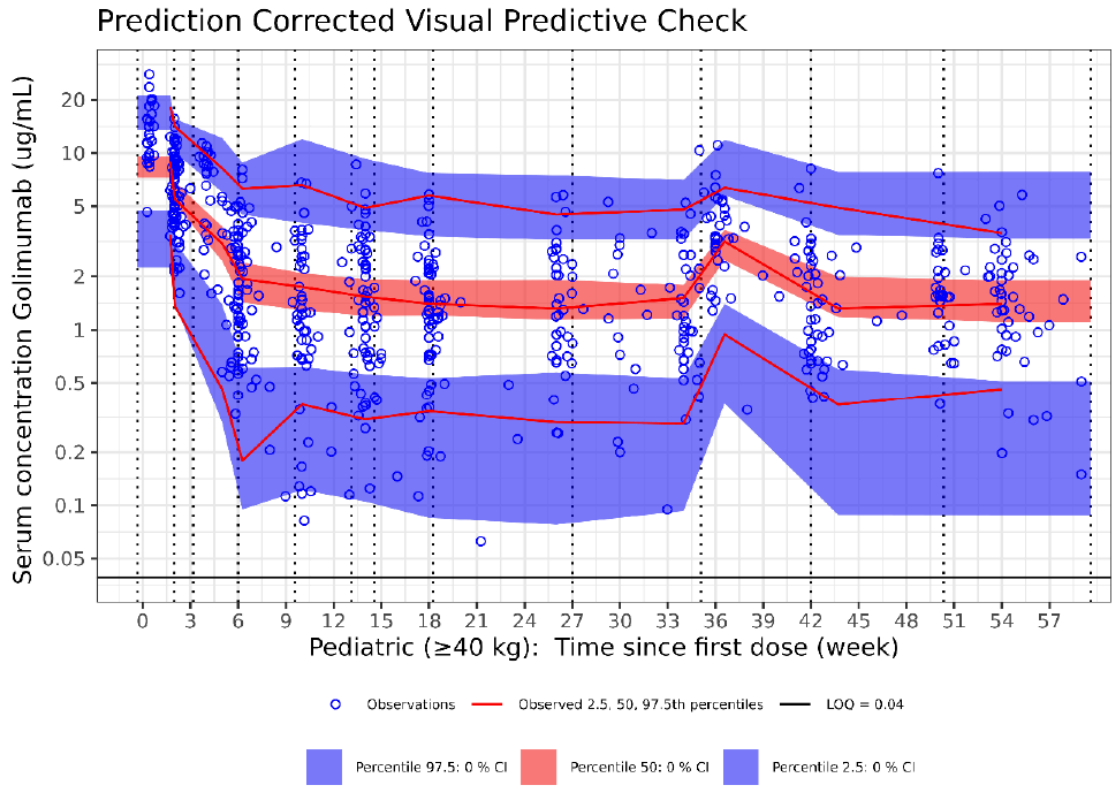
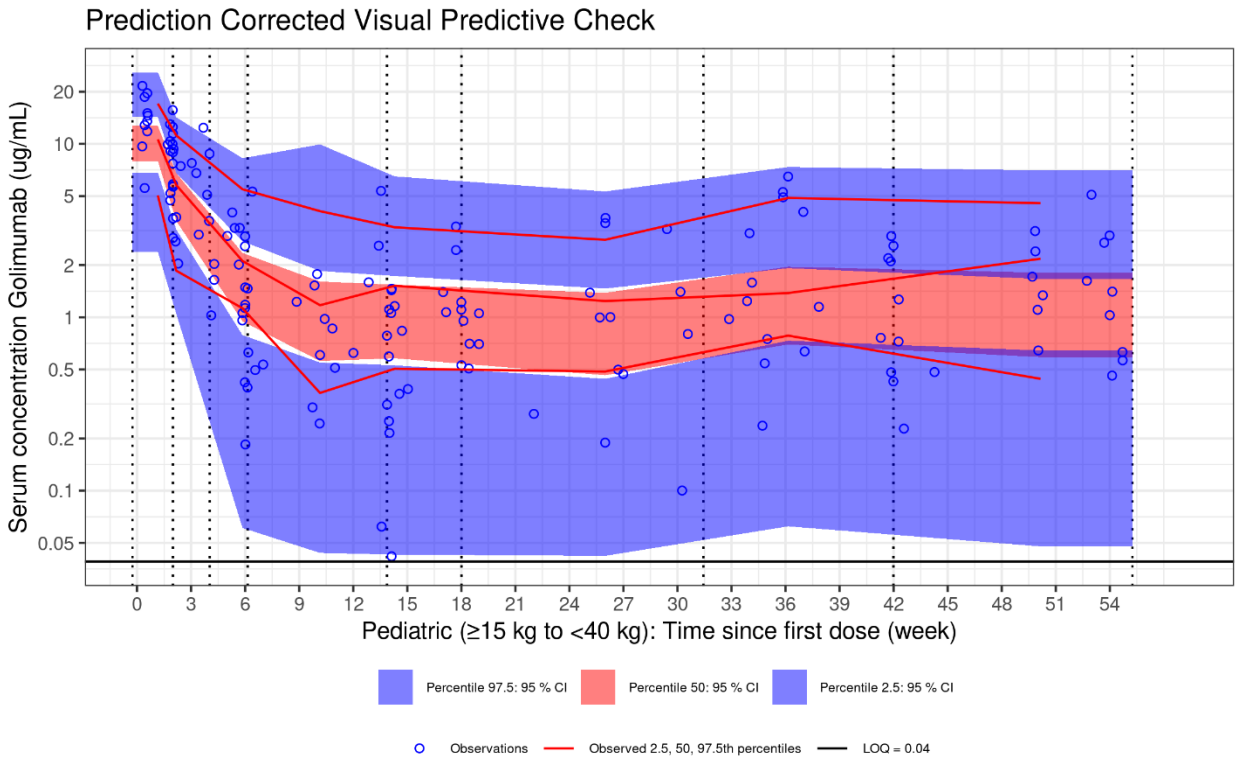


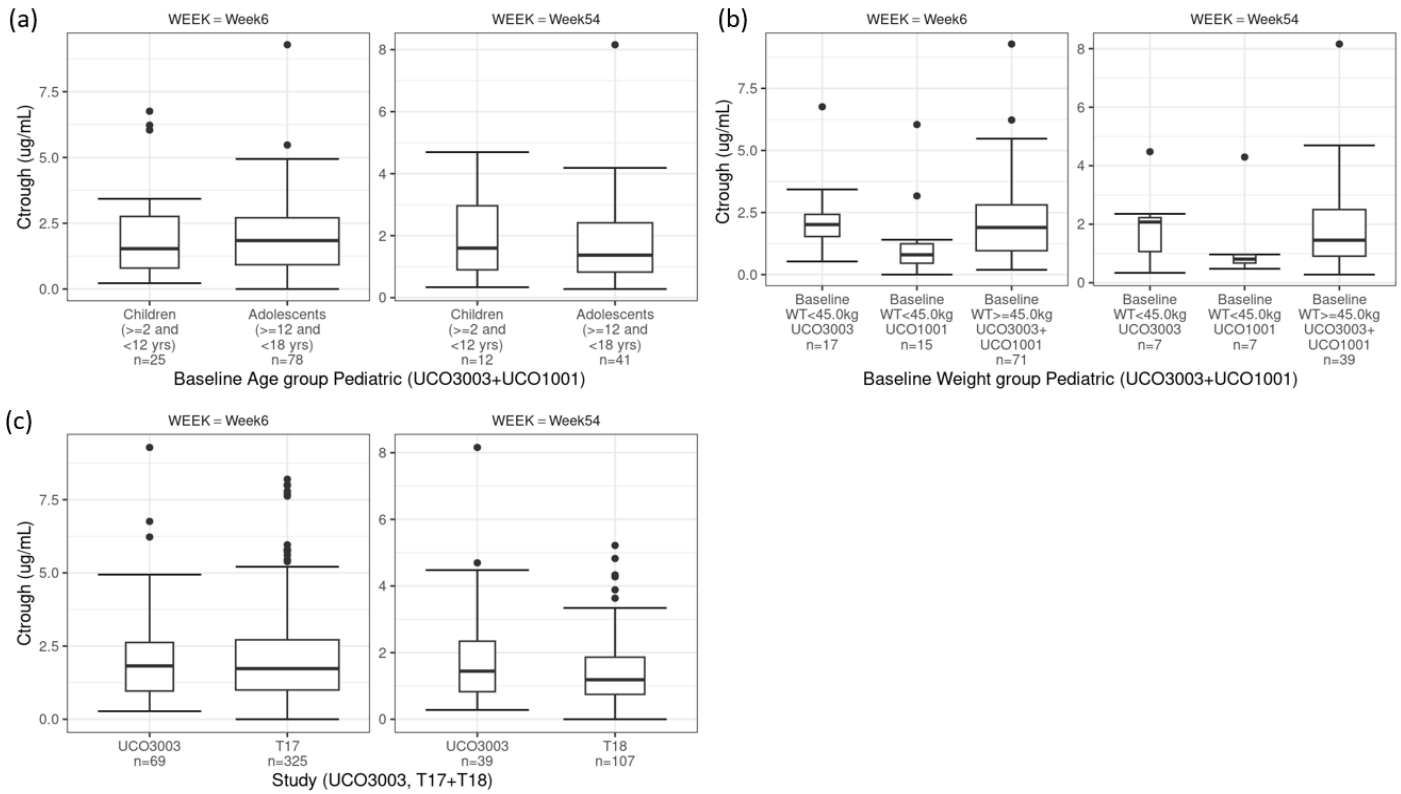
Figure 3: pcVPC for the Paediatric Participants With UC in the ⩾40 kg Body Weight Category (N=82)



Notes: Blue open circles indicate the observed data (the percentile lines of the observed data were not shown due to the limited data points). Blue and red ribbons indicate 95% CIs of the 2.5, 50, and 97.5th percentiles of the simulated data. Vertical dotted lines indicate time bins used to calculate the percentiles. Five hundred simulation replicates were generated to obtain the CIs.

Figure 4: pcVPC for the Paediatric Participants With UC in the ⩾15 – <40 kg Body Weight Category (N=22)

Individual exposure metric parameters in the paediatric and adult participants were simulated using individual estimates of the popPK parameters from the final refined model runs and actual dosage records. As shown in Figure 5, the model-derived trough concentrations ($C_{trough,W6}$ and $C_{trough,W54}$) were comparable between the baseline age groups (adolescents versus children), between the baseline WT groups (<45kg in Study UCO3003 versus ≥45 kg in Studies UCO3003 and UCO1001), and between the studies (Study UCO3003 versus Studies T17 or T18). Among the baseline WT groups, $C_{trough,W6}$ and $C_{trough,W54}$ tended to be lower in the <45 kg group from Study UCO1001, which was considered attributable to the lower dose employed for the <45 kg group in Study UCO1001 (ie, 90 mg/m^2 → 45 mg/m^2 in Study UCO1001 versus 120 mg/m^2 → 60 mg/m^2 in Study UCO3003).



Key: C_{trough}=trough concentration; $C_{trough,W6}$=trough concentration at Week 6; $C_{trough,W54}$=trough concentration at Week 54; n=number of participants; q4w=every 4 weeks; WT=weight; yrs=years.

Notes: For the baseline age group comparison (upper left panels), the pediatric participants in Studies UCO3003 and UCO1001 were stratified by the age category as indicated in the plots. For the baseline WT group comparison (upper right panels), pediatric participants weighing <45 kg were stratified by study, since a different dose was employed in Studies UCO3003 and UCO1001 (ie, UCO3003:120 mg/m^2 [Week 0] to 60 mg/m^2 [Week 2, 6 and q4w thereafter], UCO1001: 90 mg/m^2 [Week 0] to 45 mg/m^2 [Week 2, 6 and q4w thereafter]). The dose for participants weighing ≥45 kg was the same in both studies (200 mg [Week 0] to 100 mg [Week 2, 6 and q4w thereafter]). In the interstudy comparison (bottom left panels), "T17" and "T18" indicate data from the adult UC studies. The adult participants who received 200 mg [Week 0] to 100 mg [Week 2, 6 and q4w thereafter] were included. Study UCO1001 was not included due to the lower dose employed for pediatric participants weighing <45 kg.

Figure 5: Summary of Simulated Serum Golimumab Exposure Metrics: Ctrough,W6 and Ctrough,W54 by Baseline Age Group in Paediatrics (a), Baseline WT Group in Paediatrics (b), and Adults Versus Paediatrics (c)

Pharmacokinetics in target population

Paediatric Study UCO1001

After induction with SC golimumab at week 0 and week 2 in UCO1001, peak serum golimumab concentration was observed at day 4 (median: 13.17 µg/mL; mean: 13.86 µg/mL). The median serum golimumab concentrations were 5.72, 7.61, and 2.64 µg/mL at Weeks 2, 4, and 6, respectively (mean: 6.46, 6.51, and 2.56 µg/mL at weeks 2, 4, and 6, respectively).

In paediatric participants who were in clinical response to golimumab at week 6 and therefore received doses of golimumab at weeks 6 and 10, median serum golimumab concentration at week 14 (a steady-state trough time point) was 1.68 µg/mL (mean: 2.09 µg/mL).

Paediatric Study UCO3003

Following the administration of the SC induction golimumab dose regimen (<45 kg:120 mg/m^2 → 60 mg/m^2; ≥45 kg: 200 mg → 100 mg at weeks 0 and 2, respectively) in UCO3003, median (mean) serum golimumab concentrations at week 6 (the time of the assessment of key induction efficacy endpoints) was 1.56 (2.08) µg/mL.

In the UCO3003 study, median and mean serum golimumab concentrations through week 6 were generally comparable between participants with body weight <45 kg, who received 120 mg/m² at week 0, 60 mg/m² at week 2 and those at ≥ 45 kg receiving doses of 200 mg at week 0, 100 mg at week 2.

Steady-state serum trough golimumab concentration was achieved approximately 10 weeks after starting golimumab treatment.

Comparison of Pharmacokinetics Between Paediatric Participants and Adult Participants with Ulcerative Colitis

Table 4 presents median serum golimumab concentrations through week 6 in paediatric participants (from UCO1001 [>45kg population] and UCO3003 [all weights]) and in adult participants from T17. During induction, median (mean) serum golimumab concentrations in paediatric participants were similar to those in adult participants. Table 5 presents golimumab exposure during maintenance, calculated as the average serum golimumab concentrations at steady-state (from Week 14 to Week 54) between paediatric participants and the adult participants who received 50 mg or 100 mg in maintenance. During maintenance, the median (mean) serum golimumab concentration in paediatric participants (1.50 µg/mL [1.80 µg/mL]) was similar to that in adult participants (1.43 µg/mL [1.63 µg/mL]) who received the 100 mg maintenance dose.

Table 4 Summary of Serum Golimumab Concentrations (µg/mL) From Week 0 Through Week 6; PK Analysis Set During Induction (Studies UCO3003, UCO1001, and T17)

	Golimumab	
	Paediatric UC Studies UCO3003 (all weight) and UCO1001 (≥45 kg)	**Adult UC Study T17 200 mg -> 100 mg**
Analysis set: PK Analysis Set During Induction	87	331
Baseline		
N	87	323
Mean (SD)	0.00 (0.000)	0.02 (0.013)
Median	0.00	0.02
IQ range	(0.0; 0.0)	(0.0; 0.2)
Range	(0.00; 0.00)	(0.02; 0.02)
Week 2		
N	84	322
Mean (SD)	7.33 (3.141)	6.40 (2.899)
Median	7.33	6.27
IQ range	(2.1; 15.7)	(0.2; 19.4)
Range	(4.77; 9.14)	(4.21; 8.09)
Week 6		
N	80	292
Mean (SD)	2.35 (1.702)	2.11 (1.477)
Median	1.93	1.78
IQ range	(0.0; 8.0)	(0.0; 8.9)
Range	(1.00; 3.39)	(1.06; 2.75)

Key: IQ=interquartile; PK=pharmacokinetic(s); SD=standard deviation.

Table 5 Summary of Average Serum Golimumab Concentrations (µg/mL) at Steady State (From Week 14 Through Week 54); PK Responder Analysis Set During Maintenance (Studies UCO3003, UCO1001, and T18)

	Golimumab		
	Paediatric UC Studies	**Adult UC Study T18[a]**	
	UCO3003 (all WT) and UCO1001 (≥45 kg)	**50 mg**	**100 mg**
Analysis set: PK Responder Analysis Set During Maintenance	50	150	152
Average concentration of steady state (from Week 14 through Week 54)[b]			
N[c]	50	137	144
Mean (SD)	1.80 (1.159)	0.83 (0.521)	1.63 (0.959)
Median	1.50	0.76	1.43
IQ range	(0.3; 6.3)	(0.0; 2.7)	(0.0; 5.8)
Range	(1.00; 2.33)	(0.45; 1.12)	(1.03; 1.99)

Key: IQ=interquartile; N=number of participants; PK=pharmacokinetic(s); SD=standard deviation; UC=ulcerative colitis; WT=weight.

Notes:

[a] Includes data up to the time of dose adjustment for those who increased dose.

[b] Steady state (from Week 14 through Week 54) includes time points: Week 14, Week 18, Week 26, Week 34, Week 42, Week 50, Week 54 for UCO3003; Week 14, Week 18, Week 30, Week 42, Week 54 for UCO1001; Week 8 of maintenance, Week 12 of maintenance, Week 20 of maintenance, Week 28 of maintenance, Week 36 of maintenance, Week 44 of maintenance for T18.

[c] Number of participants who had at least one available PK sample among the selected timepoints.

Summary of PopPK results in paediatric UC patients

The observed serum concentration-time profiles following SC administration of golimumab in the paediatric UC participants from Studies UCO3003 and UCO1001 were adequately described by a 1-compartment popPK model with the model parameters refined using data from the adult UC participants from Studies T17 and T18.

- In the refined model, the typical population values of CL/F and V/F for a participant with median baseline WT of 70 kg were 0.948 L/day and 13.5 L, respectively.
- The effect of body weight on CL/F and V/F was described by fixed allometric scaling (exponents 0.75 and 1, respectively). Additional covariates on CL/F were baseline albumin and immune response positive (IRP).
- The model-derived exposure metric parameters were generally comparable between the baseline WT subgroups in the paediatric participants, and between the paediatric and adult studies. The results suggested that the dose regimen investigated in study UCO3003 (<45 kg:120 mg/m² at Week 0, 60 mg/m² at Week 2 and q4w thereafter; ≥45 kg: 200 mg at Week 0, 100 mg at Week 2 and q4w thereafter) achieved appropriate golimumab exposure in the paediatric UC participants, matching the exposure in the adult UC population.

Modelling and Simulation to Support Proposed Dosing Regimen

The administration of the BSA-based dose regimen for the paediatric participants weighing <45 kg employed in Study UCO3003 led to many participants requiring up to 3 injections for the initial Week 0 induction dose and requiring 2 different device presentations (PFS-V and PFS-U). Similarly, for many maintenance doses, up to 2 injections are needed that possibly require 2 different device presentations (PFS-V and PFS-U).

To enable simpler dosing in paediatric UC patients, an alternative dose regimen was explored by PK simulations using the final popPK model (see Population PK section above). The objectives of the model-based simulation analysis were two-fold. First, it proposed fixed dosing for patients ≥40 kg utilising the same dose regimen as studied for participants ≥45 kg in UCO3003, which was consistent with the approved dosing in adult UC patients weighing >80 kg as follows:

- Induction: 200 mg SC at week 0 and 100 mg at week 2
- Maintenance: 100 mg SC q4w beginning at week 6

Second, for participants <40 kg, a simplified weight-based (tiered) dosing approach was proposed, which would include up to 2 device injections for the required induction dose. In addition, only 1 device presentation would be used for each maintenance dose.

To address the abovementioned issues, an alternative dose regimen than was used in UCO3003 is proposed, which provides a simplified and more convenient dosing regimen for paediatric patients (Table 6).

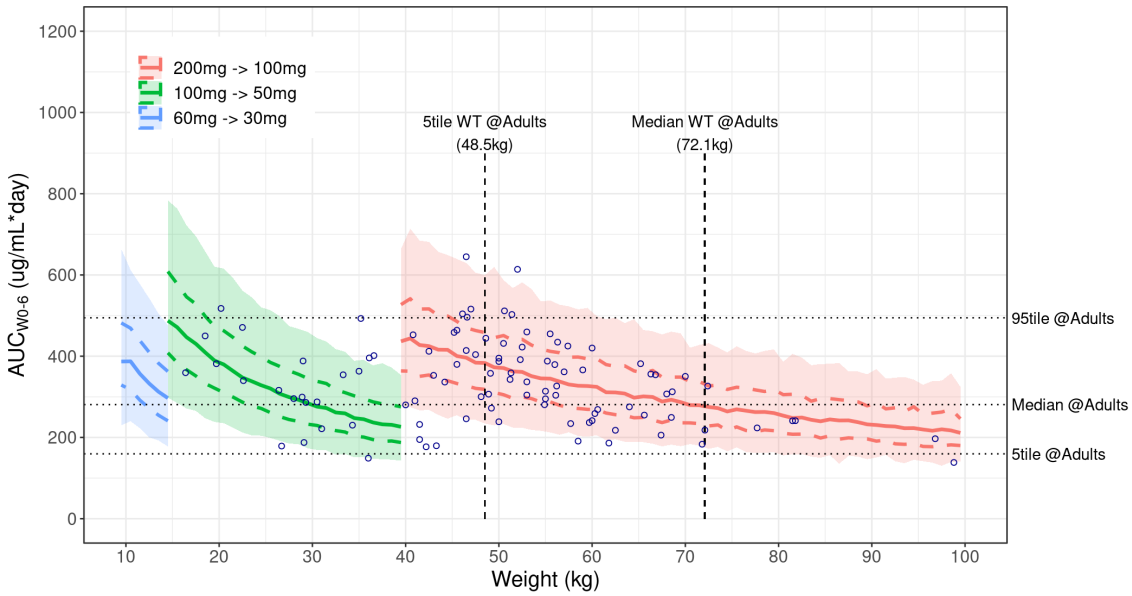
Table 6 Proposed Dose Regimen for Paediatric Patients

Weight Range	Induction Dose Regimen (Week 0 and Week 2)	Maintenance Dose Regimen (Week 6 and q4w thereafter)
≥40 kg	200→100 mg	100 mg q4w
≥15 kg to <40 kg	100→50 mg	50 mg q4w
≥10 kg to <15 kg	60→30 mg	30 mg q4w

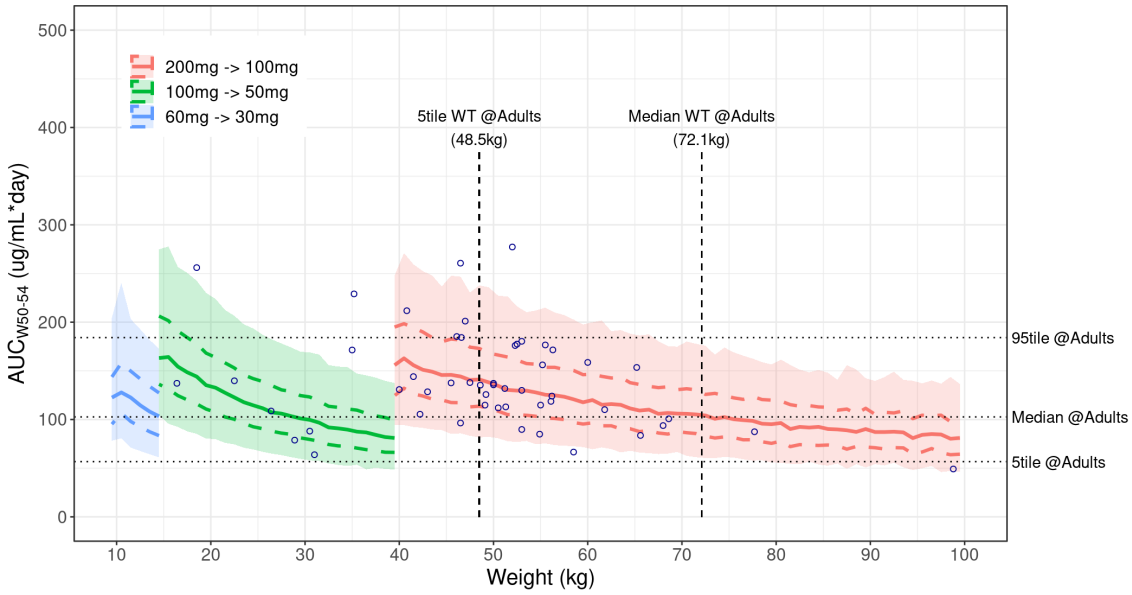
Key: q4w=every 4 weeks.
Notes: In Study UCO3003, participants <45 kg were treated with the BSA-based dose regimen (120→60 mg/m^2 and 60 mg/m^2 q4w thereafter). The adult dose regimen (200→100 mg and 100 mg q4w thereafter) was used for participants ≥45 kg.
Source: Mod5.3.3.5/PopPK-ER Report/TabE2

To support the proposed alternative dose regimen, the predicted golimumab exposure levels in paediatric patients receiving the alternative paediatric dose regimen were compared with the predicted reference exposure levels in the participants from the adult studies (T17 and T18), as well as the individually-predicted exposure levels in paediatric participants from the paediatric studies (UCO3003 and UCO1001). Simulations for the paediatric population were conducted using the final refined popPK model and demographic information (weight linked with age) of the paediatric population sampled from the National Health and Nutrition Examination Survey (NHANES) 2017-2018 database.

The predicted golimumab AUC_{W0-6}, AUC_{W50-54}, $C_{trough,W6}$, and $C_{trough,W54}$ in paediatric patients receiving the alternative golimumab dose regimen compared with the predicted reference exposures in the adult UC patients are presented in Figure 6 and Figure 7, respectively. The predicted golimumab exposures were consistent with the individual predicted exposures of the paediatric participants from studies UCO3003 and UCO1001.



a) AUC AUC_{W0-6}

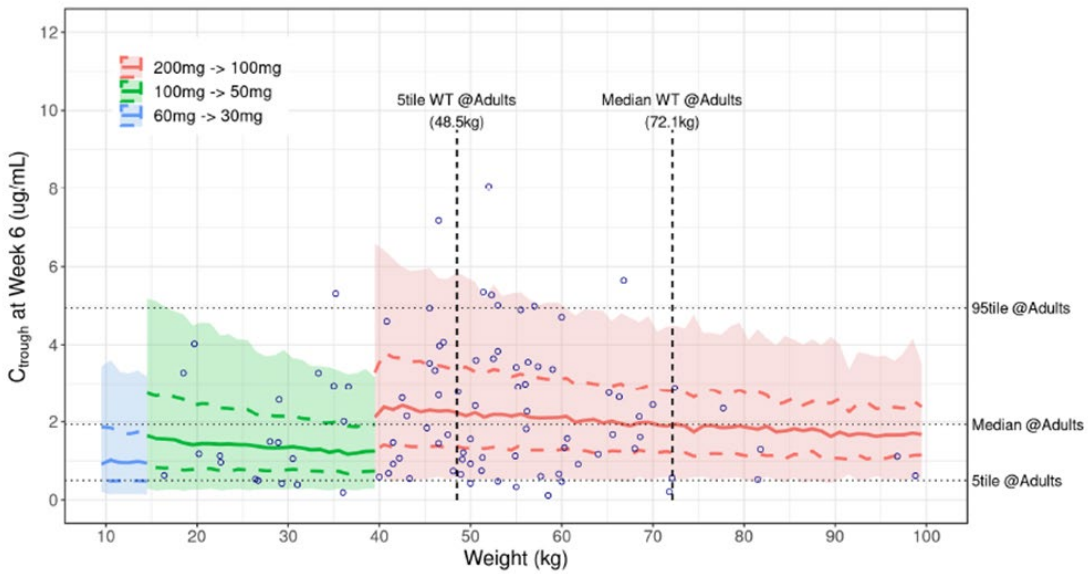


b) AUC_{W50-54}

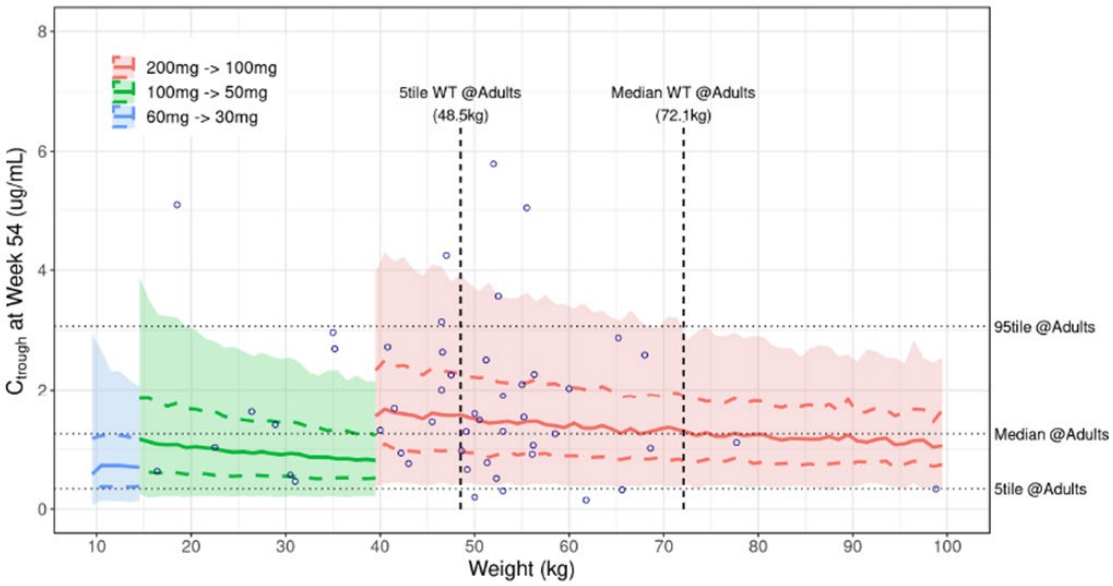
Key: ALB=albumin; AUC=area under the concentration-time curve; AUC_{W0-6}=area under the concentration-time curve from Week 0 to 6; AUC_{W50-54}=area under the concentration-time curve from Week 50 to 54; IRP=immune response (antibodies to golimumab) positive; N=number; NHANES=National Health and Nutrition Examination Survey; PK=pharmacokinetics; q4w=every 4 weeks; UC=ulcerative colitis; WT=weight; 5tile=5th percentile; 95tile=95th percentile.

Notes: Dose labels connected with arrows in legends indicate proposed induction and maintenance doses. The predicted exposure metric parameters in the virtual pediatric population were binned by 1 kg weight to plot the median (colored solid lines), 25-75th percentiles (colored dashed lines), and 5-95th percentiles (colored ribbons) by weight group (distinguished by different colors). Horizontal dotted lines indicate the simulated exposures in the adult patients (Studies T17 and T18) assuming the patients received golimumab doses of 200 mg at Week 0 and 100 mg at Week 2 (induction phase), and 100 mg q4w starting at Week 6 (maintenance phase). Blue open circles indicate individually-predicted AUCs from the pediatric participants (Studies UCO3003 and UCO1001). For the pediatric PK simulation, weight data for N=10,000 per age (in years) were sampled from the NHANES 2017-2018 database. Baseline ALB=4.2 g/dL and IRP=0 were assumed in the simulations.

Figure 6: Simulated Golimumab AUC_{W0-6} and AUC_{W50-54} According to the Alternative Dose Regimen, Binned by Weight Group (Rainbow Plots)



a) $C_{trough,W6}$



b) $C_{trough,W54}$

Key: ALB=albumin; C_{trough}=trough concentration; $C_{trough,W6}$=trough concentration at Week 6; $C_{trough,W54}$=trough concentration at Week 54; IRP=immune response (antibodies to golimumab) positive; N=number; NHANES=National Health and Nutrition Examination Survey; PK=pharmacokinetics; q4w=every 4 weeks; UC=ulcerative colitis; WT=weight; 5tile=5th percentile; 95tile=95th percentile.

Notes: Dose labels connected with arrows in legends indicate proposed induction and maintenance doses. The predicted exposure metric parameters in the virtual pediatric population were binned by 1 kg weight to plot the median (colored solid lines), 25-75th percentiles (colored dashed lines), and 5-95th percentiles (colored ribbons) by weight group (distinguished by different colors). Horizontal dotted lines indicate the simulated exposures in the adult patients (Studies T17 and T18) assuming the patients received golimumab doses of 200 mg at Week 0 and 100 mg at Week 2 (induction phase), and 100 mg q4w starting at Week 6 (maintenance phase). Blue open circles indicate individually-predicted C_{trough} from the pediatric participants (Studies UCO3003 and UCO1001). For the pediatric PK simulation, weight data for N=10,000 per age (in years) were sampled from the NHANES 2017-2018 database. Baseline ALB=4.2 g/dL and IRP=0 were assumed in the simulations.

Figure 7: Simulated Golimumab $C_{trough,W6}$ and $C_{trough,W54}$ According to the Alternative Dose Regimen, Binned by Weight Group (Rainbow Plots)

These results informed the final proposed dose recommendation for paediatric patients. The proposed paediatric dose was optimised to ensure exposure levels consistent with those in the adult UC patients >80 kg. The dose regimen was also optimised from that studied in UCO3003 to weight-tiered fixed dosing for all paediatric patients, as the BSA-based dosing regimen led to many participants requiring 3 injections for the initial week 0 induction dose, including 2 different device presentations.

Immunogenicity

UCO1001

Of 32 golimumab-treated paediatric participants in UCO1001 with appropriate samples, 2 (6.3%) participants were positive for antibodies to golimumab through week 6, with both participants having low titers. One additional paediatric participant tested positive for antibodies to golimumab through Week 14 with a titer of 1:96. All participants who were positive for antibodies to golimumab were also positive for neutralising antibodies.

UCO3003

Among the treated participants in UCO3003 with an appropriate PK sample, 4 (5.8%) tested positive for antibodies to golimumab through week 6, and all with low titers (≤1:24). Of these 4 participants, only 1 (25%) tested positive for neutralising antibodies.

Of the 69 participants treated with golimumab and with an appropriate PK sample, 15 (21.7%) participants were positive for antibodies to golimumab through the final safety visit, with relatively low titers (≤1:96). Of these 15 participants, 3 (20%) participants tested positive for neutralising antibodies.

Comparison of Antibodies to Golimumab Between Paediatric and Adult Participants

The incidence of antibodies to golimumab from week 0 of induction through week 54 of maintenance was comparable between paediatric (UCO1001 and UCO3003) and adult participants (Week 0 of T16/T17 through week 54 of T18) with UC. Using the drug-tolerant EIA, through week 54, 20.2% (21 of 104) of paediatric participants were positive for antibodies to golimumab compared with 21.3% (254 of 1,195) of adult participants. Due to the small number of participants having neutralising antibodies, no formal comparison to adults was performed.

Effect of Antibodies to Golimumab on Pharmacokinetics

Median trough golimumab concentrations in paediatric UC participants were lower in participants who were positive for antibodies to golimumab than in participants who were negative for antibodies to golimumab during induction and maintenance periods.

2.3.3. Pharmacodynamics

Golimumab is a fully human mAb with an immunoglobulin G1 heavy chain isotype and a kappa light chain isotype. Golimumab binds to human TNFα with high affinity and specificity and neutralises TNFα bioactivity.

2.3.4. PK/PD modelling

The objective of the exposure-response (E-R) analysis was:

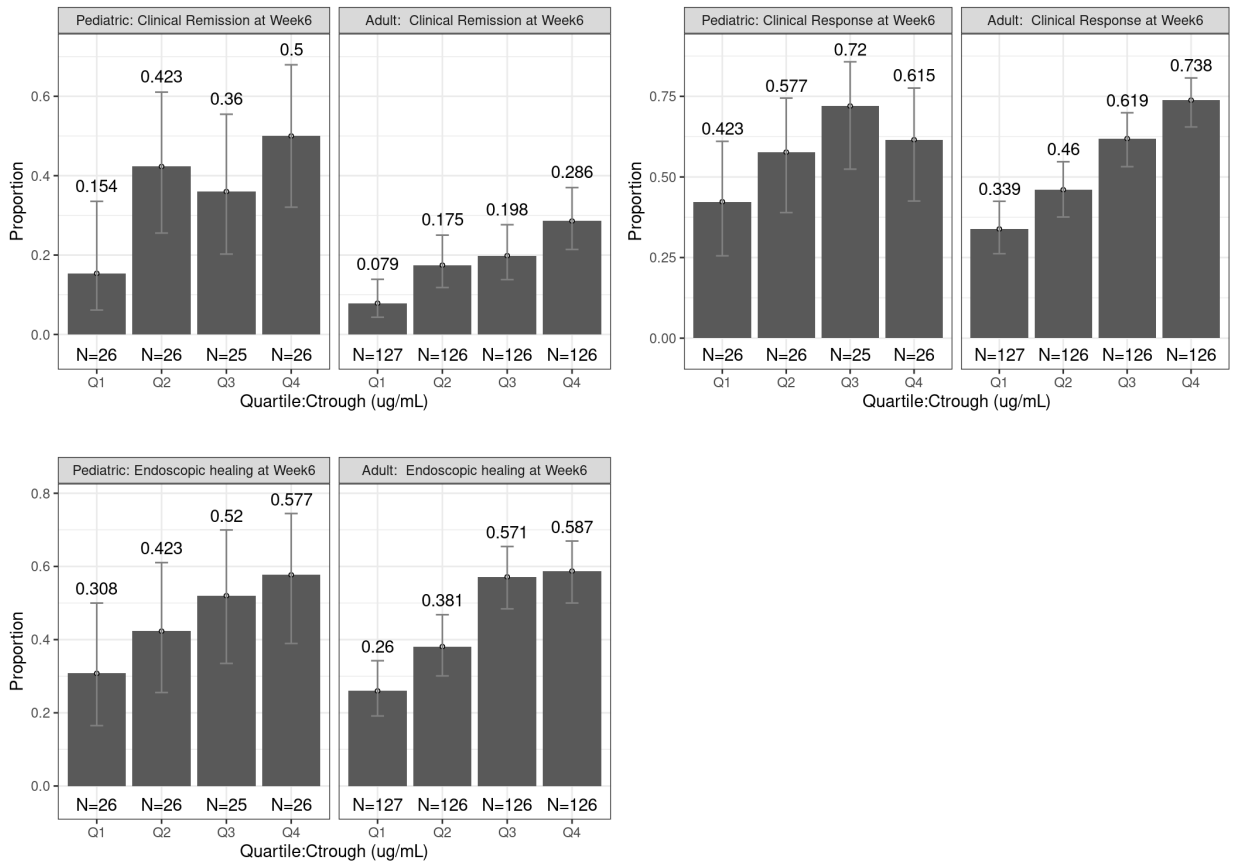
- To explore the exposure-efficacy relationships in the paediatric UC population and assess the similarity of ER between the paediatric and adult UC patients.

An overview of the studies included in the popPK and E-R analyses and the dose regimens investigated in the respective studies are summarised in Table 1. In the paediatric studies, participants with WT <45 kg received the BSA-based doses while participants weighing ≥45 kg received the fixed doses (ie, 200→100 mg for the induction dose regimen and 100 mg q4w for the maintenance dose regimen).

The E-R relationships between the simulated golimumab exposure and the selected efficacy endpoints in the induction and maintenance phases were explored based on data from the paediatric studies UCO3003 and UCO1001. In addition, similarity of the E-R relationships in the paediatric participants to those in the adult participants (from Studies T17 and T18) were assessed by visual comparison. Participants who were included in the efficacy analysis sets and had exposure metric parameters available from the popPK analysis were included in the E-R analysis.

A positive E-R trend was graphically apparent for all selected efficacy endpoints at week 6 (induction phase) across the simulated exposure ($C_{trough,W6}$) quartile groups in paediatric participants from studies UCO3003 and UCO1001 (Figure 8a). The positive E-R trend was also observed in adult participants from study T17 on the corresponding efficacy endpoints at week 6 (Figure 8a). The univariate logistic

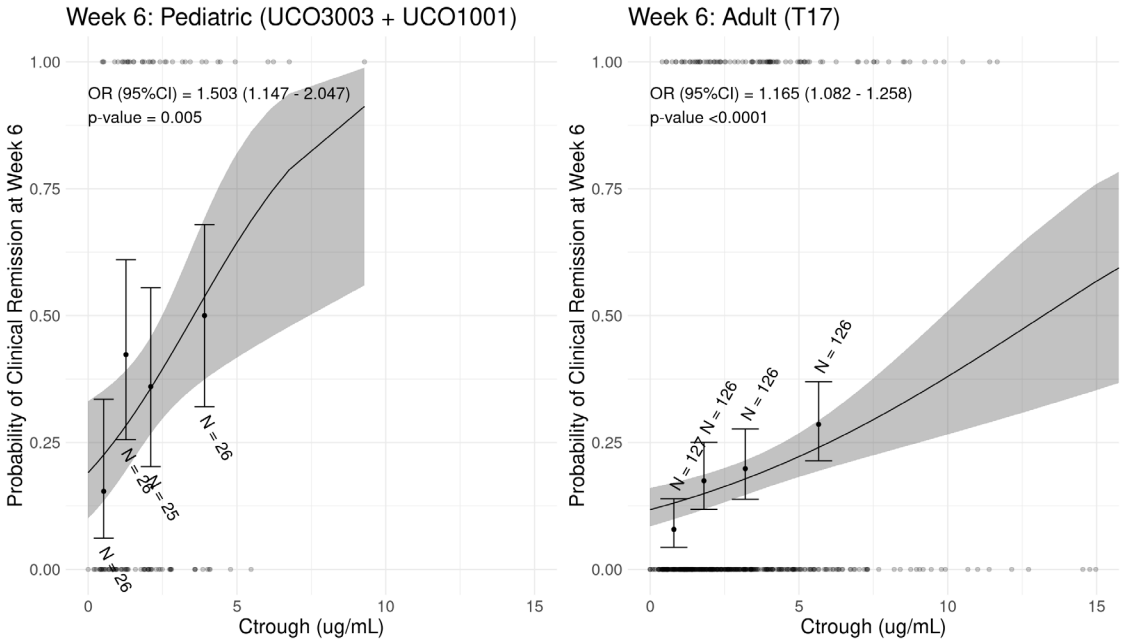
regression on the primary endpoint (clinical remission at week 6 based on Mayo score) supported the positive E-R relationship in the paediatric participants (p=0.005) and adult participants (p<0.0001) (Figure 9b).



(a) Bar plots stratified by exposure quartile in the pediatric and adult participants (top left: clinical remission based on Mayo score, top right: clinical response based on Mayo score, bottom left: endoscopic healing, all at Week 6)

$C_{trough,W6}$ (µg/mL)	Q1	Q2	Q3	Q4
Paediatric (UCO3003 + UCO1001)	(0-0.916)	[0.916-1.82)	[1.82-2.75)	[2.75-9.29)
Adult (T17)	(0-1.28)	[1.28-2.40)	[2.40-4.06)	[4.06-24.1)

Figure 8: Relationships Between the Efficacy Endpoints and the Simulated Exposure Metrics by Exposure Quartile at Week 6 (Induction Phase: Studies UCO3003, UCO1001, T17)



(b) Univariate logistic regression on clinical remission based on Mayo score at Week 6 in the pediatric and adult participants

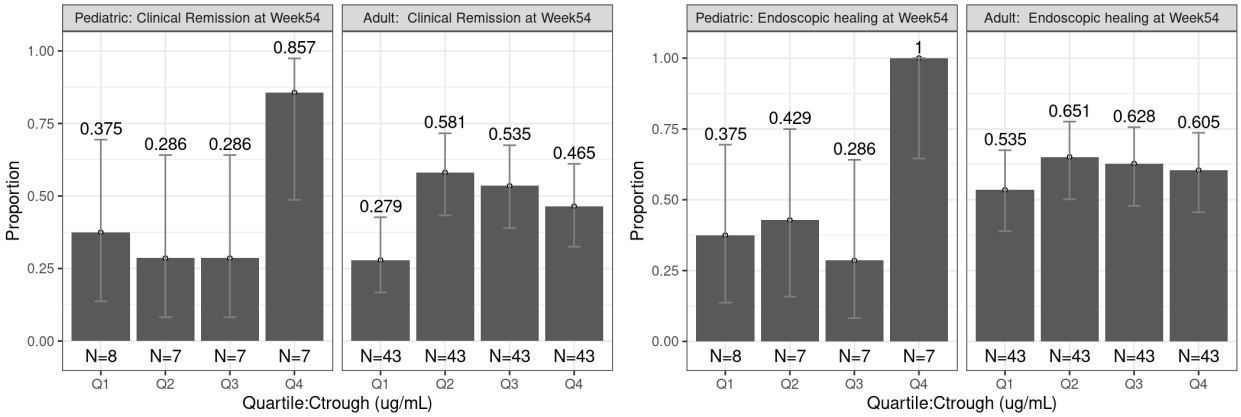
Key: CI=confidence interval; C_{trough}=trough concentration; $C_{trough,W6}$=trough concentration at Week 6; E-R=exposure-response; N=number of participants by quartile; OR=fitted odds ratio of logistic fit; Q1=first quartile of C_{trough}; Q2=second quartile of C_{trough}; Q3=third quartile of C_{trough}; Q4=fourth quartile of C_{trough}.

Notes for panel (a): For each panel block by efficacy endpoint, left panel is for pediatric participant and right panel is for adult participants. Error bars indicate the 95% CI of the calculated proportion. Quartile ranges were independently calculated for the pediatric studies and adult studies. The numerical summaries are provided in the table beneath the figures (round brackets and square brackets indicate including and excluding the value, respectively).

Notes for panel (b): Solid dots with error bars indicate proportion and the 95% CI of responders in the respective exposure quartile groups, plotted at the median exposure value. The smoothed solid lines and ribbons indicate logistic regression model predicted E-R relationships and the 95% CI. Dots at the lower and upper part of the plotting area represent the derived individual $C_{trough,W6}$ in nonresponders and responders for clinical remission at Week 6, respectively. In the adult participants (right panel), 2 data points of $C_{trough,W6}$ >15 µg/mL are not shown in the plot but were included in the logistic regression analysis.

Figure 9: Relationships Between the Efficacy Endpoints and the Simulated Exposure Metrics by Exposure Quartile at Week 6 (Induction Phase: Studies UCO3003, UCO1001, T17)

A clear E-R relationship was not observed in the efficacy endpoints during the maintenance phase: in the adult participants, the proportion of responders did not show a positive E-R relationship across the simulated exposure ($C_{trough,W54}$) quartile groups (Figure 10). In the paediatric participants, the proportion of the responders appeared to be higher in the fourth (ie, highest) quartile of the simulated exposure groups than in the other exposure groups (Figure 10); however, no clear conclusion could be drawn due to high variability of the exposures in the maintenance phase.



Barplots stratified by exposure quartile in the paediatric and adult participants (left: clinical remission based on Mayo score, right: endoscopic healing)

$C_{trough,W54}$ (µg/mL)	Q1	Q2	Q3	Q4
Paediatric (UCO3003)	(0.279-0.827)	[0.827-1.69)	[1.69-2.36)	[2.36-8.16)
Adult (T18)	(0-0.672)	[0.661-1.12)	[1.12-1.68)	[1.68-7.01)

Key: CI=confidence interval; C_{trough}=trough concentration; $C_{trough,W54}$=trough concentration at Week 54; N=number of participants; Q1=first quartile of C_{trough}; Q2=second quartile of C_{trough}; Q3=third quartile of C_{trough}; Q4=fourth quartile of C_{trough}.
Notes: In Study T18, the efficacy assessment during the maintenance phase was conducted at Week 54 of Study T18, which corresponds to 60 weeks after the first induction dose in Study T17. The last golimumab dose before the Week 54 efficacy assessment was given at Week 52 of Study T18. In the plots, the efficacy data at Week 54 of Study T18 and the predicted exposure at Week 52 of Study T18 (ie, 60 and 58 weeks after the first induction dose in Study T17) were used. For each panel block by efficacy endpoint, left panel is for pediatric participant and right panel is for adult participant. Error bars indicate the 95% CI of the calculated proportion. Quartile ranges were independently calculated for the pediatric studies and adult studies. The numerical summaries are provided in the tables beneath the figures (round brackets and square brackets indicate including and excluding the value, respectively).

Figure 10: Relationships Between the Efficacy Endpoints and the Simulated Exposure Metrics by Exposure Quartile in the Maintenance Phase (Studies UCO3003 and T18)

2.3.5. Discussion on clinical pharmacology

The aim with the PK analyses in the paediatric population was to describe golimumab PK in the paediatric UC population and to compare the exposure with the exposure in the adult UC population. Due to the sparse PK sampling in the paediatric studies, population PK modelling was used as the main analysis method.

Adequate methodology has been used in the population PK analysis. The initial popPK model based on adult data was revised to include fixed allometric scaling on CL/F and V/F parameters, methotrexate was removed as a covariate on CL/F and inter-individual variability on the absorption parameter (ka) was also removed due to non-informative data. The revisions were accepted by CHMP. The model evaluations indicated that the paediatric data is sufficiently well described by the model. Since the model was used to simulate a revised dosing regimen it is of importance that the model could adequately describe the PK data across all body weights. The MAH was asked to provide pcVPCs stratified on body weight for the lower body weight group including median and outer percentiles for the observed data to facilitate assessment of model performance. The provided graph indicated that the population PK model was adequate for the lower body weight range.

The exposure comparison between adult and paediatric patients were made using boxplots over and under 45 kg. Upon request, the MAH provided exposure comparisons between the studied dosing regimen in paediatric patients and adults, across body weights. The graphs indicated that the exposure given the BSA-based dosing remains consistently high across body weights.

Exposure predictions for C_{trough} and AUC have also been provided. Although, C_{trough} and AUC are viewed as the exposure metric relevant for efficacy of mAbs, comparison between adult and paediatric C_{max} values (after the first dose and during maintenance administration) was requested to inform the extrapolation of safety. The requested exposure comparison of C_{max} showed similar trends as of those for AUC. In addition, comparisons that reflect the adult reference range where positive B/R has been evaluated, i.e. the full exposure range studied in adult studies T17 and T18 were provided.

The comparison of observed data (average serum concentration) between adult and paediatric patients indicated that the serum concentrations were similar in the induction phase, and in the maintenance phase when comparing with adult patients who received 100 mg. A 50 mg dose is the recommended dose for adults under 80 kg and in comparison with that exposure range, paediatric patients have a doubled serum concentration. The section 5.2 of the SmPC has been updated to reflect this similar or slightly higher serum golimumab exposure in paediatric subjects as compared to adults. The potential safety concern with expected exposure in the paediatric population is addressed in the safety section (section 2.5. .

The adult reference range was equivalent to the dosing regimen for adult patients >80 kg and the MAH stated that the proposed paediatric dosing regimen was optimised to ensure exposure levels consistent with those in the adult UC patients. However, the current reference range did not fully reflect the exposure range where positive B/R has been determined, given that the predicted exposure range in paediatric patients (15-25 kg and 40-60 kg) exceeded the adult reference, and that this is not the recommended exposure range in adult patients <80 kg. It is acknowledged that the paediatric studies were designed to target a high exposure in order to maximise long-term remission rates. However, from an exposure point of view, the main concern is that the paediatric exposure exceed the adult reference range (given 200/100 mg dosing). As such, a proportion of the paediatric patients may experience an exposure that may not be covered by the safety database acquired in adult patients. The MAH therefore proposed the addition of an optional dose reduction which offers an opportunity to decrease the exposure for patients in remission at week 54, this was acceptable. This is further discussed in the safety sections (2.5. and 2.5.1.).

No clinical data was available in the age group <4 years, and less than 16 kg. Thus, the simulated dosing regimen (i.e exposure range) for patients 10-15 kg could not be verified. In combination with the fact that there are limited data in the body weight group of 15-40 kg to inform the model, the simulated exposure below 15 kg was considered uncertain. Furthermore, the predicted exposure for the proposed dosing regimen in the body weight group 10-15 kg was lower than for body weights >15kg and the reasoning for targeting a different exposure range was unclear. Given the uncertainty in the dosing recommendation for 10-15 kg patients, due to lack of observed data and unclear exposure target, CHMP recommended to restrict the indication and dosing recommendation to paediatric patients with a body weight of at least 15 kg.

Similar rates of immune response positive (ADA formation) was observed in the adult and paediatric studies. IRP was retained as a covariate on CL/F in the popPK model, resulting in a lower concentration for patients with IRP.

Mainly graphical analysis to investigate exposure-response relationships has been provided, which was acceptable. The aim with the E-R analysis was to assess similarity between paediatric and adult UC patients. Graphical inspection indicated similar trends between paediatric and adult patients. However,

due to the limited number of paediatric patients, especially in the maintenance phase, the results should be interpreted with caution. The similarity assessment between paediatric and adult patients relies on the exposure comparison.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of golimumab in paediatric UC patients has mainly been described with a population PK analysis. The proposed dosing recommendation is based on modelling and simulation, and subsequent exposure comparison with adult exposure.

The pharmacokinetics of golimumab were similar between paediatric and adult patients with ulcerative colitis. Population pharmacokinetics confirmed that the recommended dosing regimen for Simponi resulted in similar or slightly higher serum golimumab exposure in paediatric subjects as compared to adults across the body weight range.

The proposed dosing recommendation is supported given the possibility to reduce the dose after the induction phase.

However, given the uncertainty in the dosing recommendation for 10-15 kg patients, due to lack of observed data and unclear exposure target, CHMP recommended restricting the indication and dosing recommendation to paediatric patients with a body weight of at least 15 kg.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was performed in the paediatric population.

2.4.2. Main study

Study CNTO148UCO3003 - A phase 3 randomised, open-label study to assess the efficacy, safety, and pharmacokinetics of golimumab treatment, a human anti-TNFα monoclonal antibody, administered subcutaneously in paediatric participants with moderately to severely active ulcerative colitis

Methods

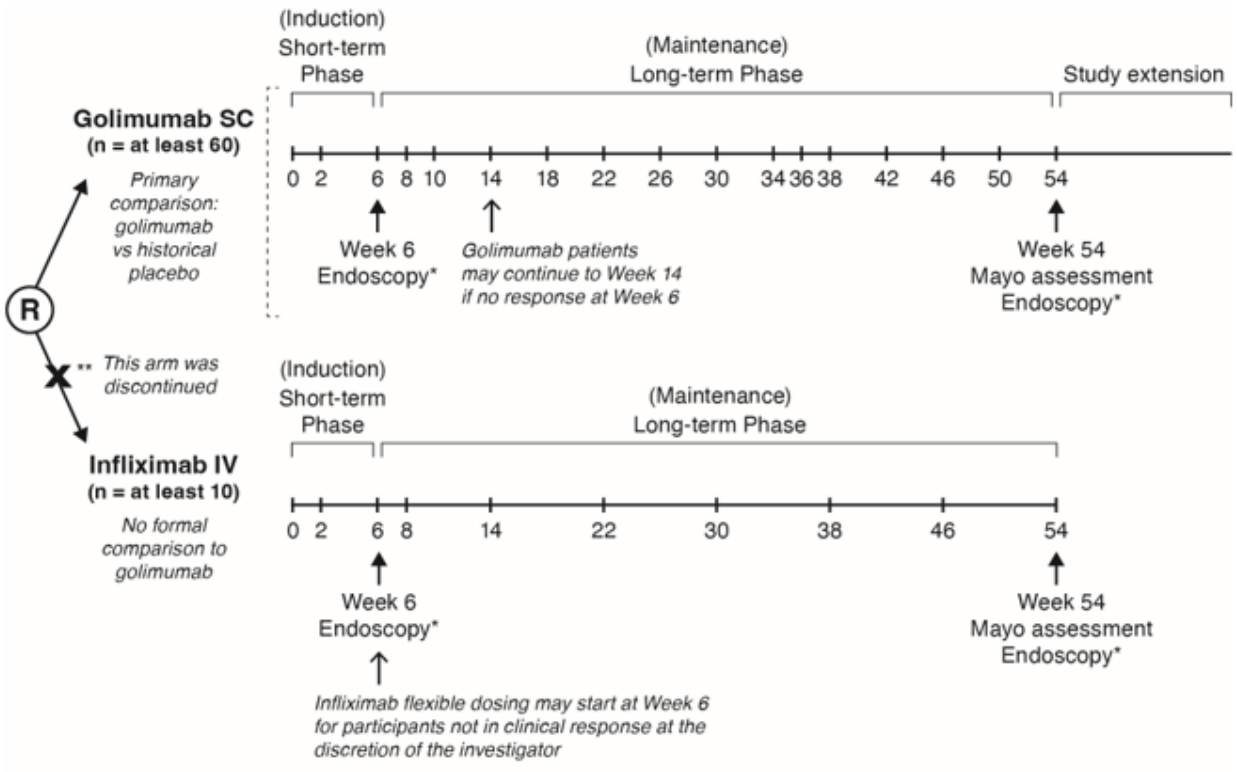
CNTO148UCO3003 is a phase 3 multicentre, open label golimumab study in paediatric participants aged 2 to <18 years with moderately to severely active UC, defined as a baseline full Mayo score of 6 through 12, inclusive, with an endoscopy subs core of ≥2. The Mayo score consists of 4 sub scores (stool frequency, rectal bleeding, endoscopy findings, and physician's global assessment), each of which is rated on a scale from 0 to 3, indicating normal to severe activity. Additionally, all study participants must have demonstrated an inadequate response to, have failed to tolerate, or have a medical contraindication to conventional therapies (ie, IV or oral corticosteroids or the immunomodulators MTX, AZA, or 6-MP). Participants with prior exposure to biologic anti-TNFα agents were ineligible.

Prior to Protocol Amendment 4, participants ≥30 kg were randomised in a 3:1 ratio to golimumab and infliximab, respectively; participants who weighed <30 kg were not randomised and only allocated to the golimumab arm. Enrolment into the infliximab arm was terminated because interpretable

golimumab study data would be available without the infliximab arm, anticipated limited ability to interpret the infliximab data, and updated study feasibility assessments, as agreed as part of PIP Modification 3 (EMEA-000265-PIP02-11-M03) and implemented in the UCO3003 Protocol

This 54-week study consists of a 6-week induction period and a 48-week maintenance period followed by a study extension (for eligible golimumab-treated participants) as presented in Figure 10. The study extension is currently ongoing.

At week 6, participants in clinical response (defined as decrease from baseline in the Mayo score of ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding sub score of ≥1 or a rectal bleeding sub score of 0 or 1) continued to receive open label golimumab during the long-term phase. Participants not in clinical response at week 6 could discontinue study intervention (and complete a safety follow-up at least 16 weeks after the last administration of golimumab) or continue to receive golimumab for up to 2 additional doses at weeks 6 and 10 at the discretion of the investigator. At week 14, these participants were evaluated for partial Mayo response (defined as a decrease from the Week 0 partial Mayo score of ≥3 points); participants in partial Mayo response continued receiving open-label golimumab (q4w) during the long-term phase. Participants who were not partial Mayo responders at week 14 discontinued study intervention and completed a final safety follow-up at least 16 weeks following the last administration of study intervention.



Golimumab at Week 0 and Week 2:
≥ 45 kg: 200 mg → 100 mg
< 45 kg: 120 mg/m² → 60 mg/m² (max 200 mg → 100 mg)

Golimumab every 4 weeks (Weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50):
≥ 45 kg: 100 mg
< 45 kg: 60 mg/m² (max 100 mg)

Infliximab at Week 0 and Week 2:
5 mg/kg infliximab

Infliximab every 8 weeks (Weeks 6, 14, 22, 30, 38, 46):
5 mg/kg infliximab

Infliximab flexible dosing may start at Week 6 for participants not in clinical response at the discretion of the investigator; the first step is increase to 10 mg/kg (dosing escalation is unapproved) and next step (if needed) is shorten dosing interval to every 4 weeks. Interval change should not occur before Week 14.

* Endoscopy will include central and local readings.
** Upon implementation of Amendment 4, no new participants will be randomized to the infliximab arm.

1365_v22

Figure 11: Study schema for CNTO148UCO3003

Study participants

A summary of the main inclusion criteria is provided:

Main inclusion criteria

1. Must be 2 to 17 years of age (at the time of the first administration of study intervention at Week 0) of either gender with a body weight ≥10 kg and >70 cm height.

2. Must have had UC diagnosed for at least 1 month prior to screening.

3. Must have the diagnosis of UC confirmed by a prior endoscopic biopsy that is consistent with a diagnosis of UC (eg, crypt distortion, crypt abscess, goblet cell depletion, and continuous distribution).

4. Must have moderately to severely active UC (as defined by baseline Mayo score of 6 through 12 [endoscopy {sigmoidoscopy or colonoscopy} subscore assigned by local endoscopist], inclusive).

5. Must have a Mayo endoscopy (sigmoidoscopy or colonoscopy) subscore ≥2 (subscore assigned by local endoscopist) at baseline endoscopy (indicative of moderately to severely active UC). Baseline endoscopy (sigmoidoscopy or colonoscopy) must be performed with study software and occur no more than 2 weeks before first study intervention administration.

Exclusion criteria

1. Have severe, extensive colitis.

2. Participants with very severe active UC disease who are currently hospitalised for UC disease exacerbation when initiating study screening and who have a Mayo score of 12 should be excluded from the study.

3. History of liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric (including suicidality), or metabolic disturbances.

4. Presence or history of any malignancy or macrophage activation syndrome or hemophagocytic lymphohistiocytosis.

5. Contraindications to the use of golimumab or infliximab or anti-TNFα therapy per local prescribing information.

6. Taken any disallowed therapies before the planned first dose of study intervention.

7. Pregnant, or breast feeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study intervention.

8. Have received concomitant or previous medical therapies (e.g. any anti-TNFα biologic agents)

9. Have infections or predisposition to infections

10. Have coexisting medical conditions or past medical history (e.g. known allergies, a known hypersensitivity to human immunoglobulin proteins or other components of golimumab)

Treatments

Golimumab was supplied as a sterile liquid for SC injection in single use prefilled syringe (PFS-U, UltraSafe) or prefilled pen (PFP-V [also referred to as PFS-V], VarioJect). Each PFS-U contains either 100 mg or 50 mg of golimumab, with each 0.1 mL of liquid containing 10 mg of golimumab. The prefilled pen for paediatric use can deliver a dose between 10 and 45 mg in 5 mg increments.

Paediatric participants received SC golimumab according to the table below.

Table 7: Golimumab Dosing Schedule

Body Weight	Induction phase	Maintenance phase†
<45 kg	120 mg/m^2 at Week 0* 60 mg/m^2 at Week 2*	60 mg/m^2 every 4 weeks from Week 6*†
≥45 kg	200 mg at Week 0 100 mg at Week 2	100 mg every 4 weeks from Week 6†
† Participants in clinical response to golimumab at Week 6 or partial Mayo response at Week 14 *BSA doses are capped at 200 mg and 100 mg for the 120 mg/m^2 and 60 mg/m^2 doses, respectively.		

Participants' golimumab doses for all administrations through week 10 (inclusive) were based on the participants' weight and height at week 0 or the most recent height and weight from screening. Golimumab doses from week 14 through week 54 were based on the participants' weight and height obtained with that week's visit or the last recorded height and weight.

At entry into the study extension (week 54) or any time thereafter during the study extension, participants had the option to decrease their dose one-time, at the discretion of the investigator, to mimic the approved local product label for adult UC. After this decrease in dose, participants could, at the discretion of the investigator, resume their original study intervention dosage, but no further dose adjustments were permitted while the participant was enrolled in the study.

Concomitant therapy

The following were permitted medications:

- Over-the-counter medications, vitamins, herbal supplements
- Prescription therapies, including antibiotics, special diets or dietary supplements

The following concomitant medications for UC were allowed: 5-ASAs, corticosteroids, and immunomodulators (ie, 6-MP, AZA, MTX). For participants receiving concomitant therapy with 5-ASAs, immunomodulators and/or corticosteroids for UC, the dosage of these medications had to be stable for 2 weeks before the first administration of study intervention at week 0. Immunomodulators (ie, 6-MP, AZA, or MTX) were not allowed to be initiated between week 0 and week 6. For participants receiving immunomodulators at week 0, dose increase was not allowed (except for weight-based adjustments) through week 6.

Objectives

Primary Objectives

- To evaluate the efficacy of golimumab in inducing clinical remission as assessed by the full Mayo score (or total Mayo score, hereafter referred as Mayo score) in paediatric participants with moderately to severely active UC.
- To evaluate the safety profile of golimumab in paediatric participants with moderately to severely active UC.

Secondary Objectives

- To evaluate the efficacy of golimumab in inducing clinical response as assessed by the Mayo Score and clinical remission as measured by the Paediatric Ulcerative Colitis Activity Index (PUCAI) Score.
- To evaluate the efficacy of golimumab on endoscopic healing.
- To evaluate the efficacy of golimumab during the maintenance (long-term) phase.
- To evaluate the effect of golimumab on additional efficacy and QoL measures.
- To evaluate the PK and exposure response of golimumab during induction (short-term) and maintenance phases.

Additional Objective (Usability Assessment Sub study)

- To evaluate the potential for at home use of golimumab in the participant population during the Usability Assessment Sub study.

Outcomes/endpoints

Primary Endpoint

The primary endpoint was clinical remission at week 6 as assessed by the Mayo score. Clinical remission as measured by the Mayo score was defined as a Mayo score ≤2 points, with no individual sub score >1 (based on Mayo endoscopy sub score assigned by the local endoscopist).

Major Secondary Endpoints

For endpoints beyond Week 6, analyses were performed on participants who were in clinical response at week 6 as assessed by the Mayo score.

1. Symptomatic remission at week 54 (Mayo stool frequency sub score of 0 or 1 and a rectal bleeding sub score of 0).

2. Clinical remission at week 54 as assessed by the Mayo score (based on Mayo endoscopy sub score assigned by the local endoscopist: Mayo score ≤2 points, with no individual sub score >1).

3. Clinical remission at week 54 as assessed by the PUCAI score (PUCAI score <10).

4. Clinical remission at week 6 as assessed by the PUCAI score (PUCAI score <10).

5. Clinical response at week 6 as assessed by the Mayo score (based on Mayo endoscopy sub score assigned by the local endoscopist: decrease from baseline score of ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding sub score of ≥1 or a rectal bleeding sub score of 0 or 1).

6. Endoscopic healing at week 6 (based on Mayo endoscopy sub score assigned by the local endoscopist: endoscopy sub score of 0 or 1).

7. Endoscopic healing at week 54 (based on Mayo endoscopy sub score assigned by the local endoscopist: endoscopy sub score of 0 or 1).

8. Clinical remission at week 54, as assessed by the Mayo score, for participants who were in clinical remission at Week 6 (based on Mayo endoscopy sub score assigned by the local endoscopist: Mayo score ≤2 points, with no individual sub score >1).

9. Participants who were not receiving corticosteroids for at least 12 Weeks prior to Week 54 and in corticosteroid-free clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy sub score assigned by the local endoscopist: Mayo score ≤2 points, with no individual sub score >1).

Other Endpoints Related to Inflammatory Markers and HRQoL

1. Change from baseline for CRP concentration during induction phase and maintenance phase.

2. Change from baseline for faecal calprotectin concentration during induction phase and maintenance phase.

3. Change from baseline for IMPACT III scores during induction phase and maintenance phase.

Sample size

Initially, approximately 125 participants were to be included in UCO3003. Of these, at least 5 participants <30 kg were to receive golimumab, and the remaining 120 participants were to be randomised 3:1 to golimumab (90 participants) or infliximab (30 participants). With removal of the infliximab arm per the amended study design (UCO3003 Protocol Amendment 4), 100 participants were to be included (90 participants to receive golimumab, and at least 10 participants to receive infliximab). The golimumab sample size was further reduced from 90 to at least 60 golimumab participants for a total of at least 70 participants (minimum 60 golimumab + minimum 10 infliximab) in Protocol Amendment 5 as agreed upon by EMA. The final design included 60 golimumab participants, of which at least 15 were to have a body weight <45 kg and at least 5 were to have a body weight <30 kg.

Randomisation

Prior to Protocol Amendment 4, participants ≥30 kg were randomised in a 3:1 ratio to golimumab and infliximab, respectively; participants who weighed <30 kg were not randomised and only allocated to the golimumab arm. Upon implementation of Protocol Amendment 4, all newly enrolled participants received golimumab.

Blinding (masking)

The study was open label.

Statistical methods

The primary analysis was based on the proportion of paediatric participants who received golimumab and who were in clinical remission at Week 6 based on the Mayo score (endoscopy sub score assigned by local endoscopist) and its associated 90% confidence interval (CI) using the asymptotic formula based on the normal approximation to the binomial distribution. The criteria for the primary analysis were met if the lower limit of the two-sided 90% CI for the proportion of paediatric golimumab participants in clinical remission at Week 6 was greater than the upper bound of the 95% CI for the historical placebo control (ie, >10.0%) estimated with a fixed- effects meta-analysis using inverse-variance weighting method.

For the purpose of the meta-analyses for the placebo rate to be descriptively compared with the primary endpoint, Clinical Remission at Week 6, studies were chosen that met the following criteria:

1. Studies that had a similar adult patient population

2. Studies that had similar trial design

3. Studies with similar definition for the primary efficacy endpoint

4. Studies with route of administration IV or SC

5. Phase 3, global clinical studies

6. Studies with endpoint ~6 weeks after study start 7. Studies that used local endoscopic assessment

Adalimumab, infliximab, golimumab, and vedolizumab are the only biologic products approved to treat adult UC that fit the above criteria. Thus, seven phase 3 adult studies were identified (golimumab [C0524T16 and C0524T17], and five phase 3 adult UC studies including infliximab [C0168T37 and C0168T46], adalimumab [ULTRA 1 and ULTRA 2], and vedolizumab [GEMINI 1]) that enrolled TNF naïve UC participants (as the primary population or included as a subpopulation). Data from these studies were included in the meta-analysis (Table 8) to estimate the historical placebo rate.

Table 8 Characteristics of Past Ulcerative Colitis Studies in Adult Participants with Moderately to Severely Active Ulcerative Colitis, timing of clinical remission endpoint ~6 weeks after study start

Study	Population	Route of Administration /Dosing Strategy for Induction	Timing of Clinical Remission Endpoint	Clinical Remission Definition	Placebo Point Estimate	Point Estimate for Active Labeled Dose
REMICADE ACT 1*$ (C0168T37)	Naïve to TNF	IV Weeks 0, 2, 6	Week 8	Mayo score ≤2 with no individual subscore >1	14.9% (n=121)	38.8% (n=121)
REMICADE ACT 2*$ (C0168T46)	Naïve to TNF	IV Weeks 0, 2, 6	Week 8	Mayo score ≤2 with no individual subscore >1	5.7% (n=123)	33.9% (n=121)
Adalimumab – ULTRA 1*$	Naïve to TNF	SC 160 mg at Week 0, 80 mg at Week 2, then 40 mg every other week starting at Week 4	Week 8	Mayo score ≤2 with no individual subscore >1	9.2% (n=130)	18.5% (n=130)
Adalimumab – ULTRA 2*$	Naïve to TNF subset	SC 160 mg at Week 0, 80 mg at Week 2, then 40 mg every other week starting at Week 4	Week 8	Mayo score ≤2 with no individual subscore >1	11.0% (n=145)	21.3% (n=150)
SIMPONI PURSUIT IV*$ (CO524T16)	Naïve to TNF	IV Week 0	Week 6	Mayo score ≤2 with no individual subscore >1	11.0% (n=73)	16.0% for 2 mg/kg (n=75)
SIMPONI PURSUIT	Naïve to	SC Weeks 0, 2	Week 6	Mayo score ≤2	6.4% (n=251)	17.8% (n=253)

Study	Population	Route of Administration /Dosing Strategy for Induction	Timing of Clinical Remission Endpoint	Clinical Remission Definition	Placebo Point Estimate	Point Estimate for Active Labeled Dose
SC*$ (C0524T17)	TNF			with no individual subscore >1	Randomized participants in Part 2 of C0524T17 after the dose selection 7.2% in all rand (n=320); used in the meta-analysis	Randomized participants in Part 2 of C0524T17 after the dose selection; assumed clinical remission rate for the pediatric study 17.9% in all rand (n=324)
Vedolizumab (GEMINI 1) *$	Naïve to TNF subset	IV Weeks 0, 2	Week 6	Mayo score ≤2 with no individual subscore >1	6.6% (n=76)	23.1% (n=130)
Ustekinumab (UNIFI) $	Naïve to TNF subset	IV Week 0	Week 8	Mayo score ≤2 with no individual subscore >1	9.9% (n=151)	30% for 130 mg/kg (n=145) 27% for 5 mg/kg (n=147)

All efficacy analyses were descriptive with no hypothesis testing. The following analyses were conducted :

- Side-by-side presentations for the individual paediatric studies UCO1001 and UCO3003 for induction endpoints through Week 6.
- Pooled data from paediatric studies UCO1001 and UCO3003 were evaluated for key efficacy endpoints at week 6 (Clinical Remission at week 6 as assessed by the Mayo Score, Clinical Remission at week 6 as Assessed by the PUCAI Score, Clinical Response at week 6, Endoscopic/Mucosal Healing at week 6) and summarised by age (2 to <12, 12 to <18) and by weight (<45 kg, ≥45 kg).
- Subgroup analyses were provided to examine the consistency of the primary endpoint across subgroups defined by demographics, clinical disease characteristics, and concomitant medication use.

Comparisons of Efficacy Between Golimumab Paediatric UC Studies and Adult UC Studies

- Comparison of E-R relationship for the paediatric population and the adult population.
- Side-by-side descriptive comparisons between combined paediatric studies UCO3003 and UCO1001 and adult UC study T17 for key efficacy endpoints during induction, through Week 6.
- Side-by-side descriptive comparisons between study UCO3003 and adult UC study T18 (including T16 and T17 randomized participants entering the maintenance phase) for key efficacy endpoints during maintenance, through week 54.

Results

Participant flow

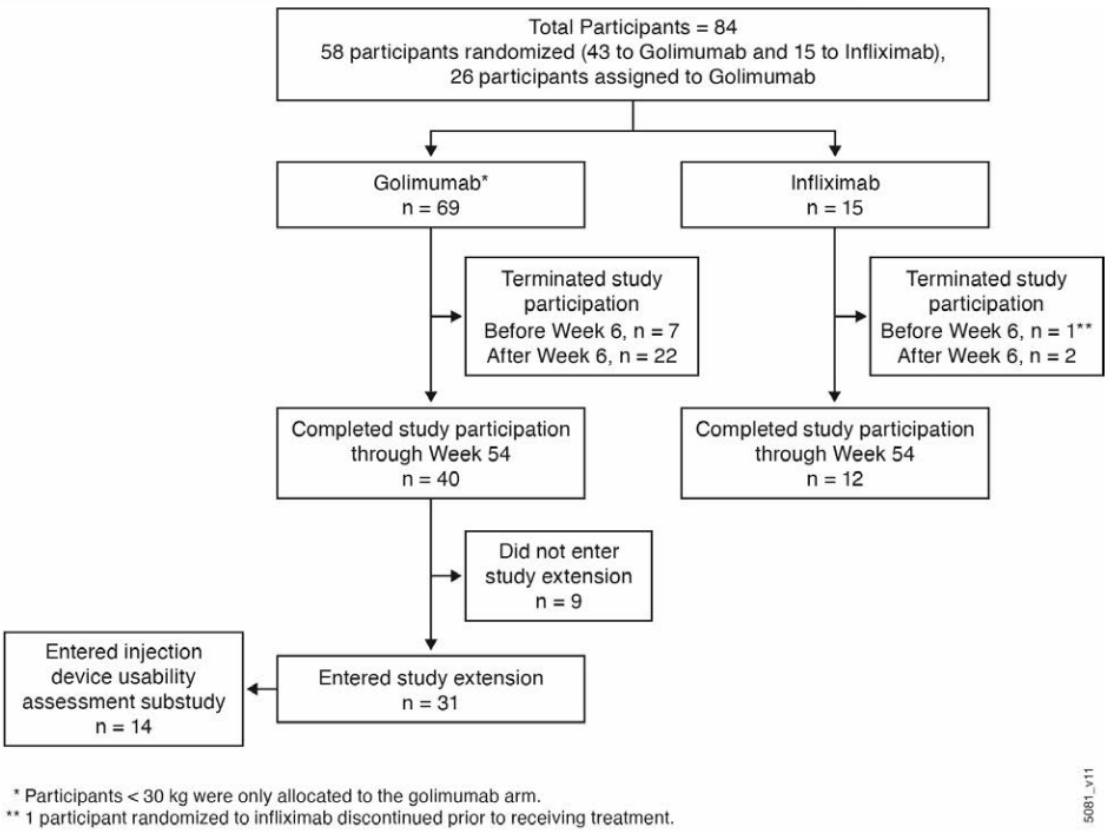


Figure 12: Subject Disposition During the Induction and Maintenance Phases

Table 9: Study Disposition From Week 0 Through Final Safety Visit; Safety Golimumab Analysis Set (Study NTO148UCO3003)

	Golimumab
Analysis set: Safety Golimumab	69
Subjects treated	69
Terminated study participation prematurely from week 0 through final safety visit	32 (46.4%)
Reason for termination	
Adverse event	2 (2.9%)
Adverse event - worsening of UC disease	15 (21.7%)
Death	0
Disease relapse	0
Initiated prohibited medication	1 (1.4%)
Lack of efficacy	8 (11.6%)
Lost to follow-up	1 (1.4%)
Non-compliance with study drug	0
Physician decision	1 (1.4%)
Pregnancy	0
Product quality complaint	0
Protocol deviation	1 (1.4%)
Recovery	0
Study terminated by sponsor	0
Subject refused further study treatment	0
UC surgery/ procedure	0
Site terminated by sponsor	0
Withdrawal by parent or guardian	1 (1.4%)
Withdrawal by legally authorized representative	0
Withdrawal by subject	0
Enrolling in another study	0
Lack of improvement	0
Lack of transportation	0
Loss of informant	0
Moving	0
Study tests too hard	0
Other	0
Other	2 (2.9%)
COVID-19 related	0
No mucosal healing achieved	1 (1.4%)
PI decision, disease progression	1 (1.4%)

Recruitment

Study Initiation Date: 20 December 2018 (date first participant was screened)

Study Completion Date: Not applicable, study extension is ongoing

This study was conducted at 27 centres that enrolled participants in Belgium, Brazil, France, Israel, Italy, South Korea, Poland, Spain, and the United States.

Conduct of the study

There were 6 amendments to the study.

Table 10: Summary of changes table.

Amendment (date)	Overall Rationale for the Amendment
Amendment 6 (11 November 2023)	Upon implementation of this amendment, laboratory assessments will be streamlined and PUCAI will be eliminated after Week 90 to reduce subject burden while maintaining collection of meaningful safety data during the study extension.
Amendment 5 (14 October 2022)	Upon implementation of Amendment 5, no new participants will be enrolled. The sample size is being reduced from n=90 to n=60 golimumab-treated participants as 60 participants will provide sufficient safety, efficacy, and PK data.
Amendment 4 (16 March 2021)	Upon implementation of Amendment 4, no additional participants will be randomised to infliximab; all newly enrolled participants will receive golimumab. Participants already randomized to the infliximab arm prior to Amendment 4 implementation will continue treatment and remain in the study, but no newly enrolled participants will be randomized to infliximab.
Amendment 3 (8 Jul 2019)	To incorporate the following changes: 1) changed the allowable timeframe for a chest radiograph prior to screening for assessment of undiagnosed medical conditions in the exclusion criteria and clarified the rationale for having a chest radiograph; and 2) clarified permitted allowable nutrition in the inclusion criteria for participants with UC who may enrol in the study.
Amendment 2 (13 May 2019)	To incorporate the following changes: 1) expansion of the Usability Assessment Substudy to additional countries instead of US only; 2) added a major secondary endpoint and modified the order of the major secondary endpoints per FDA request; and 3) updated the blood sampling scheme to comply with allowable blood sample volumes with the EU guideline on clinical trials conducted with minors. Clarification of wording and editorial updates were made to improve readability.
Amendment 1 (27 June 2018)	An important exclusion criterion was inadvertently included as an inclusion criterion. This correction together with other changes to improve structure and readability of the document have been made.

Baseline data

Table 11: Summary of Demographics at Baseline; Full Golimumab 1 Analysis Set (Study CNTO148UCO3003)

	Golimumab
Analysis set: Full Golimumab 1	69
Age, years	
N	69
Mean (SD)	13.4 (3.30)
Median	14.0
Range	(4; 17)
2 - <12 years	15 (21.7%)
2 - <6 years	2 (2.9%)
6 - <12 years	13 (18.8%)
12 - <18 years	54 (78.3%)
Sex	
N	69
Female	37 (53.6%)
Race	
N	69
Asian	12 (17.4%)
Black or African American	2 (2.9%)
White	50 (72.5%)
Weight, kg	
N	69
Mean (SD)	52.4 (17.55)
Median	51.2
Range	(16; 107)
<45 kg	17 (24.6%)
<30 kg	8 (11.6%)
≥30 - <45 kg	9 (13.0%)
≥45 kg	52 (75.4%)
Region	
N	69
Asian	
N	12 (17.4%)
Korea	12 (17.4%)
Europe	
N	32 (46.4%)
Belgium	3 (4.3%)
Poland	16 (23.2%)
France	1 (1.4%)
Italy	9 (13.0%)
Spain	3 (4.3%)
North America	
N	4 (5.8%)
United States	4 (5.8%)
Rest of World	
N	21 (30.4%)
Brazil	11 (15.9%)
Israel	10 (14.5%)

Table 12: Summary of Baseline UC Disease Characteristics; Full Golimumab 1 Analysis Set (Study CNTO148UCO3003

	Golimumab
Analysis set: Full Golimumab 1	69
UC disease duration, years	
N	69
Median (Range)	1.43 (0.2; 7.8)
UC symptoms duration prior to diagnosis (months)	
N	69
Median (Range)	3.0 (0; 149)
Mayo Score	
N	69
Median (Range)	7.0 (5; 11)
Severity of disease by Mayo Score	
N	69
No or mild disease: <6	2 (2.9%)
No disease: ≤2	0
Mild disease: ≥3 - ≤5	2 (2.9%)
Moderate: ≥6 - ≤10	63 (91.3%)
Severe: >10	4 (5.8%)
Pediatric ulcerative colitis activity index (PUCAI) Score	
N	69
Median (Range)	40.0 (0; 85)
Severity of disease by PUCAI Score	
N	69
No or mild disease: ≤34	21 (30.4%)
No disease: <10	1 (1.4%)
Mild disease: ≥10 - ≤34	20 (29.0%)
Moderate: >34 - <65	37 (53.6%)
Severe: ≥65	11 (15.9%)
Extent of disease [a]	
N	69
Limited to left side of colon	32 (46.4%)
Extensive	37 (53.6%)
C-reactive protein (CRP), mg/L	
N	68
Median (Range)	1.59 (0.1; 92.4)
Abnormal CRP (>3 mg/L)	26 (38.2%)
Fecal calprotectin concentrations, mg/kg	
N	63
Median (Range)	1590.0 (36; 36000)
Abnormal fecal calprotectin (>250 mg/kg)	56 (88.9%)

	Golimumab
IMPACT III	
N	60
Mean (SD)	119.1 (21.51)
Median (Range)	118.0 (65; 171)

[a] Based on Local Endoscopy
The Mayo score is calculated as the sum of the 4 subscores of stool frequency, rectal bleeding, physician's global assessment, and the findings of local endoscopy

Prior UC therapy

Table 13: Summary of UC-related Non-biologic Medication History (History of Response to or Tolerance of Corticosteroids, 6-MP/AZA/MTX) at Baseline; Full Golimumab 1 Analysis Set (Study CNTO148UCO3003)

	Golimumab
Analysis set: Full Golimumab 1	69
Subjects with inadequate response, intolerance, or dependence to corticosteroids and/or 6-MP/AZA/MTX	53 (76.8%)
Corticosteroids	
Subjects refractory, dependent, or intolerant	43 (62.3%)
Subjects refractory	26 (37.7%)
Subjects intolerant	3 (4.3%)
Subjects dependent	29 (42.0%)
6-MP/AZA/MTX	
Subjects refractory or intolerant	35 (50.7%)
Subjects refractory	35 (50.7%)
Subjects intolerant	4 (5.8%)

Concomitant UC therapy

Table 14: Summary of UC-related Concomitant Medications at Baseline; Full Golimumab 1 Analysis Set (Study CNTO148UCO3003).

	Golimumab
Analysis set: Full Golimumab 1	69
Subjects who received any of the following UC medications	67 (97.1%)
Corticosteroid use	36 (52.2%)
Oral/Parenteral Corticosteroid use (excluding budesonide and beclomethasone dipropionate)	26 (37.7%)
Rectal Corticosteroid use (excluding budesonide and beclomethasone dipropionate)	0
Budesonide[a]	6 (8.7%)
Beclomethasone dipropionate[a]	4 (5.8%)
Immunomodulatory drugs	33 (47.8%)
6-mercaptopurine/azathioprine	33 (47.8%)
Methotrexate	0
Oral 5-Aminosalicylate	61 (88.4%)

[a] Including oral or rectal
Note: Subjects may appear in more than one category.

Numbers analysed

Table: 15 Numbers analysed

Analysis Set	Description
Full Golimumab Analysis Set 1 (FGAS1) includes (n=69)	All enrolled participants who received at least 1 dose (complete or partial) of golimumab during the Induction Phase.
Full Golimumab Analysis Set 2 (FGAS2) (n=41)	Participants who were in clinical response at Week 6 to golimumab (determined by the IWRS) as assessed by the Mayo score (local reader) and who received at least 1 dose (complete or partial) of golimumab during the Maintenance Phase.
Full Golimumab Analysis Set 3 (FGAS3) (n=53)	This analysis set includes the following: • Participants who were in clinical response at Week 6 to golimumab (determined by the IWRS), as assessed by the Mayo score (local reader), • Participants who were not in Mayo clinical response at Week 6 but were in partial Mayo response (ie, a decrease from the Week 0 partial Mayo score of ≥3 points) at Week 14 for participants receiving continued golimumab, and who received at least 1 dose (complete or partial) of golimumab during the Maintenance Phase.
Full Golimumab Analysis Set 4 (FGAS4) (n=12)	Participants who were not in Mayo clinical response at Week 6 but were in partial Mayo response at Week 14 for participants receiving continued golimumab. This is a subpopulation of FGAS3 above. These participants were included in the ad hoc analysis described in Section 3.8.2.
Safety Golimumab Analysis Set (n=69)	All enrolled participants who received at least 1 dose (complete or partial) of golimumab.
Safety Golimumab Analysis Set During the Induction Phase (n=69)	All enrolled participants who received at least 1 dose (complete or partial) of golimumab during the Induction Phase.
Safety Golimumab Analysis Set During the Maintenance Phase (n=62)	All enrolled participants who received at least 1 dose (complete or partial) of golimumab during the Maintenance Phase.
PK Evaluable Golimumab Analysis Set (n=67)	All participants who have received at least one dose of golimumab (complete or partial) and have at least one valid blood sample drawn for PK analysis. Two participants were excluded due to receipt of an incorrect SC golimumab dose.
PK Evaluable Golimumab Analysis Set During the Induction Phase (n=67)	All participants who have received at least one dose of golimumab (complete or partial) and have at least one valid blood sample drawn for PK analysis during the Induction Phase.
PK Evaluable Golimumab Analysis Set During the Maintenance Phase (n=53)	All participants who have received at least one dose of golimumab (complete or partial) during the Maintenance Phase and have at least one valid blood sample drawn for PK analysis during the Maintenance Phase.
Immunogenicity Golimumab Analysis Set (n=69)	All participants who received at least one dose (partial or complete) of golimumab and have appropriate samples for detection of antibodies to golimumab.
Immunogenicity Golimumab Analysis Set During the Induction Phase (n=69)	All participants who received at least one dose (partial or complete) of golimumab and have appropriate samples for detection of antibodies to golimumab during the Induction Phase.
Immunogenicity Golimumab Analysis Set During the Maintenance Phase (n=69)	All participants who received at least one dose (partial or complete) of golimumab and have appropriate samples for detection of antibodies to golimumab during the Maintenance Phase.

Outcomes and estimation

Primary efficacy endpoint

The UCO3003 study met the prespecified success criterion for the primary endpoint of Mayo clinical remission at week 6 relative to a historical adult placebo control. In UCO3003, 22 (31.9%) of 69

participants were in clinical remission as assessed by Mayo Score at week 6, which was higher than the historical placebo control rate of 6.4% from T17.

Table 16: Key Efficacy Endpoints at Week 6; Full Golimumab 1 Analysis Set (Study CNTO148UCO3003).

	Golimumab
Analysis set: Full Golimumab 1	69
Primary Endpoint	
Subjects in clinical remission as assessed by the Mayo score[a,e,i,j]	22 (31.9%)
90% CI for proportion of subjects in clinical remission[k]	(22.7%, 41.1%)
95% CI for proportion of subjects in clinical remission[k]	(20.9%, 42.9%)
Major Secondary Endpoints	
Subjects in clinical remission as assessed by the PUCAI score[b,f,i,j]	23 (33.3%)
90% CI for proportion of subjects in clinical remission[k]	(24.0%, 42.7%)
95% CI for proportion of subjects in clinical remission[k]	(22.2%, 44.5%)
Subjects in clinical response[c,g,i,j]	39 (56.5%)
90% CI for proportion of subjects in clinical response[k]	(46.7%, 66.3%)
95% CI for proportion of subjects in clinical response[k]	(44.8%, 68.2%)
Subjects with endoscopic healing[d,h,i,j]	28 (40.6%)
90% CI for proportion of subjects in endoscopic healing[k]	(30.9%, 50.3%)
95% CI for proportion of subjects in endoscopic healing[k]	(29.0%, 52.2%)

[a] Clinical remission is defined as a Mayo score ≤2 points, with no individual subscore >1.
[b] Clinical remission as measured by the PUCAI score is a PUCAI score <10.
[c] Clinical response is defined as 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.
[d] Endoscopic healing is defined as an endoscopy subscore of 0 or 1 based on local endoscopy.
[e] Subjects who had all 4 Mayo subscores missing at Week 6 are considered not to be in clinical remission.
[f] Subjects who had >3 PUCAI subscores missing at Week 6 are considered not to be in clinical remission.
[g] Subjects who had all 4 Mayo subscores missing at Week 6 are considered not to be in clinical response.
[h] Subjects who had a missing endoscopy score at Week 6 were considered not to have endoscopic healing.
[i] Subjects who had a prohibited change in UC medication, an ostomy or colectomy, or discontinued study agent due to lack of efficacy or an AE of worsening of UC prior to the Week 6 visit were considered not to be in clinical remission, clinical response, or endoscopic healing.
[j] Data after a discontinuation of study agent due to COVID-19 related reasons will be used as available.
[k] The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

Secondary endpoints

Results of other key efficacy endpoints at week 6 are presented in Table 16. The results of efficacy endpoints at week 54 are shown in Table 17.

Table 17: Key Efficacy Endpoints at Week 54; Full Golimumab 2 Analysis Set (Study CNTO148UCO3003).

	Golimumab
Analysis set: Full Golimumab 2	41
Major Secondary Endpoints	
Subjects in symptomatic remission[a,e,j,k]	16 (39.0%)
90% CI for proportion of subjects in symptomatic remission[n]	(26.5%, 51.6%)
95% CI for proportion of subjects in symptomatic remission[n]	(24.1%, 54.0%)
Subjects in clinical remission as assessed by the Mayo score[b,f,i,j,k]	13 (31.7%)
90% CI for proportion of subjects in clinical remission[n]	(19.8%, 43.7%)
95% CI for proportion of subjects in clinical remission[n]	(17.5%, 46.0%)
Subjects in clinical remission as assessed by the PUCAI score[c,g,j,k]	14 (34.1%)
90% CI for proportion of subjects in clinical remission[n]	(22.0%, 46.3%)
95% CI for proportion of subjects in clinical remission[n]	(19.6%, 48.7%)
Subjects with endoscopic healing[d,h,j,k]	15 (36.6%)
90% CI for proportion of subjects in endoscopic healing[n]	(24.2%, 49.0%)
95% CI for proportion of subjects in endoscopic healing[n]	(21.8%, 51.3%)
Subjects in clinical remission as assessed by the Mayo score,for participants who are in clinical remission at Week 6[b,f,i,j,k,l]	12 (54.5%)
90% CI for proportion of subjects in clinical remission[n]	(37.1%, 72.0%)
95% CI for proportion of subjects in clinical remission[n]	(33.7%, 75.4%)
Subjects in clinical remission as assessed by the Mayo score and not receiving corticosteroids for at least 12 weeks prior to Week 54[b,f,i,j,k,m]	13 (31.7%)
90% CI for proportion of subjects in clinical remission[n]	(19.8%, 43.7%)
95% CI for proportion of subjects in clinical remission[n]	(17.5%, 46.0%)

[a] Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
[b] Clinical remission is defined as a Mayo score ≤2 points, with no individual subscore >1.
[c] Clinical remission as measured by the PUCAI score is a PUCAI score <10.
[d] Endoscopic healing is defined as an endoscopy subscore of 0 or 1 based on local endoscopy.
[e] Subjects who had both stool frequency and rectal bleeding subscores missing at Week 54 will be considered to not have achieved symptomatic remission at Week 54.
[f] Subjects who had all 4 Mayo subscores missing at Week 54 are considered not to be in clinical remission.
[g] Subjects who had >3 PUCAI subscores missing at Week 54 are considered not to be in clinical remission.
[h] Subjects who had a missing endoscopy score at Week 54 were considered not to have endoscopic healing.
[i] Subjects who had a missing endoscopy score at Week 54 were considered not to be in clinical remission.
[j] Subjects who had a prohibited change in UC medication, an ostomy or colectomy, or used a rescue medication after clinical flare, or discontinued study agent due to lack of efficacy or an AE of worsening of UC prior to the Week 54 visit were considered not to be in clinical remission, endoscopic healing, or symptomatic remission.
[k] Data after a discontinuation of study agent due to COVID-19 related reasons will be used as available.
[l] Denominator is subjects who were in clinical remission at Week 6.

Other Efficacy Endpoint Results

Remission

- At week 6, 33 (47.8%) treated participants achieved symptomatic remission (Mayo stool frequency sub score of 0 or 1 and a rectal bleeding sub score of 0), and 15 (45.5%) of these participants remained in symptomatic remission at week 54.
- At week 6, 23 (33.3%) treated participants achieved clinical remission by the PUCAI score (PUCAI score <10); 14 (60.9%) of these participants maintained clinical remission by the PUCAI score at week 30, and 12 (52.2%) of these participants maintained clinical remission by the PUCAI score at week 54.
- Partial Mayo remission (Mayo score ≤2) provides another way to assess remission over time in a UC study without the need for endoscopy (which is required for Mayo clinical remission endpoint). At week 6, 33 (47.8%) treated participants achieved partial Mayo remission. At week 54, 17 (41.5%) of 41 week 6 clinical responders (determined by IWRS) were in partial Mayo remission.

Clinical Response at week 54

- At week 54, 18 (43.9%) of 41 week 6 clinical responders (determined by IWRS) were still in clinical response by the Mayo score.

Mayo Score

- An improvement in clinical disease activity was observed based on the reduction in the Mayo score from baseline to week 6. The median (mean) reduction in the Mayo score from baseline to week 6 was 3.0 (2.8) for all treated participants.
- Among the week 6 clinical responders, the median (mean) reduction in the Mayo score from baseline to week 54 was 0.0 (2.8).

Partial Mayo Score

- Improvement was seen as early as week 2 for the partial Mayo score for all treated participants, with a median (mean) reduction from baseline of 2.0 (2.5) followed by a median (mean) reduction from baseline of 2.0 (2.2) at week 6.
- Among the week 6 clinical responders, the median (mean) reduction in partial Mayo score from baseline was 4.0 (3.7) at week 10, 3.0 (3.0) at week 14, 4.0 (2.9) at week 22, 3.0 (2.5) at week 30, 3.0 (2.3) at week 36, 0.0 (2.2) at weeks 42 and 46, and 0.0 (2.1) through week 54.

PUCAI Score

- Improvement was seen as early as week 2 for the PUCAI score for all treated participants, with a median reduction from baseline of 20.0. At week 6, the median reduction from baseline was 25.0.
- Among the week 6 clinical responders, the reduction in PUCAI score changed gradually during the maintenance period. The median reduction from baseline was 35.0 in both week 8 and week 10 followed by a reduction of 30.0 at week 14. A reduction of 25.0 from baseline was maintained from week 18 until week 26 followed by reductions of 20 at week 30 and 10 at Week 34; and the reduction from baseline was 0.0 starting from week 36 through week 54.
- A decrease in the PUCAI score of 20 points (from baseline) was considered a minimally clinically important change (Turner 2007). At week 6, 40 (58.0%) treated participants showed clinically important change by the PUCAI score. At week 30 and week 54, 21 (51.2%) and 16 (39.0%) week 6 clinical responders showed clinically important change by the PUCAI score, respectively.

Corticosteroid-related Endpoints

- At week 54, 15 (36.6%) week 6 clinical responders were in symptomatic remission and not receiving corticosteroids, all of whom had been corticosteroid free for at least 12 weeks prior to week 54. Among the week 6 clinical responders, 22 (53.7%) were on concomitant corticosteroids at baseline, and 6 (27.3%) of these baseline corticosteroid users were in symptomatic remission and corticosteroid free at week 54.
- Among the week 6 clinical responders who were on concomitant corticosteroids at baseline, 6 (27.3%) were in clinical remission by the Mayo score and corticosteroid free at week 54.

Inflammatory Markers: Faecal Calprotectin

- The median (mean) reduction in faecal calprotectin level from baseline to week 6 was 227 (1230.2) mg/kg.

- At baseline, 56 (81.2%) enrolled participants had abnormal faecal calprotectin (>250 mg/kg), and at week 6, 11 (19.6%) of these participants had normalized faecal calprotectin (≤ 250 mg/kg).
- Among the week 6 clinical responders, the median (mean) reductions in faecal calprotectin from baseline were 86.0 (812.1) mg/kg at week 14, 0.0 (365.2) mg/kg at week 36, and 0.0 (373.8) mg/kg at Week 54.
- At baseline, 33 (80.5%) week 6 clinical responders had abnormal faecal calprotectin, and by week 54, 6 (18.2%) of these clinical responders had normalized faecal calprotectin.

Health-related Quality of Life

- Health-related Quality of Life was assessed in participants ≥10 to <18 years of age using the IMPACT-III questionnaire. The IMPACT-III uses a 5-point Likert scale ranging from 1 to 5 for all answers. The outcome score ranges from 35 to 175, with higher scores suggesting better quality of life (Otley 2008).
- In the 60 treated participants ≥10 years old, the mean (SD) change from baseline IMPACT-III scores at week 6 was 11.1 (17.12). Using distribution-based methods, derived from statistical analysis, key stakeholders have identified a 0.5 SD as reasonable threshold in confirming that between group differences reflect clinically meaningful levels of improvement in HRQoL (Homco 2019; Norman 2003). Based on this criterion, the improvement in IMPACT-III total score from baseline to week 14 suggests that the magnitude of change may be clinically meaningful to participants.
- The change from baseline in IMPACT-III score from week 6 through week 54 was assessed in the 35 week 6 clinical responders (≥10 years old). The magnitude of change from baseline was maintained through Week 14 (mean change of 18.8 to 17.3). Mean (SD) difference effects sizes were somewhat attenuated at week 30 and week 54 (12.7 [19.27] and 9.1 [19.25]).

Usability Assessment Sub study

Participants who chose at home administration (AHA) during the study extension were included in a Usability Sub study Analysis Set. The objective of the Sub study (from week 62 to week 66) was to provide supportive data that the Prefilled Syringe with UltraSafe (PFS-U) and Prefilled Pen VarioJect (PFP-V) as designed, together with the appropriate training and written instructions for use, were suitable for AHA by paediatric participants or their caregivers. An Injection Device Observer Injection Checklist was completed by the trainer to determine if the first AHA training dose was delivered successfully. No training outcomes were below average, and all were either average (28.6%) or above average (71.4%), which was considered as passing the training.

At DBL, 4 (28.6%) and 10 (71.4%) participants (or their caregivers) completed the week 62 PFS-U and PFP-V Injection Assessment Questionnaires, respectively; 5 (41.7%) and 7 (58.3%) participants (or their caregivers) completed the week 66 PFS-U and PFP-V Injection Assessment Questionnaires, respectively.

PFS-U Assessment

Among the 4 and 5 participants (or their caregivers) who completed the PFS-U assessment questionnaire at weeks 62 and 66, respectively, all (100%) reported successful injection for self-dosing, with handling and use experience as "easy" to "very easy".

PFP-V Assessment

Among the 10 and 7 participants (or their caregivers) who completed the PFP-V assessment questionnaire at weeks 62 and 66, respectively, all (100%) reported successful injection for self-dosing, with handling and use experience ranging from "somewhat easy" to "very easy".

Ancillary analyses

n/a

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of Efficacy for trial CNTO148UCO3003

Title: A Phase 3 Randomized, Open-label Study to Assess the Efficacy, Safety, and Pharmacokinetics of Golimumab Treatment, a Human anti-TNFα Monoclonal Antibody, Administered Subcutaneously in Paediatric Participants with Moderately to Severely Active Ulcerative Colitis		
Study identifier	CNTO148UCO3003 EudraCT Number: 2017-004496-31 EU TRIAL NUMBER: 2023-507142-83	
Design	Phase 3, multicenter, randomised, open-label study, Prior to implementation of protocol amendment 4, eligible participants weighing ≥30 kg were to be randomized in a 3:1 ratio to golimumab or infliximab. Participants < 30 kg were not to be randomized and were to receive golimumab only. Upon implementation of protocol amendment 4, all newly enrolled participants were to receive golimumab.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	54 Weeks not applicable Variable, from Week 54 to end of study
Hypothesis	Superiority: The primary hypothesis is that golimumab is an effective therapy in paediatric UC relative to a historical placebo control as assessed by clinical remission based on the Mayo score.	

Treatments groups	Golimumab		**≥45 kg** Induction: 200 mg SC at week 0, followed by: 100 mg SC at wk 2 and then maintenance q4w (ie, at weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50 **<45 kg:** Induction: 120 mg/m^2 SC (max 200 mg) at week 0; followed by 60 mg/m^2 SC (max 100 mg) at wk 2 and then maintenance q4w (ie, at weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50)
	Infliximab		Induction: 5 mg/kg IV at weeks 0, 2; followed by Maintenance: 5 mg/kg IV q8w (ie, at weeks 6, 14, 22, 30, 38, 46) [dose escalation was allowed]
Endpoints and definitions	Primary endpoint	Clinical remission at Week 6 – Mayo score	Mayo score ≤2 points, with no individual subscore >1
	Secondary endpoint	Clinical remission at week 6 – PUCAI score	A PUCAI score <10
	Secondary endpoint	Clinical response at week 6 as assessed by Mayo Score	decrease from baseline score of ⩾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.
	Secondary endpoint	Endoscopic healing at week 6	An endoscopy subscore of the Mayo score of 0 or 1
	Secondary endpoint	Symptomatic remission at Week 54	Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
	Secondary endpoint	Clinical remission at week 54 – Mayo Score	Mayo score ≤2 points, with no individual subscore >1
	Secondary endpoint	Clinical remission at week 54 – PUCAI score	PUCAI score <10
	Secondary endpoint	Endoscopic healing at Week 54	Endoscopy subscore of 0 or 1
	Secondary endpoint	Clinical remission at Week 54, not received corticosteroids for at least 12 weeks	Mayo score ≤2 points, with no individual subscore >1)

Database lock	11 April 2024	
Results and Analysis		
Analysis description	**Primary Analysis - Clinical remission at Week 6 – Mayo score**	
Analysis population and time point description	All enrolled participants who received at least 1 dose of golimumab during the Induction Phase Week 6	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	69
	Number (%) of participants in Clinical remission at Week 6 – Mayo Score	22 (31.9%)
	90% CI	(22.7%, 41.1%)
Notes	Subjects who had a prohibited change in UC medication, an ostomy or colectomy, or discontinued study agent due to lack of efficacy or an AE of worsening of UC prior to the Week 6 visit were considered not to be in clinical remission. Data after a discontinuation of study agent due to COVID-19 related reasons were used as available. Subjects who had all 4 Mayo subscores missing at Week 6 were considered not to be in clinical remission. From Week 0 through Week 6, 7/69 (10.1%) treated participants discontinued golimumab, and the most common reason for discontinuation was AE of worsening of UC disease (7.2%). From Week 6 through Week 54, 25/62 (40.3%) treated participants discontinued golimumab, and the most common reasons for discontinuation were an AE of worsening of UC disease and lack of efficacy (14.5% each)	
Analysis description	**Secondary analysis - Clinical remission at week 6 – PUCAI score**	
Analysis population and time point description	All enrolled participants who received at least 1 dose of golimumab during the Induction Phase Week 6	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	69
	Number (%) of participants	23 (33.3%)
	90% CI	(24.0%, 42.7%)
Analysis description	**Secondary analysis - Clinical response at week 6 – Mayo score**	
Analysis population and time point description	All enrolled participants who received at least 1 dose of golimumab during the Induction Phase Week 6	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	69
	Number (%) of participants	39 (56.5%)
	90% CI	(46.7%, 66.3%)

Analysis description	**Secondary analysis - Endoscopic healing at week 6 defined as an endoscopy subscore of 0 or 1 based on local endoscopy**	
Analysis population and time point description	All enrolled participants who received at least 1 dose of golimumab during the Induction Phase Week 6	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	69
	Number (%) of participants	28 (40.6%)
	90% CI	(30.9%, 50.3%)
Analysis description	**Symptomatic remission at Week 54**	
Analysis population and time point description	Participants who were in clinical response at Week 6 as determined by the IWRS (ie, Week 6 clinical responders) and received at least 1 dose of golimumab during the maintenance phase Week 54	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	41
	Number (%) of participants	16 (39.0%)
	90% CI	(26.5%, 51.6%)
Analysis description	**Clinical remission at week 54 – Mayo Score**	
Analysis population and time point description	Participants who were in clinical response at Week 6 as determined by the IWRS (ie, Week 6 clinical responders) and received at least 1 dose of golimumab during the maintenance phase Week 54	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	41
	Number (%) of participants	13 (31.7%)
	90% CI	(19.8%, 43.7%)
Analysis description	**Clinical remission at week 54 – PUCAI score**	
Analysis population and time point description	Participants who were in clinical response at Week 6 as determined by the IWRS (ie, Week 6 clinical responders) and received at least 1 dose of golimumab during the maintenance phase Week 54	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	41
	Number (%) of participants	14 (34.1%)
	90% CI	(22.0.%, 46.3%)
Analysis description	**Endoscopic healing at Week 54 defined as an endoscopy subscore of 0 or 1 based on local endoscopy**	

Analysis population and time point description	Participants who were in clinical response at Week 6 as determined by the IWRS (ie, Week 6 clinical responders) and received at least 1 dose of golimumab during the maintenance phase Week 54	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	41
	Number (%) of participants	15 (36.6%)
	90% CI	(24.2.%, 49.0%)
Analysis description	**Clinical remission at Week 54 by the Mayo score, not received corticosteroids for at least 12 weeks**	
Analysis population and time point description	Participants who were in clinical response at Week 6 as determined by the IWRS (ie, Week 6 clinical responders) and received at least 1 dose of golimumab during the maintenance phase Week 54	
Descriptive statistics and estimate variability	Treatment group	Golimumab
	Number of participants	41
	Number (%) of participants	13 (31.7%)
	90% CI	(19.8.%, 43.7%)

Analysis performed across trials (pooled analyses and meta-analysis)

Combined Results of Paediatric Studies UCO3003 and UCO1001

Clinical Remission as Assessed by the Mayo Score at week 6

In UCO3003, 31.9% of 69 participants were in clinical remission at week 6 as assessed by the Mayo score. The proportion of participants in Mayo clinical remission at week 6 in UCO3003 pooled with UCO1001 (≥45 kg) was 33.7% of 89 participants.

Clinical Remission as Assessed by the PUCAI Score at week 6

In UCO3003, 33.3% of 69 participants were in clinical remission at week 6 as assessed by PUCAI Score. The proportion of participants in PUCAI clinical remission at week 6 in UCO3003 pooled with UCO1001 (≥45 kg) was 33.7% of 89 participants.

Clinical Response as Assessed by the Mayo Score at week 6

In UCO3003, 56.5% of 69 participants were in clinical response at week 6 as assessed by the Mayo score. The proportion of participants in clinical response in UCO3003 pooled with UCO1001 (≥45 kg) was 56.2% of 89 participants.

Endoscopic/Mucosal Healing at week 6

In UCO3003, 40.6% of 69 participants achieved endoscopic/mucosal healing (endoscopy sub score of 0 or 1 based on local endoscopist reading) at week 6. The proportion of participants who achieved endoscopic/mucosal healing in UCO3003 pooled with UCO1001 (≥45 kg) was 42.7% of 89 participants.

Supportive studies

Study CNTO148UCO1001 - A phase 1b open-label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFα antibody, in paediatric subjects with moderately to severely active ulcerative colitis

Methods

CNTO148UCO1001 was a supportive phase 1b, multicentre, open-label study to assess the PK and safety of SC golimumab induction followed by SC golimumab maintenance in paediatric participants aged 2 through <18 years with moderately to severely active UC without prior exposure to biologic anti-TNFα agents. There were 2 parts to the study: the PK portion (through week 14) and the study extension. The primary focus of the study was to assess the PK of golimumab over time.

Participants received SC golimumab at week 0 and week 2. At week 6, participants in clinical response were eligible to receive open-label maintenance therapy with golimumab and to enter the study extension at Week 14. Participants not in clinical response at week 6 were withdrawn from further study intervention administration.

Subjects in the study extension continued to receive study agent 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. The study extension continued after week 126 for the subjects who were eligible at week 114 to continue to receive golimumab q4w.

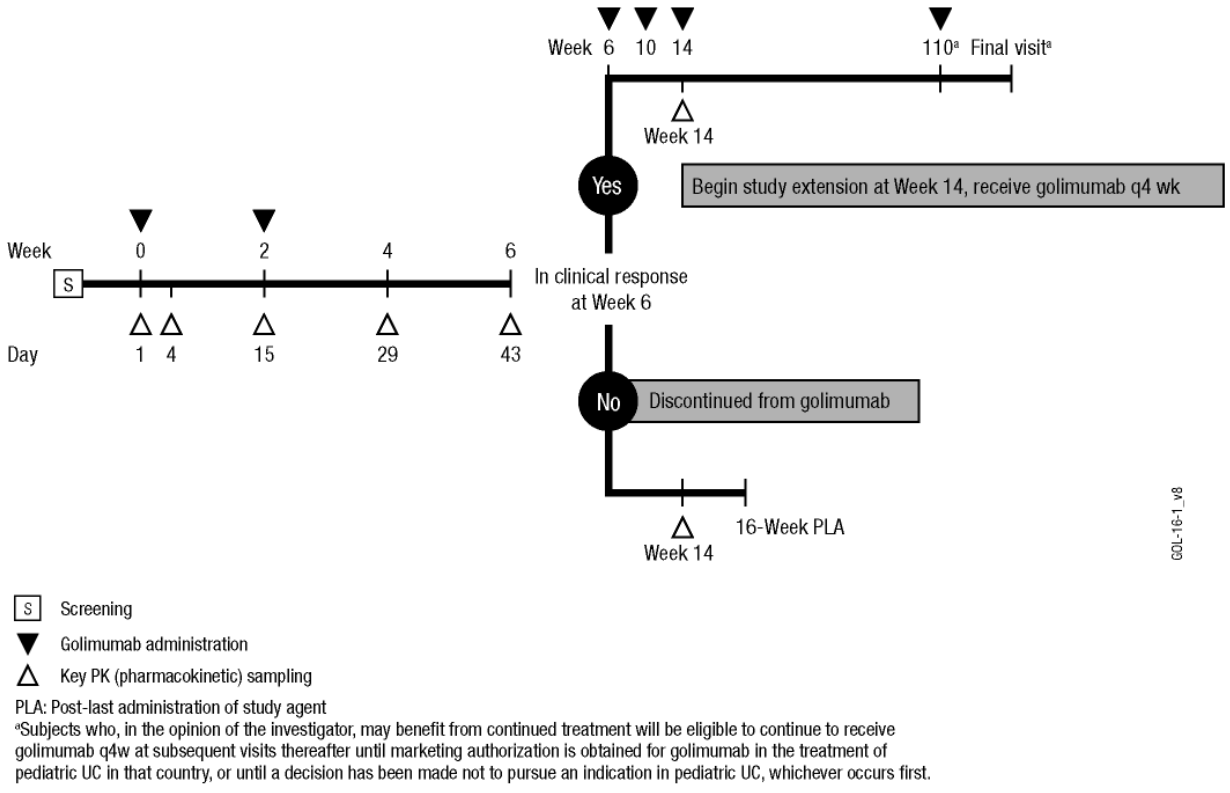


Figure 13: Study Schema for CNTO148UCO1001.

Study participants

Eligible subjects were to be 2 through 17 years of age with moderately to severely active UC, defined as a baseline Mayo score of 6 through 12, inclusive, with an endoscopy sub score of ≥2. Subjects must have had a diagnosis of UC confirmed by a previous biopsy or a biopsy conducted at the screening endoscopy procedure that is consistent with a diagnosis of UC (eg, crypt distortion, crypt abscess, goblet cell depletion, and continuous distribution). Subjects must have demonstrated an inadequate response to, failed to tolerate, or had a medical contraindication to conventional therapies (ie, intravenous or oral corticosteroids or the immunomodulators AZA or 6-MP), and were naïve to anti-TNFα agents.

Treatments

There were 2 study periods:

- PK portion: Week 0 through week 14
- Study extension
    - Week 14 through week 126
    - Week 126 through the final visit (the final visit for the last subject was at week 434)

Participants received induction and maintenance dose regimens of SC golimumab based on body weight during the PK portion and the study extension as shown in Table 18 and Table 19, respectively.

Table 19: Golimumab SC Dose Regimens by Body Weight; Pharmacokinetic Portion of UCO1001

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

Table 20: Golimumab SC Dose Regimens by Body Weight; Study Extension of UCO1001 (Participants in Clinical Response at Week 6)

Week 14 and every 4 weeks through Week 110[a]		
Body Weight	**Subjects who receive 100 mg equivalent dose**	**Subjects who decrease to 50 mg equivalent dose[b]**
<45 kg	45 mg/m^2 (up to a maximum of 100 mg)	22.5 mg/m^2 (up to a maximum of 50 mg)
≥45 kg	100 mg	50 mg

[a] At Week 114, participants who, in the opinion of the investigator, may have benefited from continued treatment were eligible to continue to receive golimumab every 4 weeks until marketing authorization was obtained for golimumab in the treatment of pediatric UC in that country, or until a decision had been made not to pursue an indication in pediatric UC, whichever occurred first.

[b] All participants entering the study extension had the option to decrease their golimumab dose to the 50 mg equivalent dose at the discretion of the investigator. A single dose increase back to 100 mg or 45 mg/m^2 was permitted based on the investigator's assessment of an increase in a participant's UC disease activity.

Subjects in the study extension continued to receive study agent 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.

Objectives and endpoints

There were 2 parts to the study: the PK portion (through week 14) and the study extension. The primary focus of the study was to assess the PK of golimumab over time. The objective of the extension was to assess the PK and safety of an additional 2 years of treatment with golimumab in

paediatric subjects 2 through 17 years of age with moderately to severely active UC who were in clinical response at week 6 and entered the study extension at week 14. An additional objective was to evaluate the efficacy of golimumab maintenance treatment in this population.

Major outcomes for efficacy were as follows:

- Clinical response at week 6
- Clinical remission at week 6 as measured by the Mayo score
- Clinical remission at week 6 as measured by the PUCAI score
- Mucosal healing at week 6
- Clinical remission at week 54 and week 110 as measured by the PUCAI score

The efficacy endpoint definitions were 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 sub score of ≥ 1 or a rectal bleeding sub score of 0 or 1.
- Clinical remission as measured by the Mayo score: a Mayo score ≤ 2 points, with no individual sub score > 1.
- Clinical remission as measured by the PUCAI score: a PUCAI score < 10.
- Mucosal healing: an endoscopy sub score of the Mayo score of 0 or 1.

The following study evaluations were conducted during the study extension:

- PK: Serum golimumab concentration
- Immunogenicity: Antibodies to golimumab
- Efficacy: PUCAI score
- Safety: AEs, clinical laboratory tests, vital signs, physical examinations including skin examination, injection-site reactions, concomitant medication review, TB evaluations, ANA and anti-dsDNA antibodies, and pregnancy testing.

Sample size

The sample size for this study was not based on statistical considerations. A sample size of 30 subjects was chosen empirically based upon experience from an interim analysis of PK data in the golimumab study of JIA (CNTO148JIA3001), where 30 subjects were sufficient to provide adequate PK information in paediatric subjects with JIA. The proposed sample size is consistent with the sample size framework derivation for paediatric PK studies (Wang et al 2012).

The study was to enrol 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.

Results

Participant flow

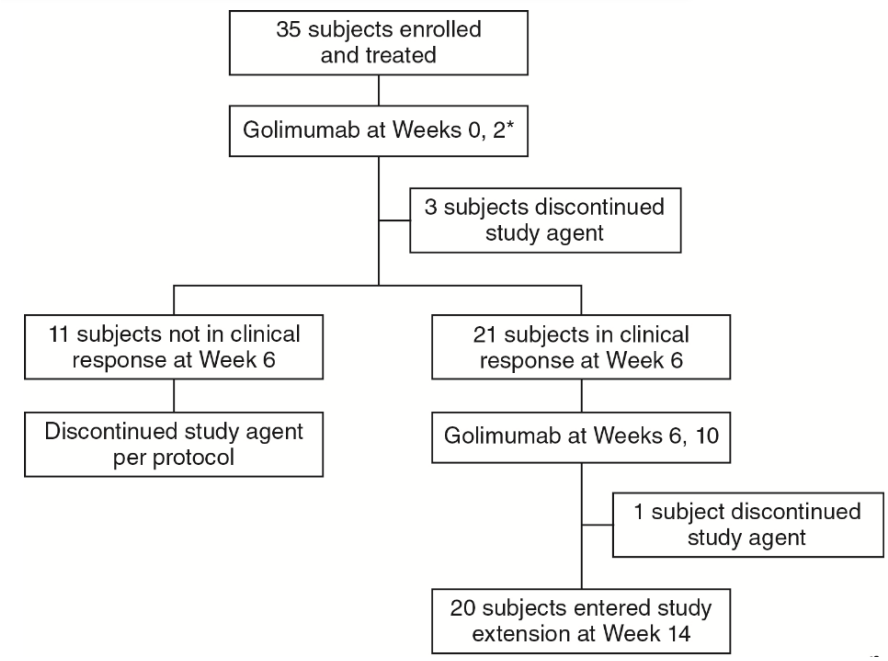


Figure 14: Subject Disposition at Week 14 in CNTO148UCO1001.

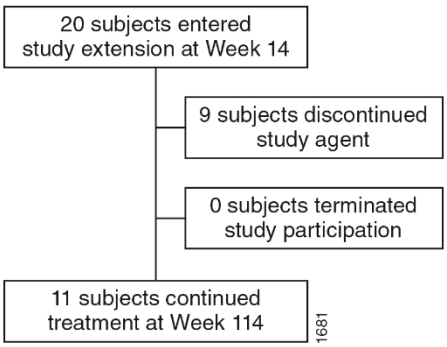


Figure 15: Subject Disposition at Week 114 in CNTO148UCO1001

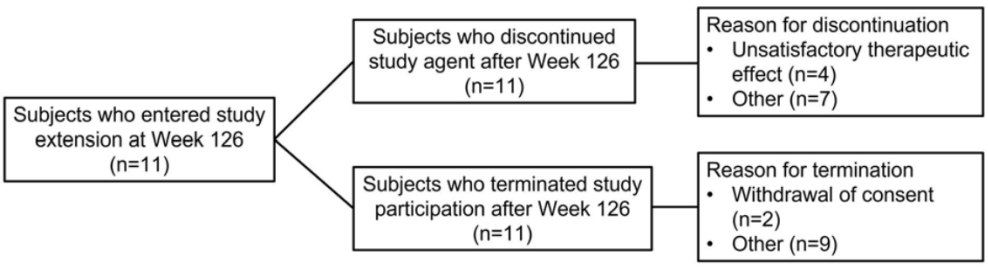


Figure 16: Subject Disposition During the Study Extension after Week 126 in CNTO148UCO1001

Recruitment

Study Initiation Date: 25 September 2013

Study Completion Date: 18 February 2015

This study was conducted at 24 sites in North America and Europe.

Baseline data

Table 21: Summary of demographics at baseline; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Sex	
N	35
Male	17 (48.6%)
Female	18 (51.4%)
Race	
N	35
White	30 (85.7%)
Black or African American	1 (2.9%)
Asian	1 (2.9%)
American Indian or Alaska Native	1 (2.9%)
Native Hawaiian or Other Pacific Islander	0
Other	0
Unknown	0
Multiple	1 (2.9%)
Not reported	1 (2.9%)
Ethnicity (Hispanic/Latino ?)	
N	35
Yes	5 (14.3%)
No	28 (80.0%)
Unknown	2 (5.7%)
Age (yrs)	
N	35
Mean (SD)	13.4 (3.21)
Median	15.0
IQ range	(11.0; 16.0)
Range	(6; 17)
Age categories (yrs)	
N	35
2-11	10 (28.6%)
12-17	25 (71.4%)
Weight (kg)	
N	35
Mean (SD)	51.74 (22.694)
Median	50.60
IQ range	(35.20; 59.00)
Range	(19.7; 134.0)
Weight categories (kg)	
N	35
<45	15 (42.9%)
<30	5 (14.3%)
≥ 45	20 (57.1%)
Height (cm)	
N	35
Mean (SD)	157.61 (16.903)
Median	158.00
IQ range	(144.00; 168.00)
Range	(113.4; 186.0)

Table 22: Summary of UC disease characteristics at baseline; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
UC disease duration (yrs)	
N	35
Mean (SD)	2.35 (3.125)
Median	1.22
IQ range	(0.62; 3.11)
Range	(0.2; 16.0)
Extent of disease	
N	35
Limited to left side of colon	10 (28.6%)
Extensive	25 (71.4%)
Severity of UC disease	
N	35
Moderate disease (Mayo score >= 6 to <= 10)	30 (85.7%)
Severe disease (Mayo score > 10)	5 (14.3%)
Baseline Mayo score	
N	35
Mean (SD)	8.1 (1.82)
Median	8.0
IQ range	(6.0; 9.0)
Range	(6; 12)
Baseline PUCAI score	
N	35
Mean (SD)	48.1 (17.02)
Median	45.0
IQ range	(35.0; 65.0)
Range	(15; 80)
Baseline CRP concentrations (mg/L)	
N	34
Mean (SD)	10.05 (23.945)
Median	2.65
IQ range	(0.71; 6.38)
Range	(0.1; 116.0)
Baseline fecal calprotectin concentrations (ug/g)	
N	31
Mean (SD)	1554.74 (1608.235)
Median	727.65
IQ range	(569.13; 2129.63)
Range	(231.1; 5871.0)
Baseline fecal lactoferrin concentrations (ug/g)	
N	32
Mean (SD)	355.29 (278.486)
Median	284.70
IQ range	(158.03; 454.62)
Range	(29.3; 1000.0)

Prior UC therapy

Table 23: Summary of UC medication history; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
UC medication	
N[a]	35
Subjects who used any UC medication	35 (100.0%)
Corticosteroids (excluding budesonide)	
N[a]	35
Never used	2 (5.7%)
Used ≤1 year	27 (77.1%)
Used > 1 to ≤2years	4 (11.4%)
Used > 2 years	2 (5.7%)
Budesonide	
N[a]	35
Never used	29 (82.9%)
Used ≤1 year	5 (14.3%)
Used > 1 to ≤2years	0
Used > 2 years	1 (2.9%)
Immunomodulatory agents	
N[a]	35
Subjects who used any immunomodulatory agent	25 (71.4%)
6-mercaptopurine	
N[a]	35
Never used	29 (82.9%)
Used ≤1 year	4 (11.4%)
Used > 1 to ≤2years	1 (2.9%)
Used > 2 years	1 (2.9%)
Azathioprine	
N[a]	35
Never used	15 (42.9%)
Used ≤1 year	15 (42.9%)
Used > 1 to ≤2years	2 (5.7%)
Used > 2 years	3 (8.6%)
Methotrexate	
N[a]	35
Never used	33 (94.3%)
Used ≤1 year	2 (5.7%)
Used > 1 to ≤2years	0
Used > 2 years	0
Mycophenolate mofetil	
N[a]	35
Never used	35 (100.0%)
Used ≤1 year	0
Used > 1 to ≤2years	0
Used > 2 years	0
Cyclosporine	
N[a]	35
Never used	35 (100.0%)
Used ≤1 year	0
Used > 1 to ≤2years	0
Used > 2 years	0
Sirolimus	
N[a]	35
Never used	35 (100.0%)
Used ≤1 year	0
Used > 1 to ≤2years	0

	Golimumab
Used > 2 years	0
Tacrolimus	
N[a]	35
Never used	35 (100.0%)
Used ≤1 year	0
Used > 1 to ≤2years	0
Used > 2 years	0
Aminosalicylates	
N[a]	35
Subjects who used any aminosalicylates	32 (91.4%)
Olsalazine	
N[a]	35
Never used	35 (100.0%)
Used ≤1 year	0
Used > 1 to ≤2years	0
Used > 2 years	0
Balsalazide	
N[a]	35
Never used	32 (91.4%)
Used ≤1 year	2 (5.7%)
Used > 1 to ≤2years	1 (2.9%)
Used > 2 years	0
Sulfasalazine	
N[a]	35
Never used	28 (80.0%)
Used ≤1 year	5 (14.3%)
Used > 1 to ≤2years	0
Used > 2 years	2 (5.7%)
Mesalamine	
N[a]	35
Never used	4 (11.4%)
Used ≤1 year	16 (45.7%)
Used > 1 to ≤2years	8 (22.9%)
Used > 2 years	7 (20.0%)
Antibiotics	
N[a]	35
Subjects who used any antibiotics	16 (45.7%)
Ciprofloxacin	
N[a]	35
Never used	33 (94.3%)
Used ≤1 year	2 (5.7%)
Used > 1 to ≤2years	0
Used > 2 years	0
Metronidazole	
N[a]	35
Never used	19 (54.3%)
Used ≤1 year	15 (42.9%)
Used > 1 to ≤2years	0
Used > 2 years	1 (2.9%)
Rifaximin	
N[a]	35
Never used	32 (91.4%)
Used ≤1 year	3 (8.6%)
Used > 1 to ≤2years	0
Used > 2 years	0

Concomitant UC therapy

Table 24: Summary of concomitant medications for UC at baseline; Treated subjects (Study CNTO148UCO1001)

	Golimumab
Treated subjects	35
Subjects with 1 or more concomitant medications	30 (85.7%)
Corticosteroids (parenteral or oral)[a]	12 (34.3%)
Subjects with baseline ≤1 mg/kg P.Eq	12 (34.3%)
Subjects with baseline > 1 mg/kg P.Eq	0
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

Outcomes and estimation

Efficacy endpoints

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, the proportion of treated subjects in clinical response as measured by the Mayo score was 60.0%. At week 6, 19 subjects (54.3%) achieved mucosal healing (improvement in the endoscopic appearance of the mucosa), based on a Mayo endoscopy sub score of 0 or 1 (indicating normal or inactive disease, or mild disease).

Table 25: Summary of Week 6 Efficacy Endpoint Results; Treated Participants (UCO1001).

Treated participants	**35**
Clinical response[a] as assessed by the Mayo score	
Participants in clinical response	21 (60.0%)
Clinical remission as assessed by the Mayo score (Mayo score ≤2 points, with no individual subscore >1)	
Participants in clinical remission	15 (42.9%)
Clinical remission as assessed by the PUCAI score (PUCAI score <10)	
Participants in clinical remission	12 (34.3%)
Mucosal healing (endoscopy subscore of 0 or 1)[b]	
Participants with mucosal healing	19 (54.3%)

a Clinical response is defined as 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.

Extrapolation concept and plan provided by the MAH

Extrapolation concept

Ulcerative colitis is a chronic GI inflammatory disorder that involves the surface mucosa, crypt epithelium, and submucosa of the colon. UC is characterised by continuous mucosal inflammation of the colon starting from the rectum and extending proximally (Conrad 2017).

Genetics

The pathogenic mechanisms mediating paediatric-onset IBD are closely related to those in adult-onset disease (Imielinski 2009). A genome-wide association study comparing paediatric-onset with adult-onset UC demonstrated that:

- Most genes associated with the pathogenesis of adult UC are also associated with paediatric UC.
- Novel genes identified in paediatric cohorts have been confirmed subsequently in adult cohorts, thereby supporting the similarities in the pathways implicated in both paediatric- and adult-onset UC (Imielinski 2009).

Adult and paediatric genome-wide association scans have not identified risk variants that are specific solely to paediatric UC and not implicated in adult UC (Sauer 2009). Furthermore, mucosal gene expression studies from colonic biopsy tissue obtained from adults and children with UC demonstrate substantial overlap in transcriptomic profiles; both populations share similar canonical pathways and upstream regulators (Li 2018).

Mucosal Innate and Adaptive Immune Responses

Both the innate and the adaptive immune systems are involved in the pathogenesis of UC. Intestinal epithelial cells encounter commensal and pathogenic bacteria regularly and constitutively express membrane-bound and intracellular receptors to sense gut microbes (Faubion 2008). Downstream signalling pathways of these receptors lead to activation of NF-kB responsive genes mediating inflammatory responses, which are essential to normal barrier function. Pathogenic and commensal bacteria may contact immune cells of the gut-associated lymphoid tissue in several ways. Firstly, infected epithelial cells can undergo apoptosis and fragments containing bacteria may be ingested by resident macrophages and DCs and presented to host T cells. Secondly, DCs and macrophages may acquire bacteria directly from the lumen, presenting bacteria to CD4+ cells (Faubion 2008). Thirdly, lymphocytes may contact bacterial antigens directly, in the absence of antigen presenting cells, and respond by proliferation and cytokine secretion (Sutmuller 2006). T cell response to bacterial presentation depends upon the expression of co-stimulatory molecules on the antigen presenting cells.

Activation of the CD4+ T cells results in cytokine release (eg, TNFα, IL23), which incites a vigorous immune response. Activated CD4+ T cells also stimulate B cells through expression of the cell surface molecule CD40 ligand, leading to initiation of antibody formation. This multifactorial antigen-driven immune response leads to a series of secondary events, such as production of matrix metalloproteinases (Heuschkel 2000) and oxygen reactive metabolites which are toxic to cells and lead to necrosis and tissue damage (Pavlick 2002).

Importantly, maturation of the human mucosal immune system is a continuum, with no definitive markers defining a "mature" or "immature" status (Faubion 2008). The adaptive immune system requires post-natal exposure to dietary and microbial antigens to develop immunologic memory. On the contrary, innate immune responses are for the most part germline-encoded through recognition of microbial ligands by pathogen recognition receptors (Faubion 2008). Within hours, the GI tract is colonized with facultative and anaerobic bacteria. Specific secretory IgA response to organisms such as E.coli are produced within the first week of life (Mackie 1999). Infants and young children can generate the full spectrum of functional T cells (Th1, Th2, etc) and T cell dependent B cell responses (Fadel 2000).

Tumour Necrosis Factor α

In the immune cascade, cytokines can exhibit pro-inflammatory or anti-inflammatory activity, affecting the synthesis and secretion of reactive oxygen species, nitric oxide, leukotrienes, platelet activating factor, and prostaglandins. TNFα is a pro-inflammatory cytokine that is secreted by macrophages,

monocytes, neutrophils, CD4+ T lymphocytes, and NK cells following their stimulation by bacterial lipopolysaccharides. TNFα is required for normal host immune responses in adults and children, but overexpression can have severe pathologic consequences, as exemplified by mice in which transgenic overexpression is associated with severe colitis (Neurath 1997). In human studies in both adults and children with IBD, elevated levels of TNFα are observed in serum, stool, and mucosal tissue (Murch 1991; Reimund 1996).

Similarity of measurements used to define manifestations of disease

Monitoring tools used in paediatric and adult-onset UC are the same, including clinical disease activity indexes, serum biomarkers, faecal biomarkers, imaging modalities, and endoscopic scoring systems (Turner 2021). The Mayo score has been widely used in studies of both children and adults with UC and has been the primary outcome assessment in trials of infliximab and adalimumab, the only 2 biologics approved in children with UC (Croft 2021; Hyams 2012a).

There are some child-specific measures that are incorporated into paediatric studies, including a patient-reported outcome measure for children with IBD (TUMMY-UC) (Marcovitch 2023), a QoL measure for children with IBD (IMPACT) (Otley 2002), and a clinician-reported outcome assessment (PUCAI) (Turner 2007).

Similarity of clinical approach and treatment

The Selecting Therapeutic Targets in IBD (STRIDE) program was initiated by the International Organization for the Study of IBD (IOIBD) in 2013 using an evidence-based expert consensus process. This subsequently led to a position statement determining therapeutic targets for adult IBD to be used for a "treat-to-target" clinical management strategy (Peyrin-Biroulet 2015). The STRIDE initiative proposed updates in 2021, which included incorporation of international evidence and consensus-based recommendations for short-term, intermediate, and long-term treatment targets for paediatric UC (Turner 2021). Treatment targets for the adult and paediatric population are identical, except for use of paediatric specific measurement scales (eg, PUCAI vs. Mayo in adults) and restoration of normal growth as a formal treatment target in paediatrics. Furthermore, treatments for UC in adults and children are identical; following the adult approval, therapies are used off-label by paediatric prescribers where available and are recommended for use in paediatric treatment guidelines (Rosh 2024; Turner 2021).

Similarity of pharmacology

The pharmacology of golimumab is similar in adults and children. Unlike small-molecule drugs, mAbs are not metabolised by hepatic cytochrome P450 enzymes. Thus, age-related changes in hepatic phase I and phase II metabolism are not likely to affect golimumab elimination and impairment of hepatic or renal functions may have a negligible effect on metabolism and clearance. As a mAb, golimumab is metabolized by the same catabolic pathways as endogenous immunoglobulins and is typically broken down into small peptides and amino acids through proteolysis. A common pathway shared by endogenous IgG and mAbs is non-specific Fc receptor mediated catabolism. FcRn is a salvage protein that protects IgG from catabolism. It binds to IgG in the acidic conditions of endosomes and recycles back to the extracellular surface (Ryman 2017). In the body, vascular endothelial cells make up the capillary walls and therefore, have extensive access to mAb in plasma. Golimumab is distributed predominantly within the vascular compartment. Therefore, age-related changes in body composition (ie, water and lipid composition) are not expected to affect distribution of golimumab.

Similarity of response to therapy

Response to treatment is similar among patients with adult-onset and paediatric-onset UC. It has been speculated that patients with paediatric-onset UC may have different responses than those with adult-

onset UC due to living longer with their UC. However, no relationship between disease duration and biologic treatment outcomes in randomized controlled trial data has been established in patients with UC (Ben-Horin 2022). Also supporting this concept, an analysis of adult IBD registrational clinical studies revealed similar odds of response and remission among participants with adult-onset and adolescent-onset disease, before and after adjustment for disease duration (Rosh 2024).

Hitting the therapeutic target, in this case anti-TNF, results in the same pharmacodynamic effects in both adults and children. The response rates to anti-TNFα agents in paediatric participants with IBD (including both UC and Crohn's disease) appear to either be comparable to or numerically higher than that observed in adult IBD studies (Hyams 2012a; Hyams 2012b; Hyams 2006; Croft 2021). In addition, the E-R to anti-TNFα therapies in children with UC is similar to that observed in the adult population (Xu 2019; Adedokun 2013). Overall, adolescents and adults with UC exhibit similar biological and clinical features, and there are no drugs used to treat UC which are effective in adults but not effective in adolescents and children.

Extrapolation plan

There is a strong rationale, as described in the Extrapolation Concept, to support extrapolation of PK, efficacy and safety from adults to children with UC. Therefore, the efficacy and PK of golimumab in children was supported by extrapolation from 2 adult UC phase 3 studies that assessed efficacy and safety, C0524T17 and C0524T18, which completed in 2010 and 2015, respectively.

In addition to these 2 adult studies, the safety of golimumab in children with UC was also supported by data from a third study in adults, C0524T16, which completed in 2009.

The extrapolation plan also includes modeling and simulation to assess similarity of exposure and response data in the treatment of UC between adults and children and modeling and simulation to support paediatric dose selection.

Summary

The uncertainties that could not be fully resolved based on the available data/knowledge, and which required further data collection in children, were as follows:

- Data supporting the relationship between modelled dosing and predicted exposures in paediatric UC.
- Efficacy data generated in children with UC, supporting the proposed dose regimen for labelling in ages 2 to 17 years of age.
- Safety data with objective outcomes generated in paediatric UC during chronic administration (52 weeks).

These uncertainties were planned to be addressed by the data produced in CNTO1480UCO3003.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

To support this extension of indication application, the MAH has conducted two open label studies in paediatric participants with moderately to severely active UC: a phase 3 study, CNTO148UCO3003 (completed through week 54, study extension ongoing at time of assessment), and a supportive study CNTO148UCO1001 (completed) which was assessed in a previous variation (EMEA/H/C/000992/II/0113).

Furthermore, to support the paediatric UC indication, the MAH has proposed to use an extrapolation approach to establish efficacy and safety in the patient population ages 2 to <18 years according to the ICH E11A 2022 Guideline on paediatric extrapolation (EMA/CHMP/ICH/205218/2022). The MAH has conducted a literature review to support the extrapolation of pathogenic mechanisms, immune responses, role of TNFα, disease monitoring tools, clinical approach and treatment, pharmacology of golimumab, and response to treatment from adults to children with UC. Extrapolation of efficacy/or safety from adults with UC to children with UC is also supported by the Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1). Additionally, the PDCO has accepted the extrapolation concept in the PIP of Simponi (EMEA-000265-PIP02-11-M02). The arguments for the extrapolation approach are acknowledged, and the extrapolation concept is endorsed.

PK and efficacy of golimumab were thus extrapolated from 2 adult UC phase 3 studies assessing efficacy and safety, C0524T17 and C0524T18, which were completed in 2010 and 2015, respectively. Uncertainties identified and listed in the extrapolation plan, which were to be addressed by the paediatric study UCO3003, included relation between modelled dosing and predicted exposures, efficacy data supporting the proposed dose regimen in ages 2 to 17 years, and safety data in children with objective outcomes generated during chronic administration (52 weeks). The CHMP agreed that PK and efficacy could be extrapolated from the adult UC studies, and that the results from study UCO3003 should contribute with further knowledge on paediatric dosing, efficacy data, and safety data.

Study UCO3003

Study design

The study UCO3003 is a phase 3 multicentre, open label golimumab study designed to enroll paediatric participants aged 2 to <18 years with moderately to severely active UC, defined as a baseline full Mayo score of 6 through 12, inclusive, with an endoscopy sub score of ≥2. All study participants must also have demonstrated an inadequate response to, have failed to tolerate, or have a medical contraindication to conventional therapies (ie, IV or oral corticosteroids or the immunomodulators MTX, AZA, or 6-MP). Participants with prior exposure to biologic anti-TNFα agents were not included in the study. The inclusion criteria of study UCO3003 were comparable to those of the adult golimumab Phase 2/3 studies C0524T16 and C0524T17, from which PK and efficacy data were extrapolated. Inclusion of study participants with moderate to severe disease activity is also recommended by the EMA Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1) to enable demonstration of sufficient treatment response. The eligibility criteria were consistent with the proposed paediatric indication.

According to the guideline (CHMP/EWP/18463/2006 Rev.1), a clinical development program for paediatric UC should include children from 2 years of age and older unless there are significant safety concerns or signals that preclude the inclusion of certain age groups, or if the product is not likely to be effective or beneficial in certain age groups. Hence, the age range of the study participants planned to be enrolled in study UCO3003 was in line with this guideline.

Initially, participants ≥30 kg were randomised in a 3:1 ratio to golimumab and infliximab, respectively; According to the MAH, the enrolment into the infliximab arm was however stopped because interpretable golimumab study data would be available without the infliximab arm, anticipated limited ability to interpret the infliximab data, and updated study feasibility assessments. This change was agreed as part of PIP Modification 3 (EMEA-000265-PIP02-11-M03). The reasons to stop the enrolment to the infliximab arm are acknowledged.

Study UCO3003 is a single armed study with no placebo control. A success criterion was set up and were met if the lower limit of the two-sided 90% CI for the proportion of paediatric golimumab participants in clinical remission at week 6 was greater than the upper bound of the 95% CI for the historical adult placebo control (ie, >10.0%). The historical placebo clinical remission rate was derived from a meta-analysis of 7 adult UC studies.

Since study UCO3003 is single armed and lacks a placebo control, it cannot be a stand-alone study to support the paediatric UC indication. Instead, the assessment of efficacy of golimumab on treatment of paediatric UC needed to be supported by extrapolation from adult UC studies, as has been proposed by the MAH and described above. Data derived from the UC3003 study were thus descriptive only.

Endpoints

In study UCO3003, the primary endpoint of clinical remission was defined as a Mayo score ≤2 points, with no individual sub score >1 (the standard definition), based on the Mayo endoscopy sub score assigned by the local endoscopist. The definition and timing of clinical remission assessment correspond to the phase 3 golimumab adult studies (C0524T16 and C0524T17). The guideline (CHMP/EWP/18463/2006 Rev.1) states that remission in paediatric patients with UC should be defined as symptomatic remission accompanied by endoscopic mucosal healing. Hence, the primary endpoint in study UCO3003 was similar to that of the adult studies but did not include any measure of symptomatic remission as suggested by the guideline. However, symptomatic remission was assessed by the PUCAI score at week 6 and analysed as a secondary endpoint. This was acceptable.

According to the MAH, the Mayo score has been used in studies of children with UC and has been the primary outcome in trials of infliximab and adalimumab, the only 2 biologics currently approved in children with UC (Croft 2021; Hyams 2012a). In the paediatric UC adalimumab study, the coprimary endpoints were the proportion of patients who were in partial Mayo score (PMS, i.e., Mayo score without endoscopy sub score) remission at week 8 and the proportion of week 8 PMS responders who were in full Mayo score remission at week 52. In the infliximab study, the primary endpoint was clinical response at week 8 as assessed by the Mayo score. Clinical remission at week 8 as assessed by the Mayo score, was a secondary endpoint. Hence, the definition of clinical remission based on Mayo score used in study UCO3003 has been used by prior paediatric UC studies, only the time point for assessment differs. However, this was not considered an issue.

Conduct of the study and demographics

A total of 84 participants were enrolled in study UCO3003. Of these, 58 were randomised either to golimumab (n=43) or to infliximab (n=15). In addition, 26 participants were directly assigned to golimumab.

Study discontinuation during the first 6 weeks was low. Of 69 initially assigned to golimumab, 62 remained in the study until week 6, when the primary endpoint was analysed. Hence, the actual sample size corresponded to the study protocol.

Most participants were from Europe (32/69, 46.4%). Most participants were >12 years old (54/69, 78.3%) or >45 kg (52/69, 75.4%). Only 2 participants were <6 years old, the youngest one 4 years and the weight span was between 16 and 107 kg, with mean/median weight around 52/51 kg. The median (range) duration of disease was 1.43 (0.2, 7.8) years. Based on Mayo score, most participants (63/69, 91.3%) had UC of moderate severity. 4/69 (5.8%) had severe disease, and 2/69 (2.9%) had mild severity.

Inclusion and exclusion criteria were in line with the proposed indication. Inclusion criteria included age 2 to <18 years, moderately to severely active UC, defined as a baseline Mayo score of 6 through 12, inclusive, with an endoscopy sub score of ≥2. However, according to the baseline characteristics, 2 of

the participants had no or mild disease (Mayo score <6). The MAH stated that 2 participants were inadvertently enrolled with Mayo score of 5 due to miscalculation and thus categorized with mild UC. Both participants had endoscopy sub scores >2 (one sub score of 2, one sub score of 3) and were allowed to remain in the study and protocol deviations were recorded.

53/69 (76.8%) of study participants had a history of inadequate response, intolerance, or dependence to corticosteroids and/or 6-MP/AZA/MTX. 43/69 (62.3%) were refractory, dependent or intolerant to corticosteroids. 35/69 (50.7%) were refractory or intolerant to 6-MP/AZA/MTX. However, the number of patients refractory or intolerant to the individual medicines (6-MP, AZA or MTX) was not presented. The MAH was asked to provide the exact number of study participants refractory or intolerant to the individual medicines 6-MP, AZA, or MTX. However, the MAH stated that this could not be provided as data were collected at group level. Instead, the MAH has provided some additional information on historical use of these medicines from the concomitant medication data form. Information on the exact number of participants being refractory or intolerant to these individual medicines was not considered crucial for the assessment and the issue was therefore not further pursued.

The use of concomitant UC medication at baseline was high, 67/69 (97.1%) of study participants received any UC concomitant medication. Corticosteroids were used by 36/69 (52.2%), 6-MP/AZA by 33/69 (47.8%), and oral aminosalicylate by 61/69 (88.4%). Upon request, the MAH has specified concomitant UC medication used by the study population in the PURSUIT2-study in the section 5.1 of the SmPC:

"The majority of the 69 participants (97.1%) were receiving UC-related medications (corticosteroids, immunomodulators, and/or 5-ASA); 52.2% of participants were receiving corticosteroids, and 88.4% were receiving oral 5-ASA."

Of the 69 participants receiving golimumab, 40 participants (58%) completed week 54. Thirty-two participants (46.4%) terminated the study prior to the final safety visit. The most common reason was adverse event (worsening of UC disease), which occurred in 15 participants, followed by lack of efficacy, which occurred in 8 participants. Hence, a number of study participants experienced lack of efficacy and the MAH was requested discuss on how to proceed with treatment if no effect/worsening of disease was seen. Upon request, the MAH added a sentence in section 4.2 of the SmPC describing that continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within 12 to 14 weeks of treatment (after 4 doses). This was considered acceptable and also in line with wording in the adult UC SmPC.

Study UCO1001

This supportive study was a phase 1b, multicentre, 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. One objective of the study was to evaluate the efficacy of golimumab maintenance treatment in this population.

The dose regimen for the patients ≥45 kg was the same than in study UCO3003, but for patients <45 kg, the dose was lower in the UCO1001 study (e.g. 90 mg/m^2 followed by 45 mg/m^2). In study UCO3003, the dose regimen for patients weighing <45 kg was 120 mg/m^2 (max 200 mg), followed by 60 mg/m^2 (max 100 mg).

About half of the participants were males (48.6%), and a majority were white (85.7%). The mean age was 13.4 years (SD 3.21). 15 (42.9%) had a weight <45 kg, and 5 of these had a weight <30 kg. 20 (57.1%) had a weight equal to or above 45 kg.

Mean UC disease duration was 2.35 years. 30 (85.7%) had moderate disease activity (Mayo score 6 to 10) and 5 (14.3%) had severe disease activity (Mayo score >10).

The mean age and disease duration of the study participants in study UCO1001 were comparable to study UCO3003, but a higher proportion of study participants in UCO1001 had a weight <45 kg, and severe disease activity.

However, no patients were below 6 years old, and the weight span was between 19-134 kg. Thus, no further information is gained from this study regarding patients below 6 years or below 15 kg.

In study UCO1001, all participants (n=35) had prior use of UC medication. The most used prior therapy was corticosteroids (33/35, 94.3%). 20/35 (57.1%) had prior use of azathioprine and 6/35 (17.1%) had prior use of 6-mercaptopurin.

Efficacy data and additional analyses

Study UCO3003

Efficacy results, induction phase

Study UCO3003 showed that 31.9% (22/69) of golimumab treated participants were in clinical remission as assessed by the Mayo Score at week 6. With this result, the study met its pre-define success criterion. This proportion was also numerically higher than the proportion of adult participants in clinical remission at week 6 in the T17 golimumab 200 mg → 100 mg group (17.8%). It should however be highlighted that the adult data were based on blinded therapy. Although acknowledging the limitation of comparison between studies it could also be pointed out that the efficacy seen in clinical remission rate was somewhat lower compared to previous paediatric UC studies with other TNF inhibitors. The adalimumab study showed clinical remission at week 8 (as assessed by the PMS) in 28/47 (59.6%) in the high dose induction group, and in 13/30 (43.3%) in the low dose induction group.

In study UCO3003, improvement was shown in several secondary efficacy endpoints.

At week 6, 33.3% of 69 participants receiving golimumab were in clinical remission as assessed by PUCAI score. Corresponding figures at week 8 in the paediatric adalimumab study were 33.3% (low dose induction group) and 46.8% (high dose induction group). The paediatric infliximab study demonstrated a similar result with 33.3% being in clinical remission at week 8 as assessed by the PUCAI score.

Clinical response was achieved by 39/69 (56.5%) in study UCO3003 as assessed by the Mayo score at week 6. This proportion is similar to the proportion of adult participants in clinical response at week 6 in the T17 golimumab 200 mg → 100 mg group (51.0%).

Endoscopic/mucosal healing at week 6 was achieved in 40.6% of 69 participants in UCO3003. This proportion is similar to the proportion of adult participants who achieved endoscopic/mucosal healing at week 6 in the T17 golimumab 200 → 100 mg group (42.3%).

Efficacy results maintenance phase

At week 54, 16/41 (39%) participants in UCO3003 were in symptomatic remission (Mayo stool frequency sub score of 0 or 1 and a rectal bleeding sub score of 0).

13/41 (31.7%) were in clinical remission as assessed by the Mayo score at week 54. This proportion is similar to the proportion of induction responders in clinical remission at week 54 of the maintenance study in the T18 golimumab 100 mg group (33.8%). In the paediatric adalimumab study, 14/31

(45.2%) were in clinical remission (as assessed by the Mayo score) in the high maintenance dose group at week 52, and 9/31 (29.0%) in the standard maintenance dose group.

At week 54, 14/41 (34.1%) were in clinical remission as assessed by the PUCAI score. In the paediatric adalimumab study, PUCAI remission at week 52 was reported in 18/31 (58.1%) in the high maintenance dose group and 14/31 (45.2%) in the standard maintenance group. In the infliximab study, 8/21 (38.1%) were in clinical remission as assessed by the PUCAI score at week 54 in the q8w group, and 4/22 (18.2%) in the q12w group.

In study UCO3003, 15/41 (36.6%) had mucosal healing at week 54. The corresponding proportion of adult induction responders in study T18 who achieved endoscopic/mucosal healing was 46.4%.

Of 22 participants who were in clinical remission at week 6, 12 (54.5%) were still in clinical remission at week 54 as assessed by the Mayo score. A similar proportion of adult participants (53.7%) who were in clinical remission after induction maintained clinical remission at Week 30 in study T18.

13/41 (31.7%) were in clinical remission as assessed by the Mayo score at week 54 and had not received corticosteroids for at least 12 weeks prior to this week.

Inflammatory biomarkers

At week 6, the median reduction from baseline faecal calprotectin level was 227.0 mg/kg. Among the week 6 clinical responders, the median reductions in faecal calprotectin from baseline were 86.0 mg/kg at week 14, 0.0 mg/kg at week 36, and 0.0 mg/kg at Week 54.

Health-related quality of life

The mean (SD) change from baseline IMPACT-III scores at week 6 was 11.1 (17.12). The change from baseline in IMPACT-III score from week 6 through week 54 was assessed in the 35 week 6 clinical responders (≥ 10 years old). The mean (SD) changes from baseline IMPACT-III scores were similar between week 6 and week 14, at 18.8 (12.87) and 17.3 (20.69), respectively, and were at 12.7 (19.27) at week 30 and 9.1 (19.25) at week 54.

Subgroup analyses

Subgroup analyses by age and baseline body weight were performed to examine the consistency of the primary endpoint of clinical remission at week 6.

The clinical remission rates by Mayo score at week 6 were 46.7% (7/15) in the 2 to <12 years subgroup, and 27.8% (15/54) in the 12 to <18 years subgroup. In the <45 kg subgroup, the clinical remission rate at week 6 was 41.2% (7/17), and in the ≥45 kg subgroup 28.8% (15/52). Among the 8 participants who were under 30 kg, 3 (37.5%) achieved clinical remission at week 6. Hence, clinical remission rates were higher in children <12 years and in the <45 kg subgroup. The suggested posology leads to higher exposure of Simponi in some of the children than in the adults, however it is acknowledged that the paediatric studies were designed to target a high exposure in order to maximise long-term remission rates. A possibility for dose reduction has therefore been introduced in the SmPC, for patients in remission at week 54 or later which is acceptable (see also 2.3.5. pharmacology and 2.5.1. safety discussions).

Although no patients below the age of 4 was included in the study, it is not expected that children in the age span 2-4 years should differ substantially from children >4 years with respect of disease characteristics, response, safety or exposure (see also 2.5.1. safety discussion). Thus, extrapolation to children down to 2 years (but not below) and weighting at least 15 kg (as discussed in the pharmacology section 2.3.5.) is acceptable.

Study UCO1001

The proportion of study participants in clinical remission at week 6 was 42.9% in study UCO1001, which was slightly higher compared to the study UCO3003 (31.9%). Clinical remission assessed by the PUCAI score was achieved by 34.3% in UCO1001 and 33.3% in UCO3003. 60.0% of study participants in UCO1001 were in clinical response at week 6, which was comparable to UCO3003 (56.5%). Mucosal healing was achieved by 54.3% in UCO1001 and 40.6% in UCO3003.

Hence, improvement in some of the efficacy variables were achieved by a higher proportion of study participants in UCO1001.

2.4.4. Conclusions on the clinical efficacy

The efficacy of golimumab induction and maintenance dosing regimens in the paediatric population was demonstrated at week 6 and week 54 in the phase 3 study UCO3003. Clinical benefit was observed across multiple outcomes, including clinical remission, clinical response, symptomatic remission, mucosal healing, health-related quality of life (HRQoL), and inflammatory biomarkers. Comparable findings were reported in the supportive phase 1 study UCO1001.

Although the evidence is derived from a small, uncontrolled, single-arm, open-label phase 3 trial and a supportive phase 1 study, these results are reinforced by adult UC studies T17 and T18, which demonstrated similar efficacy profiles to those seen in paediatric patients. Furthermore, the rationale for extrapolating efficacy from adults with UC to paediatric patients (aged ≥2 years) is acknowledged and endorsed. Efficacy data was also supported by extrapolation of results seen in already approved indication in populations with a similar disease.

Therefore, based on the available paediatric data and extrapolation from adult studies, clinical efficacy in paediatric patients aged 2 years and older and weighing at least 15 kg is considered demonstrated.

2.5. Clinical safety

Introduction

To assess the safety of golimumab in paediatric participants and compare with adult safety data, the participant data were integrated into multiple analysis sets. Unless otherwise noted, all safety analyses were based on data from the pooled paediatric UC studies (UCO3003 and UCO1001) and the adult UC studies (T16, T17, and T18).

Table 26: Number of Subjects in Each Analysis Set; Safety Treated Analysis Set (Summary of Clinical Safety)

	Golimumab			
	Pediatric UC Studies			Adult UC Studies
	CNTO148UCO3003	CNTO148UCO1001	CNTO148UCO3003 and CNTO148UCO1001	Combined (C0524T16, C0524T17, C0524T18)
Safety Treated Analysis Set	69	35	104	1233
Safety Treated Analysis Set During Induction	69	35	104	734
Safety Treated Analysis Set During Maintenance	62	22	84	1075
Safety Responder Analysis Set	41	21	62	464
Safety Responder Analysis Set During Maintenance	41	21	62	384

Safety Treated Analysis Set: participants who received ≥1 dose (complete or partial) of golimumab from Week 0 of induction through Week 54 of maintenance

Safety Treated Analysis Set During Induction: participants who received ≥1 dose (complete or partial) of golimumab SC from Week 0 of induction through Week 6

Safety Treated Analysis Set During Maintenance:

- paediatric participants who received ≥1 dose (complete or partial) of golimumab from Week 6 through Week 54
- adult participants who received ≥1 dose (complete or partial) of golimumab from Week 0 of the maintenance study through Week 54

Safety Responder Analysis Set: participants who received ≥1 dose (complete or partial) of golimumab SC from Week 0 of induction to Week 54 of maintenance and were in clinical response:

- at Week 6 (as determined by the IWRS) for pediatric participants
- at Week 0 of the maintenance study (as determined by the IVRS) for adult participants

Safety Responder Analysis Set During Maintenance:

- paediatric participants who received ≥1 dose (complete or partial) of golimumab from Week 6 through Week 54 for participants in clinical response at Week 6 (as determined by the IWRS).
- adult participants who received ≥1 dose (complete or partial) of golimumab from Week 0 of the maintenance study through Week 54 for participants in clinical response at Week 0 of the maintenance study (as determined by the IVRS)

Patient exposure

Table 27: Golimumab SC Exposure in Paediatric UC Studies by Study Period

	UCO3003	UCO1001	UCO3003 + UCO1001
Induction[a]			
N	69	35	104
Avg number of administrations	2.00	1.97	1.99
Total dose (mg)			
Mean (SD)	272.9 (50.02)	238.6 (71.57)	261.4 (60.06)
Median	300.0	300.0	300.0
Maintenance[b]			
N	62	22	84
Avg number of administrations	9.00	9.00	9.00
Total dose (mg)			
Mean (SD)	839.8 (438.85)	727.2 (400.00)	810.3 (429.54)
Median	1180.0	639.5	990.0
Induction + Maintenance[a,b]			
N	69	35	104
Avg number of administrations	10.09	7.63	9.26
Total dose (mg)			
Mean (SD)	1027.5 (506.57)	695.7 (493.33)	915.9 (524.00)
Median	1210.0	600.0	846.5

a The induction period is Week 0 to prior to Week 6 dose administration.
b The maintenance period is from the Week 6 dose administration through Week 54 prior to dose administration.

Sourced from: Attachment TSIEXP01Pa; Attachment TSIEXP01Pb; Attachment TSIEXP01Pc

Adverse events

Table 28: Overall Summary of Treatment-emergent Adverse Events During Induction Period; Safety Treated Analysis Set During Induction (Summary of Clinical Safety)

	Golimumab			
	Pediatric UC Studies			
	CNTO148UCO3003	CNTO148UCO1001	CNTO148UCO3003 and CNTO148UCO1001	Adult UC Study C0524T17[a]
Analysis set: Safety Treated Analysis Set During Induction	69	35	104	734
Avg duration of follow-up (weeks)	6.3	5.7	6.1	6.1
Avg exposure (number of administrations)	2.0	2.0	2.0	2.0
Subjects with 1 or more:				
AEs	47 (68.1%)	30 (85.7%)	77 (74.0%)	287 (39.1%)
Serious AEs	10 (14.5%)	7 (20.0%)	17 (16.3%)	22 (3.0%)
AEs leading to discontinuation of study intervention	6 (8.7%)	2 (5.7%)	8 (7.7%)	4 (0.5%)
AEs reasonably related to study intervention	8 (11.6%)	11 (31.4%)	19 (18.3%)	123 (16.8%)
AEs of severe intensity	10 (14.5%)	3 (8.6%)	13 (12.5%)	17 (2.3%)
Infections[b]	17 (24.6%)	9 (25.7%)	26 (25.0%)	88 (12.0%)
Serious infections[b]	1 (1.4%)	0	1 (1.0%)	4 (0.5%)
Injection-site reactions[c]	2 (2.9%)	6 (17.1%)	8 (7.7%)	25 (3.4%)

[a] Includes data from the time of the first golimumab dose onward.
[b] Infection as assessed by the investigator.
[c] Injection-site reactions as assessed by the investigator.

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Table 29: Overall Summary of Treatment-emergent Adverse Events During Maintenance Period; Safety Treated Analysis Set During Maintenance (Summary of Clinical Safety)

	Golimumab			
	Pediatric UC Studies			
	CNTO148UCO3003	CNTO148UCO1001	CNTO148UCO3003 and CNTO148UCO1001	Adult UC Study C0524T18[a]
Analysis set: Safety Treated Analysis Set During Maintenance	62	22	84	1075
Avg duration of follow-up (weeks)	40.0	35.6	38.8	41.6
Avg exposure (number of administrations)	9.0	9.0	9.0	9.8
Subjects with 1 or more:				
AEs	58 (93.5%)	21 (95.5%)	79 (94.0%)	801 (74.5%)
Serious AEs	21 (33.9%)	7 (31.8%)	28 (33.3%)	152 (14.1%)
AEs leading to discontinuation of study intervention	9 (14.5%)	3 (13.6%)	12 (14.3%)	129 (12.0%)
AEs reasonably related to study intervention	12 (19.4%)	11 (50.0%)	23 (27.4%)	311 (28.9%)
AEs of severe intensity	14 (22.6%)	6 (27.3%)	20 (23.8%)	144 (13.4%)
Infections[b]	38 (61.3%)	15 (68.2%)	53 (63.1%)	398 (37.0%)
Serious infections[b]	9 (14.5%)	1 (4.5%)	10 (11.9%)	33 (3.1%)
Injection-site reactions[c]	3 (4.8%)	3 (13.6%)	6 (7.1%)	31 (2.9%)

[a] Includes data from the time of the first golimumab dose onward.
[b] Infection as assessed by the investigator.
[c] Injection-site reactions as assessed by the investigator.

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Table 30: Number of Subjects With Treatment-emergent Adverse Events With Frequency of at Least 5% of Golimumab Treated Subjects in Study CNTO148UCO1001 and CNTO148UCO3003 During Induction Period by Preferred Term; Safety Treated Analysis Set During Induction

	Golimumab			
	Pediatric UC Studies			
	CNTO148UCO3003	CNTO148UCO1001	CNTO148UCO3003 and CNTO148UCO1001	Adult UC Study C0524T17[a]
Analysis set: Safety Treated Analysis Set During Induction	69	35	104	734
Avg duration of follow-up (weeks)	6.3	5.7	6.1	6.1
Avg exposure (number of administrations)	2.0	2.0	2.0	2.0
Subjects with 1 or more AEs	47 (68.1%)	30 (85.7%)	77 (74.0%)	287 (39.1%)
Preferred term				
Colitis ulcerative	10 (14.5%)	8 (22.9%)	18 (17.3%)	15 (2.0%)
Headache	6 (8.7%)	8 (22.9%)	14 (13.5%)	30 (4.1%)
Abdominal pain	3 (4.3%)	6 (17.1%)	9 (8.7%)	11 (1.5%)
Fatigue	3 (4.3%)	3 (8.6%)	6 (5.8%)	9 (1.2%)

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.1.
[a] Includes data from the time of the first golimumab dose onward.

Table 31: Number of Subjects With Treatment-emergent Adverse Events With Frequency of at Least 5% of Golimumab Treated Subjects in Study CNTO148UCO1001 and CNTO148UCO3003 During Maintenance Period by Preferred Term; Safety Treated Analysis Set During Maintenance

	Golimumab			
	Pediatric UC Studies			
	CNTO148UCO3003	CNTO148UCO1001	CNTO148UCO3003 and CNTO148UCO1001	Adult UC Study C0524T18[a]
Analysis set: Safety Treated Analysis Set During Maintenance	62	22	84	1075
Avg duration of follow-up (weeks)	40.0	35.6	38.8	41.6
Avg exposure (number of administrations)	9.0	9.0	9.0	9.8
Subjects with 1 or more AEs	58 (93.5%)	21 (95.5%)	79 (94.0%)	801 (74.5%)
Preferred term				
Colitis ulcerative	34 (54.8%)	11 (50.0%)	45 (53.6%)	203 (18.9%)
Upper respiratory tract infection	12 (19.4%)	6 (27.3%)	18 (21.4%)	66 (6.1%)
Headache	8 (12.9%)	7 (31.8%)	15 (17.9%)	86 (8.0%)
Abdominal pain	6 (9.7%)	6 (27.3%)	12 (14.3%)	56 (5.2%)
Anaemia	8 (12.9%)	2 (9.1%)	10 (11.9%)	47 (4.4%)
Diarrhoea	5 (8.1%)	5 (22.7%)	10 (11.9%)	26 (2.4%)
COVID-19	8 (12.9%)	0	8 (9.5%)	0
Nasopharyngitis	4 (6.5%)	4 (18.2%)	8 (9.5%)	103 (9.6%)
Nausea	4 (6.5%)	4 (18.2%)	8 (9.5%)	39 (3.6%)
Haematochezia	7 (11.3%)	0	7 (8.3%)	11 (1.0%)
Influenza	5 (8.1%)	2 (9.1%)	7 (8.3%)	27 (2.5%)
Pyrexia	4 (6.5%)	3 (13.6%)	7 (8.3%)	40 (3.7%)
Decreased appetite	2 (3.2%)	4 (18.2%)	6 (7.1%)	5 (0.5%)
Fatigue	1 (1.6%)	5 (22.7%)	6 (7.1%)	25 (2.3%)
Arthralgia	4 (6.5%)	1 (4.5%)	5 (6.0%)	74 (6.9%)
Cough	2 (3.2%)	3 (13.6%)	5 (6.0%)	48 (4.5%)
Oropharyngeal pain	2 (3.2%)	3 (13.6%)	5 (6.0%)	23 (2.1%)
Pharyngitis	3 (4.8%)	2 (9.1%)	5 (6.0%)	29 (2.7%)
Weight decreased	2 (3.2%)	3 (13.6%)	5 (6.0%)	3 (0.3%)

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.1.
[a] Includes data from the time of the first golimumab dose onward.

Serious adverse event/deaths/other significant events

Serious Adverse Events

A higher proportion of participants in the pooled paediatric studies had 1 or more SAEs reported compared with adults in both the induction (16% vs 3%) and maintenance study (33% vs 14%). The main PT was colitis ulcerative in both groups which also was higher in the paediatric group in both the induction phase (13.5% vs 1.1%) and the maintenance phase (19.0% vs 7.3%).

Of the remaining SAEs in the paediatric population, only two were seen in more than 1 patients: pneumonia, and cytomegalovirus colitis.

According to the MAH most SAEs were resolving or resolved and were considered not related to study intervention by the investigator.

According to the MAH, potential confounding factors for the higher proportions of participants in the paediatric studies with SAEs of colitis ulcerative include a possible lower healthcare provider threshold for hospitalisation of paediatric patients with UC compared with adults leading to higher rates of

paediatric hospitalisation (which would be designated as an SAE), more aggressive intervention in younger paediatric participants who do not achieve rapid relief from symptoms, and lower use of corticosteroids at baseline amongst paediatric participants.

Deaths

From Week 0 of induction through Week 54 of maintenance, there were no deaths in the pooled paediatric studies and a total of 4 (0.3%) deaths in 1,233 participants in the combined adult UC studies.

Other significant events

Targeted AEs included death (see above), serious infections, pneumonia, opportunistic infections, tuberculosis (TB), cellulitis, demyelination, congestive heart failure, hypersensitivity reactions, anaphylactic or serum sickness-like reactions, hepatobiliary events, and malignancies.

In the pooled paediatric studies, there were no reports of death, TB, demyelination, congestive heart failure, or malignancies reported from Week 0 to Week 54 in golimumab-treated participants; these events were infrequently reported in the adult studies (T16, T17, and T18). Opportunistic infections, pneumonia, cellulitis, hypersensitivity reactions, and anaphylactic or serum sickness-like reactions were infrequently reported across the paediatric and adult UC studies.

Serious infection

There was no difference in the proportion of participants with serious infections during the induction phase of the studies. During the maintenance phase there were however more serious infections in the paediatric population (11.9%) than the adult population (3.1%). The serious infections seen in the paediatric population were cytomegalovirus colitis and pneumonia, that were seen in 2 patients each. In addition, COVID-19, Clostridium difficile infection, respiratory tract infection, stump appendicitis, UTI, colitis ulcerative (reported in error), and fungal test positive (candida famata infection) was seen in a single patient.

Opportunistic Infections

During Sponsor medical review, 3 opportunistic infections were identified in UCO3003; one participant had a positive blood culture for candida (coded in MedDRA as fungal test positive) and 2 participants had cytomegalovirus colitis during maintenance The opportunistic infections were considered serious infections.

Pneumonia

Throughout the induction and maintenance periods, cases of pneumonia were infrequent in both the pooled paediatric and adult studies. Two events of pneumonia in UCO3003 were reported as SAEs that according to the MAH were not related to study intervention and resolved.

Cellulitis

A total of 3 (2.9%) of 104 participants in the pooled paediatric studies and 11 (0.9%) of 1,233 participants in the adult studies had 1 or more AEs of cellulitis reported from Week 0 of induction to Week 54 of maintenance. The 3 cases of cellulitis reported in UCO3003 (1 case of cellulitis and 2 skin infections) were mild and did not lead to study intervention discontinuation.

Hypersensitivity Reactions

A total of 8 (7.7%) of 104 participants in the paediatric studies and 24 (1.9%) of 1,233 participants in the adult studies had 1 or more hypersensitivity reaction AEs reported from Week 0 of induction to

Week 54 of maintenance. All of the hypersensitivity reactions observed in UCO3003 and UCO1001 were mild in intensity except one moderate case of seasonal allergy; none of the events were considered reasonably related to study intervention by the investigator or resulted in study intervention discontinuation. Based on these AE characteristics and small absolute number of occurrences, the difference in proportions of hypersensitivity reaction rates between paediatric and adult studies is considered as not clinically relevant by the MAH.

Anaphylactic or Serum Sickness-like Reactions

There were no events of anaphylaxis or serum sickness-like reactions in the pooled paediatric studies and 1 event in the adult studies from Week 0 of induction to Week 54 of maintenance. The incidence rate of anaphylaxis or serum sickness-like reactions in the adult studies was 0.09 per 100 person-years.

Laboratory findings

Haematology and chemistry laboratory test

The MAH states that in general, the proportions of participants who experienced markedly abnormal values in haematology and chemistry laboratory test results were low and similar between the pooled paediatric studies and adult studies, and there were no consistent trends observed that suggested an association of golimumab with changes in routine laboratory parameters.

Antinuclear Antibodies

A total of 7 (7.7%) of 91 participants in the pooled paediatric studies and 45 (4.2%) of 1,077 participants in the adult studies, who had a negative ANA at Week 0 of induction, had a subsequent positive ANA titer ≥1:160 at some time postbaseline

Anti-double stranded DNA Antibodies

Anti-double stranded DNA antibodies were evaluated in participants who were ANA positive postbaseline. Eleven of 12 ANA-positive participants in the pooled paediatric studies and 34 of 81 ANA-positive participants in the adult studies were anti-dsDNA negative at Week 0. None of these ANA-positive/anti-dsDNA negative participants in the pooled paediatric studies and 1 (2.9%) of the participants in the adult studies were anti-dsDNA positive postbaseline

Vital signs

There were no consistent clinically meaningful changes from baseline in vital signs in the pooled paediatric studies, UCO3003 and UCO1001. Vital signs summarised were collected from baseline (week 0) through the week 54 visit. Vital signs and physical examination findings were monitored during the paediatric studies by the investigator(s). Vital sign-related AEs were reported and analysed as standard AEs and there were no concerns identified.

Safety in special populations

While the interpretation is limited by small sample sizes, the safety profile of golimumab was consistent across baseline age, weight, and concomitant medication subgroups of the pooled paediatric UC studies (UCO3003 and UCO1001).

Notable differences across the following subgroups observed from Week 0 of induction through Week 54 of maintenance included:

- Sex: A higher proportion of female participants had 1 or more infections reported compared with male participants.
- Age: Of the total 104 participants, 25 (24.0%) participants were aged 2 to <12 years, and 79 (76.0%) were aged 12 to <18 years.

  - Compared with participants aged 12 to <18 years, higher proportions of participants aged 2 to <12 years had 1 or more:

    - AEs reported in the Gastrointestinal disorders (primarily colitis ulcerative), Infections and infestations (primarily upper respiratory tract infection, pharyngitis, and nasopharyngitis), and Respiratory, thoracic, and mediastinal disorders SOCs
    - SAEs, primarily colitis ulcerative
    - AEs that led to study intervention discontinuation

  - Compared with participants aged 2 to <12 years, higher proportions of the participants aged 12 to <18 years had 1 or more:

    - AEs in the Blood and lymphatic system disorder SOC
    - AEs of COVID-19

- Body weight: An overall summary of safety across the body weight subgroups is provided in the table below.

Table 32: Overall Summary of Treatment-emergent Adverse Events From Week 0 of the Induction Period Through Week 54 of the Maintenance Period by Baseline Weight; Safety Treated Analysis Set

	Golimumab CNTO148UCO3003 and CNTO148UCO1001			
	<45 kg			
	<30 kg	30-45 kg	Combined	≥45 kg
Analysis set: Safety Treated Analysis Set	13	19	32	72
Avg duration of follow-up (weeks)	37.0	36.8	36.9	40.7
Avg exposure (number of administrations)	8.8	8.2	8.4	9.6
Subjects with 1 or more:				
AEs	13 (100.0%)	18 (94.7%)	31 (96.9%)	69 (95.8%)
Serious AEs	8 (61.5%)	8 (42.1%)	16 (50.0%)	27 (37.5%)
AEs leading to discontinuation of study intervention	5 (38.5%)	5 (26.3%)	10 (31.3%)	10 (13.9%)
AEs reasonably related to study intervention	1 (7.7%)	6 (31.6%)	7 (21.9%)	26 (36.1%)
AEs of severe intensity	5 (38.5%)	4 (21.1%)	9 (28.1%)	22 (30.6%)
Infections[a]	10 (76.9%)	10 (52.6%)	20 (62.5%)	43 (59.7%)
Serious infections[a]	2 (15.4%)	2 (10.5%)	4 (12.5%)	6 (8.3%)
Injection-site reactions[b]	0	2 (10.5%)	2 (6.3%)	8 (11.1%)

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

Additional analyses of the age and body weight subgroups showed:

- No significant differences in the overall proportions of participants with AEs, AEs considered reasonably related to study intervention by the investigator, severe AEs, infections, or injection-site reactions were observed across the age subgroups
- No significant differences in the overall proportions of participants with AEs, severe AEs, infections, or injection-site reactions were observed across the body weight subgroups.

The results observed in the age and weight subgroups for the other analysis were consistent with the results observed from week 0 to week 54.

Discontinuation due to adverse events

During the **induction period** (week 0 to week 6 Prior to Dose), AEs that led to study intervention discontinuation were reported infrequently in both the pooled paediatric studies and T17. The proportion of participants in the pooled paediatric studies (8 [7.7%] of 104 participants) who had 1 or more AEs that led to study intervention discontinuation reported during induction was slightly higher than adults in T17 (4 [0.5%] of 734 participants.

During the induction period, all AEs that led to study intervention discontinuation in the 8 (7.7%) paediatric participants were colitis ulcerative or colitis, whereas 2 (0.3%) participants in T17 discontinued study intervention due to an AE PT of colitis ulcerative.

During the **maintenance period** (Week 6 Dose to Week 54 Prior to Dose), the proportion of participants in the pooled paediatric studies (12 [14.3%] of 84 participants) who had 1 or more AEs that led to study intervention discontinuation was similar to adults in T18 (129 [12.0%] of 1,075 participants;

- Nine (10.7%) paediatric participants and 91 (8.5%) participants in T18 had an AE of colitis ulcerative that led to study intervention discontinuation.
- One paediatric participant each had an AE of diarrhoea haemorrhagic, cytomegalovirus colitis, and fungal test positive that led to study intervention discontinuation.

Additional supportive Safety data

Prospective Interventional Pediatric UC Study UCO1001 Extension

In UCO1001 from Week 14 through Week 126, a total of 8 SAEs were reported in 5 (25.0%) of 20 participants. The most frequently reported SAE PT was colitis ulcerative, reported in 3 (15.0%) participants. One of these participants 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. Among the total of 11 participants treated with golimumab after Week 126 in UCO1001, no SAEs were reported.

Observational Long-term Registry Study in IBD: DEVELOP

The DEVELOP study is a multicenter, prospective, observational, ongoing registry study of the long-term safety and clinical status of pediatric patients with IBD conducted as a post-marketing requirement for another TNF inhibitor-α (infliximab). Notably, the registry data analysed include cumulative safety data up to 30 June 2023 from all patients aged <18 years at the time of enrollment in DEVELOP. The safety data from a subgroup of golimumab-treated patients with UC aged <18 years at the time of the first golimumab exposure in the DEVELOP registry are consistent with the established overall safety profile of golimumab and the safety profile of the anti-TNF agent class. The safety results of the anti-TNF only cohort of patients with UC in the DEVELOP registry support the safety data for paediatric patients with UC treated with golimumab. All available exposure data has been provided to demonstrate the long-term safety of golimumab. Therefore, the DEVELOP data summaries include safety events reported during follow-up for patients after they have reached 18 years of age and those who have transitioned from a study physician to a non-study physician. The golimumab-treated subgroup of patients with UC is not a subset of the anti-TNF agents only cohort, rather it is a subgroup of all patients with UC included in the DEVELOP registry. During the DEVELOP registry, a total of 21 patients with UC had their initial exposure to golimumab at <18 years of age.

Among these patients, the median golimumab exposure during the DEVELOP registry was 12.4 months (IQ Range: 3.0; 43.9); the longest exposure to golimumab was 95 months. The median average dose of golimumab administered during the registry was 100.0 mg. Golimumab has yet to be approved in the United States or European Union for treatment of pediatric patients with UC. Consequently, all golimumab administered to patients aged <18 years in DEVELOP was prescribed off-label. In DEVELOP, the anti-TNF agents only cohort includes patients with UC exposed to at least 1 anti-TNF agent (ie, golimumab, infliximab and infliximab biosimilars, adalimumab and adalimumab biosimilars, certolizumab pegol, and etanercept) but not exposed to any non-anti-TNF biologic agents (ie, natalizumab, ustekinumab, vedolizumab, anakinra, sargramostim, immunoglobulin, mirikizumab, and risankizumab).

The anti-TNF agents only cohort Baseline demographic and disease characteristics were similar between the pediatric population in the UCO3003 and UCO1001 studies and UC patients in the DEVELOP study. However, in DEVELOP the use of IBD-targeted biologics is not restricted after enrollment and during registry follow-up. Thus, of the 21 patients in the golimumab-treated subgroup, 18 (85.7%) patients had received biologics prior to initial SIMPONI exposure during the registry, whereas UCO1001 and UCO3003 only enrolled participants who were biologic therapy naïve. The golimumab-treated pediatric patients with UC subgroup (n=21) in DEVELOP may have had more refractory disease based on prior medication use than those participants treated in the golimumab pediatric UC clinical development program. The safety results of the DEVELOP study do not indicate unexpected safety concerns with long-term golimumab exposure in this pediatric UC population. Although the golimumab-treated subgroup of patients with UC in DEVELOP was small and had different baseline clinical characteristics than participants in UCO3003 and UCO1001, no new safety concerns were identified as of the most recent interim analysis (30 June 2023). However, due to significant differences in study design, sample size, study population, and data collection methods, cross study safety comparisons between the subgroup of golimumab-treated patients with UC in DEVELOP and the golimumab paediatric UC clinical studies should be interpreted with caution. The SAE and targeted AE rates for the golimumab-treated subgroup of patients with UC were consistent with the anti-TNF agents only cohort of patients with UC.

SAEs:

- Golimumab-treated subgroup: 17.44 SAEs per 100 person-years (45.9 person-years of golimumab exposure)
- Anti-TNF agents only cohort: 15.64 SAEs per 100 person-years (6031.2 person-years of follow-up)

Serious infections:

- Golimumab-treated subgroup: 2.18 serious infections per 100 person-years (45.9 person-years of golimumab exposure)
- Anti-TNF agents only cohort: 3.18 serious infections per 100 person-years (6031.2 person-years of follow-up;)

Other targeted AE rates:

- Golimumab-treated subgroup: No events of TB, malignancy, or opportunistic infections; 2.18 events of new autoimmune disease per 100 person-years (45.9 person-years of golimumab exposure).

- Anti-TNF agents only cohort: 0.03 events of TB per 100 person-years, 0.07 events of malignancy per 100 person-years, and 1.16 events of autoimmune disease per 100 person-years (6031.2 person-years of follow-up)

Post marketing experience

Post-marketing information has been accruing since the first approval of golimumab on 07 April 2009 in Canada. As of 06 April 2024, golimumab is authorised in 104 countries and territories worldwide. Overall, an estimated 13,841 participants have been exposed to golimumab in the clinical development program. The exposure to commercial golimumab is 2,096,200 person-years. The evaluation of postmarketing data is part of the Sponsor's comprehensive safety surveillance program, which also includes review of data from ongoing clinical studies and registries. Periodic Safety Update Reports generated for golimumab reflect ongoing postmarketing safety surveillance, as well as assessments of all important identified and potential risks. No new ADRs were identified during the reporting interval of the most recent PBRER.

2.5.1. Discussion on clinical safety

The clinical development program to support the use of golimumab in paediatric patients with moderately to severely active UC was based on the pooled safety data from 2 prospective interventional paediatric UC clinical studies; the phase 3 open-label CNTO148UCO3003 study (UCO3003) and the phase 1 PK CNTO148UCO1001 study (UCO1001).

The pooled safety analyses included data on 104 paediatric patients, representing a total of 79 patient years (PYs) of exposure. The number of paediatric patients exposed were thus limited, especially data beyond 1 year. Upon request the MAH provided additional safety data from study UCO3003 up until 2 December 2024, thus providing additional 8 months of safety data (120 PY). In line with the previous report, the SOCs with the highest frequency of AEs were gastrointestinal disorders and infections and infestations and the most common AEs were upper respiratory tract infection, colitis ulcerative, COVID-19 and nasopharyngitis. A few additional SAEs were reported, however the types of SAEs reported were in line with those already known.

The safety results of the 2 prospective interventional pooled paediatric UC studies were also compared with the corresponding results of 3 studies in adults with moderately to severely active UC, C0524T16 (T16, in which participants received 1 golimumab IV induction dose), C0524T17 (T17, in which participants received 2 golimumab SC induction doses), and C0524T18 (T18, in which participants from T16 and T17 received golimumab SC maintenance). In addition, data from C0168Z02 (DEVELOP study), a registry study in paediatric IBD created as a postmarketing requirement for the FDA and EMA for infliximab, provided additional safety information.

In the paediatric UC studies, patients with weight >45 kg (n=72) received a dose corresponding to the adult posology (200mg week 0 and 100mg week 2) as induction treatment, and 100 mg Q4 as maintenance therapy (corresponding to the maintenance dose approved for adult patients >80 kg, and patients <80 kg who have an incomplete response). Patients with a weight <45 mg (n=32) received a dose based on their body surface area with a higher dose given in study UCO3003 than UCO1001.

In general AEs, SAEs, AEs leading to discontinuation and AEs of severe intensity were more common in the paediatric population than the adults in both the induction phase (74%, 16.3%, 7.7%, 12.5% vs 39.1%, 3%, 0.5%, 2.3%) and the maintenance phase (94%, 33.3%, 14.3%, 23.8% vs 74.5%, 14.1%, 12.0%, 13.4%)

Most common AEs in the paediatric UC population (except for ulcerative colitis, 53.6%) were upper respiratory tract infection, headache, abdominal pain, anaemia and diarrhoea. In general, most of the common AEs reported for the paediatric UC population are already included in the SmPC 4.8 as very common or common ADRs. There are however some exceptions: Covid 19 was seen in 8 patients in the paediatric population and none of the adults. This could however be explained by the fact that only the paediatric study UCO3003 was ongoing during the pandemic. In addition, the following AEs were seen more frequently in the paediatric population than adults and not currently included in the SmPC: diarrhoea, haematochezia, decreased appetite, weight decrease. Upon request, the MAH provided additional information, and it was agreed with the MAH that although diarrhea, hematochezia, decreased appetite, and weight decrease were slightly more common in the paediatric population, the overall numbers of the events were few. According to the MAH, all events were mild or moderate, and none led to study discontinuation. Also, the events in the paediatric study UCO3003 were fewer, despite a higher dose in that study. These events could also be manifestation of UC, however most of the events seem to have resolved without dose change or study discontinuation. Therefore, there was not enough evidence to consider these 4 events as ADRs and no update to the PI is warranted.

Regarding SAEs, a higher proportion of participants in the pooled paediatric studies had 1 or more SAEs reported compared with adults in both the induction (16% vs 3%) and maintenance study (33% vs 14%). The main PT was colitis ulcerative in both groups which also was higher in the paediatric group in both the induction phase (13.5% vs 1.1%) and the maintenance phase (19.0% vs 7.3%). Of the remaining SAEs in the paediatric population, only two were seen in more than 1 patients: pneumonia, and cytomegalovirus colitis. The latter is described further below.

A higher number of patients with the AE ulcerative colitis were also the main reason for the higher frequency of severe AEs in the paediatric population.

According to the MAH, potential confounding factors for the higher proportions of participants in the paediatric studies with SAEs of colitis ulcerative include a possible lower healthcare provider threshold for hospitalisation of paediatric patients with UC compared with adults, leading to higher rates of paediatric hospitalisation (which would be designated as an SAE), more aggressive intervention in younger paediatric participants who do not achieve rapid relief from symptoms, and lower use of corticosteroids at baseline amongst paediatric participants. This is acknowledged. However, there could also be a sign of lack of efficacy. Therefore, a statement has been included in the section 4.2 of the SmPC stating that continued therapy should be reconsidered in children who show no evidence of therapeutic benefit within 12 to 14 weeks of treatment. The proposed timepoint (12-14 weeks) are in line with the timepoint accepted for the adults and the MAH has provided a justification that this timepoint is acceptable also for the paediatric population, based on both data from the paediatric study and guideline recommendations.

The paediatric population had more infections than the adult population both in the induction (25% vs 12%) and maintenance phase (63.1% vs 37%). The most common infections in the paediatric population were upper respiratory tract infection, COVID-19 infections and influenza. In most cases, the infections were nonserious and mild and did not result in discontinuation. A slightly higher proportion of the paediatric patients had however more infections that needed antibiotics than the adults. This was mainly due to ear infection, clostridium difficile infection, pharyngitis, and respiratory tract infection.

There was no difference in the proportion of participants with serious infections during the induction phase of the studies. During the maintenance phase there were however more serious infections in the paediatric population (11.9%) than the adult population (3.1%). The serious infections seen in the paediatric population were cytomegalovirus colitis and pneumonia, that were seen in 2 patients each. In addition, COVID-19, Clostridium difficile infection, respiratory tract infection, stump appendicitis,

UTI, colitis ulcerative (reported in error), and fungal test positive (candida famata infection) was seen in a single patient.

Regarding pneumonia there were two cases, both reported as SAEs but according to the investigator not related to study intervention. Regarding opportunistic infections there were 3 events in the paediatric population, one had a positive blood culture for candida and 2 participants had cytomegalovirus colitis during maintenance. All those 3 events were considered serious.

A higher rate of infections in the paediatric population than adults is not unexpected and the types of infections seen are in line with the infections already displayed in the sections 4.8 and/or 4.4 of the SmPC. The sections 4.8 and 4.4 of the SmPC also include information regarding opportunistic infections. Since there are no placebo data in the paediatric population, it was however not fully clear to what extent the higher frequency of infection was caused by Simponi. Upon request, a discussion regarding the frequency of infections seen with treatment with other biologics was provided. In the clinical studies of the other two TNF-inhibitors, the frequency of infections was slightly lower than in the Simponi study. No information regarding the frequency expected in paediatric UC without biologic treatment were provided. However, the frequency of infections did not differ substantially from the numbers seen in the JiA population, despite the higher dose in the UC population. In addition, the sections 4.4 and 4.8 of the SmPC have extensive information regarding infections. Thus, additional information, describing infections in the paediatric population is not warranted.

Injection site reactions are listed as common ADRs in section 4.8 of the SmPC, and frequency and types of reaction seen in the paediatric populations did not differ from what is already known. The most common reactions were injection site erythema and injection site pain. No update of the SmPC is needed based on the findings from this study.

Regarding adverse events of special interest (AESI; named targeted events by the MAH) these included death, serious infections, pneumonia, opportunistic infections, TB, cellulitis, demyelization, congestive heart failure, hypersensitivity reactions, anaphylactic or serum sickness-like reactions, hepatobiliary events, and malignancies. There were no reports of death in the paediatric studies. In addition, there were no reports of TB, demyelination, congestive heart failure, anaphylaxis or serum sickness-like reactions, hepatobiliary events or malignancies reported from Week 0 to Week 54.

There were 3 cases of cellulitis (1 case of cellulitis and 2 skin infections), all mild.

Regarding hypersensitivity reactions a total of 8 (7.7%) of 104 participants in the paediatric studies and 24 (1.9%) of 1,233 participants in the adult studies had 1 or more hypersensitivity reaction AEs reported from week 0 of induction to week 54 of maintenance.

Regarding subgroups it was noticed that the patients with the lowest weight (<30 kg) had more serious AEs, AEs leading to study discontinuation and infections than patients with higher weight. There were only 13 patients with a weight below 30 kg, and the lowest weight in any study person was 16 kg. In addition, there were only 2 patients below 6 years of age, the youngest being 4 years old. Thus, there are limited, if any, safety data in the youngest/lightest patients. For patients within the weight span 10-15 kg there are no clinical data to support the suggested posology, and upon request, the MAH withdrew the posology for the lightest children (10-15 kg), although keeping the indication above 2 years of age. Although no patients below the age of 4 years was included in the study, it is not expected that children in the age span 2-4 years should differ substantially from children >4 years with respect of disease characteristics, response, safety or exposure. Children with very early onset IBD (VEO-IBD), i.e. the youngest of the paediatric IBD population, might have a different clinical presentation and a different aetiology (such as monogenic causes, many of which are inborn errors of immunity), however, the proportion of patients with these distinct features is highest in patients diagnosed <2 years of age. Thus, extrapolation to children down to 2 years (but not below) is

acceptable. In addition, Simponi is also already indicated in JiA children from 2 years. However, since most of the children around 2 years will weigh less than 15 kg, the MAH was requested to include also the weight span in the indication text. The updated indication text is acceptable and now reads:

Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients 2 years of age and older with a body weight of at least 15 kg, who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

The proposed maintenance dose for paediatric patients above 40 kg (100 mg Q4) is higher than the proposed dose for adults <80 kg (50mg Q4). In the adult studies, both doses were tested, with similar efficacy regarding response in both groups. However, there was a slight difference in the number of patients achieving remission, favouring the 100 mg dose, and this was the reason that this dose was chosen in the study. The dose was discussed and accepted by the PDCO.

However, the higher dose has been associated with a higher frequency of AESIs, especially malignancies and serious infections in adults. Thus, for the adults, the higher dose was restricted to patients above 80 kg and patients <80 kg with an incomplete response after induction. As part of the approval of the ulcerative colitis indication in 2013, post-marketing follow-up activities were included in the EU-RMP to gather additional information on colorectal cancer (CRC), colorectal dysplasia, hepatosplenic T-cell lymphoma (HSTCL) and colectomy; the ENEIDA registry study MK-8259-042 and the Nordic registry study MK-8259-013. Both these studies were completed in 2023 and assessed in variation EMEA/H/C/000992/II/0117/G. The conclusion was that "*a higher risk for colectomy for golimumab vs. other TNF inhibitors was observed in the Nordic registry study, but not in the ENEIDA registry study. This observed increase in risk might be explained by residual confounding. A numerically higher risk for colorectal cancer was observed for golimumab vs other TNF inhibitors or thiopurines in the ENEIDA registry study, however the precision in the estimates is low because of the low number of cases overall. Data for the colorectal cancer outcome was not provided from the Nordic registry study".*

In the current SmPC, there are extensive information regarding malignancies in section 4.4, including specific mentioning of findings in paediatric studies regarding TNF-inhibitors as a class. In addition, there are information in section 4.8 regarding a higher incidence of especially lymphoma with higher doses of golimumab. Thus, there are concerns regarding especially long-term use with a higher dose of golimumab in a young population with a chronic disease that will need treatment for several years. However, the MAH has, based on simulation, introduced a possibility for a dose reduction from 100 mg to 50 mg in children >40 kg and from 50 mg to 25 mg in children 15-40 kg. After that dose reduction, the exposures to golimumab in paediatric participants are generally comparable to that of adult participants receiving the maintenance dose of 50 mg. The predicted paediatric exposure is at the lower end of the adult reference distribution, nonetheless the paediatric exposure is within the adult reference range which is acceptable. Upon request, the MAH specified that evaluation of a dose decrease should be done in patients in remission at week 54 or after and this has been included in section 4.2 of the SmPC.

Golimumab is approved for children above 2 years old with polyarticular juvenile arthritis since 2019. Thus, some information regarding safety in small children are already known at least for lower doses. In PJiA, a dose based on body surface area are given to patients <40 kg that is substantially lower than the proposed dose for the UC population. However, upon request a summary of the clinical study safety data in the 3 paediatric studies (UC and JiA) that includes 231 participants (whereof 11 <6 years of age) exposed to golimumab from week 0 to week 54 was provided. In addition, data from the ongoing JiA PASS (178 patients, whereof 15 patients below 6 years) and post marketing data from the GMS global safety database (7 patients < 6 years of age that reported 16 AEs and 211 patients 6-18

years reporting 517 events) were provided. There were no signs in the provided information from clinical studies, registry studies or post marketing that evoke any concerns that the safety profile in children would differ substantially from the adult population. Post marketing, in most cases in both age groups, the AEs reported was due to off label use or device/product related factors.

Regarding long term use, data are scarce regarding children and long-term safety in paediatric patients are included as missing information in the RMP, with an ongoing registry study in pJiA. The MAH included also the extension of the UCO3003 in the RMP, which was endorsed by the CHMP. In addition, the MAH proposed to analyse and present Simponi data achieved from an ongoing registry study (DEVELOP) for another product, in the PSURs. This is also endorsed.

2.5.2. Conclusions on clinical safety

The safety profile of golimumab is well established and includes several known safety concerns as outlined in the SmPC and the risk management plan. No new safety concerns were identified in the paediatric UC studies, and no updates to sections 4.4 or 4.8 of the SmPC were considered necessary, other than incorporating the results of the phase 3 study in patients aged 4 to 17 years.

The short-term safety is similar to the already known safety profile of golimumab in other indications. However, there are still limited safety data in paediatric patients with UC, and the proposed doses results in systemic doses higher than the approved standard dose given to the adult population. A dose reduction for the maintenance treatment has therefore been introduced to reduce long-term exposure of children to higher dose.

The missing information about long-term safety will be further assessed in the ongoing extension of the UCO3003 study which has been included as a category 3 in the RMP and in the observational safety study of golimumab in patients with juvenile idiopathic arthritis using the BiKeR registry. Additional safety information regarding Simponi will be collected in the ongoing registry study (DEVELOP) for another TNF-product and presented as part of the PSURs.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH was requested to submit an updated RMP version 28.3 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 28.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 28.3 with the following content:

Safety concerns

Table 33: Summary of safety concerns

Important Identified Risks	Serious infections
	Demyelinating disorders
	Malignancy
Important Potential Risks	Serious depression including suicidality
	Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero
Missing Information	Long-term safety in paediatric patients

Pharmacovigilance plan

Table 34: Ongoing and planned pharmacovigilance activities

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
PCSIMMA0237: An observational post-approval safety study of golimumab in treatment of polyarticular Juvenile Idiopathic Arthritis (pJIA) using the German Biologics JIA Registry (BiKeR) Ongoing	To investigate the long-term safety of golimumab in pJIA subjects by comparing the risks of primary safety endpoints (serious infections, malignancy, autoimmune processes, and exposure during pregnancy) in the golimumab cohort with those in the comparator cohorts (contemporary anti-TNF cohort, contemporary MTX cohort, and historic anti-TNF cohort), adjusted for baseline characteristics. Secondary objectives will include crude incidence rates of: • Demyelinating disorders • Serious depression including suicidality	• Serious infections • Malignancies • Long-term safety in paediatric patients	Final report	June 2027

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
CNTO148UCO3003: A study of the efficacy and safety of golimumab in pediatric participants with moderately to severely active ulcerative colitis (PURSUIT 2) Ongoing	To assess the efficacy, safety, and pharmacokinetics of golimumab treatment in pediatric participants from 2 to 17 years old with moderately to severely active UC.	• Long-term safety in paediatric patients	Final report	August 2027

Risk minimisation measures

Table 35: Summary of risk minimisation activities and pharmacovigilance activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections	**Routine risk minimisation activities** • SmPC sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and 4.8 (Undesirable effects) • Package Leaflet (PL) sections 2 and 4 **Additional risk minimisation activities** Patient Reminder Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** TOI TFUQ for Serious Infections and Opportunistic Infections TOI TFUQ for TB TOI TFUQ for Progressive Multifocal Leukoencephalopathy (PML)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS) **Additional pharmacovigilance activities** PCSIMMA0237
Demyelinating disorders	**Routine risk minimisation activities** • SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) • PL sections 2 and 4 **Additional risk minimisation activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** PCSIMMA0237
Malignancy	**Routine risk minimisation activities** • SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) • PL sections 2 and 4 **Additional risk minimisation activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** TOI TFUQ for Malignancies (including Lymphoma, Second and Secondary Malignancies) **Additional pharmacovigilance activities**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		PCSIMMA0237
Serious depression including suicidality	**Routine risk minimisation activities** • SmPC section 4.8 (Undesirable effects) • PL section 4 **Additional risk minimisation activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** PCSIMMA0237
Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero	**Routine risk minimisation activities** • SmPC sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy, and lactation) • PL section 2 **Additional risk minimisation activities** Patient Reminder Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** None
Long-term safety in pediatric patients	**Routine risk minimisation activities** None **Additional risk minimisation activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** • PCSIMMA0237 • CNTO148UCO3003 (PURSUIT 2)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and excipients guideline, and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised.

As per GVP XVI guidance (XVI.B.2.1.1.2), if a patient card is included in the outer packaging, it is considered part of the labelling, therefore the text should be agreed to by the Agency. In the case of Simponi, the patient card is part of the outer packaging while information is currently provided in both Annex II and Annex III of the Product Information. Therefore, as requested by EMA, the MAH has taken the opportunity to delete the reference to the core Patient Card messages from Annex II.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There have not been any revisions that significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Ulcerative colitis (UC) is an inflammatory disorder which involves the surface mucosa, crypt epithelium, and submucosa of the colon. Clinically, patients with UC suffer from diarrhoea, rectal bleeding, weight loss, abdominal pain, fever, and may also display prominent extra intestinal manifestations, most commonly arthritis. Paediatric UC is similar to adult UC in terms of demographics, clinical features, pathophysiology, and response to treatment.

UC is a chronic gastrointestinal inflammatory disorder characterised by a life-long chronic course of remissions and exacerbations. While the peak occurrence of paediatric UC is in late adolescence, all ages can be affected, and 4% of paediatric IBD patients are diagnosed in early (age <5 years) childhood. Children aged 2 to 6 years account for approximately 10% of paediatric UC (Herrinton 2007[7], Loftus 2007[8]).

3.1.2. Available therapies and unmet medical need

Treatment of paediatric UC generally follows the same treatment paradigms that are used to treat adult UC. Although there are multiple therapies in several distinct drug classes approved to treat adult UC, approved pharmacologic treatment options are limited for paediatric patients with UC, especially for those who have failed to respond to or tolerate conventional therapy (5-ASA, corticosteroids, or immunomodulators).

Currently, there are 2 approved biologics for children from 6 years of age with UC: infliximab, which is given every 8 weeks during maintenance by IV infusion, and adalimumab, which is given every 2 weeks during maintenance by SC injection. While infliximab and adalimumab are generally safe and well tolerated in the paediatric UC population, less than half of paediatric UC patients achieve sustained clinical remission on infliximab or adalimumab. Additionally, secondary loss of response to infliximab after an initial response occurs in 20% to 40% of all IBD patients after 1 year of therapy.

Without an effective pharmacologic treatment, the only alternative is colectomy which is associated with notable morbidity. As such, there is a need for additional treatment options for paediatric patients with moderately to severely active UC.

3.1.3. Main clinical studies

To support the paediatric UC indication, the MAH used an extrapolation approach to establish efficacy and safety in the patient population ages 2 to <18 years and submitted the results of a phase 3 study in paediatric participants with moderately to severely active UC (CNTO148UCO3003 – PURSUIT 2).

PK and efficacy of golimumab were extrapolated from 2 adult UC phase 3 studies assessing efficacy and safety, C0524T17 and C0524T18, which were completed in 2010 and 2015, respectively. Uncertainties in the extrapolation concept that were to be addressed by the paediatric study

(CNTO148UCO3003) included relation between modelled dosing and predicted exposures, efficacy data supporting the proposed dose regimen for labelling in ages 2 to 17 years, and safety data in children with objective outcomes generated during chronic administration. Extrapolation of efficacy/or safety from adults with UC to children with UC was supported by the Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1) and the ICH E11A guideline on paediatric extrapolation (EMA/CHMP/ICH/205218/2022). Additionally, the PDCO has accepted the extrapolation concept in the PIP of Simponi (EMEA-000265-PIP02-11-M02).

The study (CNTO148UCO3003) was a phase 3, multicentre, randomised, open label study to assess the efficacy, safety, and pharmacokinetics of golimumab in paediatric participants aged 2 to <18 years with moderately to severely active UC defined as a baseline full Mayo score of 6 through 12, inclusive, with an endoscopy sub score of ≥2. The study consisted of a 6-week induction period and a 48-week maintenance period followed by a study extension (for eligible golimumab-treated participants). The study extension was still ongoing at the time of assessment. Children weighing ≥ 45 kg received induction 200 mg SC at week 0, followed by 100 mg SC at week 2 and then maintenance q4w. Children weighing <45 kg received induction 120 mg/m^2 SC (max 200 mg) at week 0, followed by 60 mg/m^2 SC (max 100 mg) at week 2 and then maintenance q4w.

Initially, participants ≥30 kg were randomised in a 3:1 ratio to golimumab and infliximab, respectively; According to the MAH, the enrolment into the infliximab arm was however stopped because interpretable golimumab study data would be available without the infliximab arm, anticipated limited ability to interpret the infliximab data, and updated study feasibility assessments. This was considered acceptable.

The primary endpoint was clinical remission at Week 6 as assessed by the Mayo score. Clinical remission as measured by the Mayo score was defined as a Mayo score ≤2 points, with no individual sub score >1 (based on Mayo endoscopy sub score assigned by the local endoscopist).

A success criterion was set up and were met if the lower limit of the two-sided 90% CI for the proportion of paediatric golimumab participants in clinical remission at Week 6 was greater than the upper bound of the 95% CI for a historical adult placebo control (i.e., >10.0%). The historical placebo clinical remission rate was derived from a meta-analysis of 7 adult UC studies.

A total of 84 participants were enrolled, aged 4–17 years. Of these, 58 were randomised either to golimumab (n=43) or to infliximab (n=15). In addition, 26 participants were directly assigned to golimumab.

Study discontinuation during the first 6 weeks was low. Of 69 initially assigned to golimumab, 62 remained in the study until week 6, when the primary endpoint was analysed.

3.2. Favourable effects

Study UCO3003 showed that 22 out of 69 (31.9%) paediatric patients achieved clinical remission at week 6, as assessed by the Mayo score. With this result, the study met its pre-define success criterion. This proportion is also numerically higher than the proportion of adult participants in clinical remission at week 6 in the T17 golimumab 200 mg → 100 mg group (17.8%) with the caveat that the adult data were based on blinded therapy.

Improvement was also shown in several secondary efficacy endpoints.

Clinical response at week 6 was achieved by 39 out of 69 (56.5%) paediatric patients as assessed by the Mayo score. This proportion is similar to the proportion of adult participants in clinical response at week 6 in the T17 golimumab 200 mg → 100 mg group (51.0%).

Endoscopic/mucosal healing at week 6 was achieved in 28 out of 69 (40.6%) paediatric patients. This proportion is similar to the proportion of adult participants who achieved endoscopic/mucosal healing at week 6 in the T17 golimumab 200 → 100 mg group (42.3%).

At week 54, clinical remission was achieved by 13 out of 41 (31.7%) paediatric patients as assessed by the Mayo score. This proportion is similar to the proportion of induction responders in clinical remission at week 54 of the maintenance study in the T18 golimumab 100 mg group (33.8%). Furthermore, 15 out of 41 (36.6%) paediatric patients had mucosal healing at week 54. The corresponding proportion of adult induction responders in study T18 who achieved endoscopic/mucosal healing was 46.4%.

Of 22 paediatric patients who were in clinical remission at week 6, 12 (54.5%) were still in clinical remission at week 54 as assessed by the Mayo score. A similar proportion of adult participants (53.7%) who were in clinical remission after induction maintained clinical remission at week 30 in study T18.

3.3. Uncertainties and limitations about favourable effects

The age range of the study participants was 4-17 years, and no clinical data is available in children below 4 years, and less than 16 kg. The simulated dosing regimen (i.e. exposure range) for patients 10-15 kg could therefore not be verified.

Given these uncertainties in the dosing recommendation for patients weighting 10-15 kg, the lack of observed data and unclear exposure target, it was agreed to restrict the indication by including a weight limit of at least 15 kg. Although no patients below the age of 4 was included in the study, it is not expected that children in the age span 2-4 years should differ substantially from children >4 years with respect of disease characteristics, response, safety or exposure (see 2.5.1. safety discussion). Thus, extrapolation to children down to 2 years (but not below) is acceptable.

In addition, given that the predicted exposure range in paediatric patients (15-25 kg and 40-60 kg) exceed the adult reference, an option for maintenance dose reduction for patients with remission at or after week 54 has been added in the section 4.2 of the SmPC (see also 2.3.5. pharmacology and 2.5.1. safety discussions).

No uncertainties about the favourable effects remains in the finally agreed indication: *treatment of moderately to severely active ulcerative colitis in paediatric patients 2 years of age and older with a body weight of at least 15 kg, who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.*

3.4. Unfavourable effects

The most frequently reported AEs in the paediatric UC population (except for ulcerative colitis 53.6%) were upper respiratory tract infection, headache, abdominal pain, anaemia and diarrhoea. Most of them are already listed in the section 4.8 of the SmPC as very common or common adverse drug reactions. Events not included in the SmPC were considered not necessary to be added as adverse drug reactions in the SmPC.

The high rate of the AE ulcerative colitis, which was also the main reason for the higher frequency of severe AEs in the paediatric population, was explained by the MAH by potential confounding factors (see 2.5.1. safety discussion). This is acknowledged; however, this could also be a sign of lack of efficacy. Therefore, a statement has been included in the section 4.2 of the SmPC stating that

continued therapy should be reconsidered in children who show no evidence of therapeutic benefit within 12 to 14 weeks of treatment.

There were more infections in the paediatric population than in the adult population both in the induction (25% vs 12%) and maintenance phase (63.1% vs 37%). There were also more serious infections in the paediatric population than the adult population during the maintenance phase (11.9% vs 3.1%). A higher rate of infections in the paediatric population than adults is not unexpected and the types of infections seen (such as upper respiratory tract infection, pharyngitis) are in line with the infections already displayed in the sections 4.8 and/or 4.4 of the SmPC.

No new safety concerns were identified in paediatric UC studies, and no update to sections 4.4 or 4.8 of the SmPC were considered necessary, other than incorporating the results of the phase 3 study in patients aged 4 to 17 years. Safety concerns are also outlined and addressed satisfactorily in the risk management plan (see section 2.6.).

3.5. Uncertainties and limitations about unfavourable effects

The number of paediatric UC patients exposed to golimumab remains limited, particularly with respect to data beyond one year of treatment. However, based on the information provided from clinical studies, registry or post-marketing, there are no signs that evoke that the safety profile in children would differentiate substantially from the adult population.

The patients with the lowest weight (<30 kg) had more serious adverse events, adverse events leading to study discontinuation and infections than patients with higher weight. There were only 13 patients with a weight below 30 kg, and the lowest weight in any paediatric patient was 16 kg. In addition, there were only 2 patients below 6 years of age, the youngest being 4 years old. Thus, there are limited, if any, safety data in the youngest/lightest patients. Therefore, as mentioned above (section 3.2. Favourable effects), the indication and dose recommendation were restricted to patients from 2 years of age and weighting at least 15 kg.

The proposed maintenance dose for paediatric patients above 40 kg (100 mg Q4) is higher than the proposed dose for adults <80 kg (50mg Q4). In the adult studies, both doses were tested, with similar efficacy regarding response in both groups. However, there was a slight difference in the number of patients achieving remission, favouring the 100 mg dose, and this was the reason that this dose was chosen in the paediatric study. The dose was discussed and accepted by the PDCO. The higher dose has been associated with a higher frequency of adverse event of special interests, especially malignancies and serious infections in adults. Therefore, for the adults, the higher dose was restricted to patients above 80 kg and patients <80 kg with an incomplete response after induction. In the current SmPC, there are extensive information regarding malignancies in section 4.4, including specific mentioning of findings in paediatric studies regarding TNF-inhibitors as a class. In addition, there are information in section 4.8 regarding a higher incidence of especially lymphoma with higher doses of golimumab. Given the risks associated with long-term use of higher dose of golimumab in a young population with a chronic disease requiring prolonged treatment, an option for maintenance dose reduction for patients in remission has been added in the section 4.2 of the SmPC.

Long-term safety in paediatric patients is considered missing information in the risk management plan and is currently being assessed through an ongoing observational safety study of golimumab in patients with juvenile idiopathic arthritis using the BiKeR registry. In addition, the long-term part of the paediatric study UCO3003 (PURSUIT 2) has been added to the risk management plan as a category 3 study and additional information regarding safety in Simponi treated paediatric ulcerative colitis patients will be gathered from the ongoing DEVELOP registry and presented in the PSURs.

3.6. Effects Table

Table 36: Effects Table for Simponi in the treatment of paediatric ulcerative colitis

Effect	Short description	Unit	Treatment golimumab	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Subjects in clinical remission at week 6	Clinical remission is defined as a Mayo score ≤2 points, with no individual sub score >1	n/N, %	22/69, 31.9%	NA	90% CI: 22.7%, 41.1%	Study UCO3003
Subjects with endoscopic healing at week 6	Endoscopy healing is defined as an endoscopy sub score of 0 or 1 based on local endoscopy	n/N, %	28/69, 40.6%	NA	90% CI: 30.9%, 50.3%	Study UCO3003
Subjects in clinical remission at week 54	Clinical remission is defined as a Mayo score ≤2 points, with no individual sub score >1	n/N, %	13/41, 31.7%	NA	90% CI: 19.8%, 43.7%	Study UCO3003
Subjects with endoscopic healing at week 54	Endoscopic healing is defined as an endoscopy sub score of 0 or 1 based on local endoscopy	n/N, %	15/41, 36.6%	NA	90% CI: 24.2%, 49.0%	Study UCO3003
Subjects in clinical remission at week 54 for participant who are in clinical remission at week 6	Clinical remission is defined as a Mayo score ≤2 points, with no individual sub score >1 among those in clinical remission at week 6	n/N, %	12/22, 54.5%	NA	90% CI: 37.1%, 72.0%	Study UCO3003
Unfavourable Effects						
Infections	-	n/N %	53/84 (63.1%)	398/1075 (37%)		UCO3001 + UCO1001 maintenance Control adult study T18
Serious infections	-	n/N %	10/84 (11.9%)	33/1075 (3.1%)	Important identified risk	UCO3001 + UCO1001 maintenance Control adult study T18

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

To support the paediatric UC indication, the MAH used an extrapolation approach to establish efficacy and safety in the paediatric population, which is acceptable. Extrapolation of efficacy/or safety from adults with UC to children with UC is also supported by the Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1). Additionally, the PDCO has accepted the extrapolation concept in the PIP of Simponi (EMEA-000265-PIP02-11-M02). The results of the phase 3 study UCO3003 demonstrated effect of golimumab on paediatric UC both at 6 weeks and at 54 weeks. Although comparison of results between studies should be performed with caution, it is noted that the results are comparable with, or slightly better than, the results of the adult studies T17 and T18. It should however be taken into consideration than the paediatric study was open-label, and the adult studies blinded. In summary, based on the available paediatric data and extrapolation from adult studies, clinical efficacy in paediatric patients aged 2 years and older and weighing at least 15 kg is considered demonstrated.

The safety profile of golimumab has been evaluated in several different indications since the approval in 2009, including UC in adult patients and pJIA in children above 2 years old. Short term safety in the paediatric UC population is similar to the already known safety profile of golimumab in other indications. The adverse reactions observed were consistent with the established safety profile of golimumab in adult patients with UC. However, there are still limited safety data in paediatric patients with UC, and the proposed doses results in systemic doses higher than the approved standard dose given to the adult population. A dose reduction for the maintenance treatment for patients in remission has therefore been introduced to reduce long-term exposure of children to higher dose. The missing information about long-term safety will be further assessed in the extension of the UCO3003 study which has been included as a category 3 in the RMP and in the observational safety study of golimumab in patients with juvenile idiopathic arthritis using the BiKeR registry. Additional safety information regarding Simponi will be collected in the ongoing registry study (DEVELOP) for another TNF-product and presented as part of the PSURs.

3.7.2. Balance of benefits and risks

Based on the totality of available data from the paediatric studies, together with the extrapolation from adults' studies, the efficacy of golimumab in paediatric UC is considered clinically relevant. The safety profile of golimumab is well established and includes several known safety concerns as already outlined in the SmPC and the risk management plan. No new safety concerns were identified in paediatric UC studies. Long term safety will be further assessed in the ongoing pharmacovigilance studies listed in the RMP for JiA (BiKer registry) and pUC (extension UCO3003), and additional safety information will be collected in the ongoing registry study DEVELOP and presented as part of the PSURs. A dose reduction for the maintenance treatment has been introduced to reduce long-term exposure of children to higher dose. Despite the lack of data in children under 4 years, extrapolation data to 2-year-olds is acceptable because children aged 2–4 are not expected to differ meaningfully from older children in disease characteristics, response, safety, or exposure. In addition, given the uncertainty in the dosing recommendation for 10-15 kg patients, due to the lack of observed data and unclear exposure target, it was agreed to restrict the indication to patients from 2 years with a body weight of at least 15 kg.

3.8. Conclusions

The overall B/R balance of Simponi in the following indication is positive.

Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients 2 years of age and older with a body weight of at least 15 kg, who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA, IIIB

Extension of indication to include treatment of paediatric ulcerative colitis, based on results from study CNTO148UCO3003; this is a phase 3 randomised, open-label study to assess the efficacy, safety, and pharmacokinetics of golimumab treatment, a human anti-TNFα monoclonal antibody, administered subcutaneously in paediatric participants with moderately to severely active ulcerative colitis. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. Version 28.3 of the RMP is approved. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is updated in accordance with the latest EMA excipients guideline and aligned with the latest QRD template version 10.4. The Annex II has also been updated to remove the reference to the core patient card messages.

The variation leads to amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA, IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0421/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Simponi-H-C-0000992-II-0121.