Janssen Research & Development

Statistical Analysis Plan

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 Ulcerative Colitis
PURSUIT 2

Protocol CNTO148UCO3003; Phase 3

SIMPONI® (golimumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Study Section	Change	Rationale
1	11 April 2019		Not Applicable	Initial release
2	22 February 2023	Section 1.2	Prior to Amendment 4, central randomization was implemented in this study. Participants ≥30 kg were randomized in a 3:1 ratio across intervention groups, golimumab and infliximab, respectively. Upon implementation of Amendment 4, no additional participants will be randomized to infliximab; all newly enrolled participants will receive golimumab.	Align with the protocol.
		Section 1.2	Sample size updated from at least 90 golimumab subjects to at least 60 golimumab subjects.	Align with the protocol Amendment 5.
		Section 1.4	Criteria for success was changed to totality of evidence.	Change due to HA feedback.
		Section 1.5, 1.6, 2.3	Upon implementation of Amendment 4, no additional participants will be randomized to infliximab; all newly enrolled participants will receive golimumab. Deleted Table 2 (probability of observing a certain remission rate or higher for infliximab). The probability of observing a clinical remission rate ≥18.3% and the precision were updated based on the revised sample size of at least 60 golimumab participants from at least 90 golimumab participants.	Align with the protocol.
		Section 2.1	Clarification on how final safety visit data is being handled.	Clarification on handling of Final Safety Visit data.
		Section 2.3	Analysis sets were separated based on whether golimumab or infliximab was administered.	Analysis sets were separated based on whether golimumab or infliximab was administered for easier description of the analysis.
		Section 4.1	Added countries to the summary of demographics.	Summary of countries needed.
		Section 4.2, 4.4	Summaries for discontinuation of study intervention, termination, and missed doses due to COVID-19 were added.	Added due to COVID-19 pandemic.

SAP Version	Approval Date	Study Section	Change	Rationale
		Section 5	Upon implementation of Amendment 4, no additional participants will be randomized to infliximab; all newly enrolled participants will receive golimumab. Section reference for infliximab endpoints provided.	Alignment with protocol about removal of infliximab arm. Clarification on where infliximab endpoints were placed.
		Section 5.2.2	Success of the study criteria has been updated to be based on the totality of evidence.	Updated based on HA feedback.
		Section 5.2.4	Sensitivity analysis ("per protocol") was removed.	Analysis will not be conducted.
		Section 5.2.5	Added section for supportive analysis of the primary endpoint which incorporates participant-level and study-level data.	Analysis added due to HA feedback.
		Section 5.3 and Section 5.4	Moved maintenance of remission and corticosteroid-free remission to become major secondary endpoints and removed from Section 5.4.	Based on HA feedback.
		Section 5.3.2.1	Update analysis for symptomatic remission to provide CI.	Based on HA feedback.
		Section 5.4.7	Section 5.4.7, section for efficacy analyses based on all infliximab participants including partial mayo responders has been deleted.	Removal of infliximab arm.
		Section 5.4.7	New section for UC-related hospitalization and surgery added.	New analysis added to incorporate number of hospitalizations and surgeries.
		Section 5.4.8	Added COVID-19 analysis.	New analysis added based on HA feedback.
		Section 5.4.9	Additional definitions for Tummy-UC were added.	Additional definition added.
		Section 5.5	Original Section 5.5 for assay sensitivity was removed and replaced by exploratory endpoints.	Removal of infliximab arm.
		Section 5.5.4	Section for comparison of pediatric participants with adult participants was created. Additional analysis was added (ratio of pediatric participants to adult participants).	All of the comparisons of pediatric participants with adult participants were brought together into one section. Additional analysis due to HA feedback.
		Section 5.6	Added section for infliximab analysis.	Section added for all of infliximab analyses to make it easier to find what analyses will be conducted for infliximab.
		Section 6	• Removed some infliximab analysis sets • Analyses through Final Safety Visit will be summarized	Removal of infliximab arm. Final Safety Visit data will be captured in the first DBL.

SAP Version	Approval Date	Study Section	Change	Rationale
		Section 6.2.1	Removed Crithidia and Farr method for anti-dsDNA and replaced with Athena multilyte.	To be consistent with Labcorp methodology.
		Section 7	Removed some infliximab analysis sets.	Removal of infliximab arm.
		Section 8.1	All efficacy analyses other than PUCAI were removed.	Alignment with protocol.
		Attachment 2	Updated laboratory toxicity grading from 4.03 to 5.0.	Use the most recent laboratory toxicity grading.
		Attachment 3	Added identification of studies.	Clarification of how studies were identified for the meta-analysis.
		Attachment 5	Added description of the Bayesian model used for the primary endpoint.	HA feedback.
Version 3	6 March 2024	Section 2.3	Edited names of Golimumab analysis sets throughout the document	Clarification on the treatment arm for the analysis sets.
		Section 2.4	Added change for all age subgroup tables: '<12' instead of '11'; '<6' instead of '5'; and '<18' instead of '17'.	Clarification on the age group.
		Section 3.2	Edited name of subsection to "Data Monitoring Committee Review".	Clarification on subsection name.
		Section 4.4	Added that "follow-up time (weeks)" and "average exposure (number of administrations)" are also required in the "week 0 through Final Safety Visit" AE tables.	Adding additional safety analyses to include all subject safety data who are not entering study extension.
		Section 4.5	Added 'Received additional dose of study agent' to list of categories of major protocol deviations. Also added details on how "incorrect doses" (for protocol deviations in study agent administrations) should be derived.	Clarification of protocol deviations categories.
		Section 5.1.2.1	Updated definition of rescue medication.	Clarification on the definition of rescue medication
		Section 5.2.4	Added Sensitivity Analysis 6-8 to address FDA's final comments.	Updated based on HA feedback.
		Sections 5.3.1 and 5.3.2	Added Sensitivity and Supportive Analyses for Clinical Remission Week 54 to address FDA's final comments.	Updated based on HA feedback.
		Section 5.3.4 and Section 5.5.6	Added CI for various confidence limits as exploratory (e.g. 80% and 95%)	Additional analyses added.
		Section 5.4	Edited name of subsection to "Other Efficacy Endpoints".	Clarification on subsection name.
		Section 5.4.1	Added three new endpoints for "corticosteroid-free" clinical	Additional analyses added.

SAP Version	Approval Date	Study Section	Change	Rationale
			remission and symptomatic remission.	
		Section 5.4.2	Added baseline and postbaseline average corticosteroid use Week 0 through Week 6, and Week 6 through Week 54 as endpoints. Added Endoscopic Normalization at Week 6 and Week 54 as endpoint.	Additional analyses added.
		Section 5.4.9.5	Added definition for the "Average daily prednisone-equivalent corticosteroid dose" analysis	Definition added for additional endpoint.
		Section 5.4.9.6	Added definition for the "Endoscopic Normalization" analysis	Definition added for additional endpoint.
		Section 5.5.2	Added Endoscopic Normalization at Week 6 and Week 54 based on Central reading as endpoints.	Definition added for additional endpoint.
		Section 5.5.5	Updated for TUMMY-UC: score comprised by 8 components (instead of 6), and range 0-144 (instead of 0-56).	Updated TUMMY-UC components.
		Section 6.1	• Added AE tables for Week 0 through Final Safety Visit. • Added Listing for "TEAEs associated with COVID-19 • Added definition for "AEs Leading to discontinuation of study agent"	Additional analysis and clarification of endpoint.
		Section 6.2	Updated the categories for the ALT, AST and Bilirubin tables with maximum postbaseline values.	Categories updated to match adult golimumab study.
		Section 7.1	Clarified the dosing deviation criteria for participants treated with golimumab and inflixumab.	Additional deviation for PK analysis.
		Attachment 3	• Updated title of Amendment 3 • Updated subsection 3.1 to describe studies selected for the "similar route" meta-analysis • Added subsection 3.2 to describe studies selected for the "any route" meta-analysis	Updated analysis based on HA feedback.
		Attachment 4	• Added details for the "sample size weighting" method • Added Table 3 to summarize all results for clinical remission Week 6 and Week 54	Updated analysis based on HA feedback.
		Attachment 5	Additional details for the Bayesian model added.	Details added to the model for clarity.
Minor editorial, grammatical, formatting, or spelling changes were made, and inconsistences were corrected.				

ABBREVIATIONS

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADA	anti-drug antibody
AEs	adverse event(s)
AHA	at home administration
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
AZA	Azathioprine
BSA	body surface area
CI	confidence interval
COVID-19	Coronavirus Disease 2019
DBL	database lock
DMC	data monitoring committee
DPS	data presentation specifications
eCRF	electronic case report form
FAS	full analysis set
GGT	gamma glutamyl transferase
IQ	Interquartile
IV	Intravenous
IWRS	interactive web response system
LOCF	last observation carried forward
MedDRA	medical dictionary for regulatory activities
MTX	Methotrexate
Nab	neutralizing antibodies
NCI-CTCAE	national cancer institute's common terminology criteria for adverse events
PFP-V	prefilled pen
PFS-U	prefilled syringe with UltraSafe
PFS-V	prefilled pen
PK	pharmacokinetic(s)
PUCAI	pediatric ulcerative colitis activity index
q4w	every 4 weeks
QOL	quality of life
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SC	Subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, data handling conventions and statistical methods for all planned analyses in protocol CNTO148UCO3003.

1.1. Trial Objectives

Primary Objectives

The primary objectives are:

- To evaluate the efficacy of golimumab in inducing clinical remission as assessed by the Mayo score, in pediatric participants with moderately to severely active ulcerative colitis (UC).
- To evaluate the safety profile of golimumab, in pediatric participants with moderately to severely active UC.

Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of golimumab in inducing clinical response as assessed by the Mayo score and clinical remission as measured by the pediatric ulcerative colitis activity index (PUCAI) Score.
- To evaluate the efficacy of golimumab on endoscopic healing.
- To evaluate the efficacy of golimumab during the Long-Term Phase.
- To evaluate the effect of golimumab on additional efficacy and quality of life (QoL) measures.
- To evaluate the pharmacokinetic (PK) and exposure-response of golimumab during Short- and Long-Term Phases.

Additional Objective (Usability Assessment Substudy)

- To evaluate the potential for at home use of golimumab in the participant population ≥45 kg during the Usability Assessment Substudy.

1.2. Trial Design

CNTO148UCO3003 is a Phase 3, multicenter, randomized, open-label golimumab study in pediatric participants aged 2 to 17 years with moderately to severely active UC, defined as a baseline Mayo score of 6 through 12, inclusive, with an endoscopy subscore of ≥2 as assessed by the local reader. Prior to Protocol Amendment 4, central randomization was implemented in this study. Participants ≥30 kg were randomized in a 3:1 ratio across intervention groups, golimumab and infliximab, respectively. Upon implementation of Protocol Amendment 4, no additional participants will be randomized to infliximab; all newly enrolled participants will receive golimumab.

Participants must also have:

- Demonstrated an inadequate response to, have failed to tolerate, or have a medical contraindication to conventional therapies (ie, intravenous [IV] or oral corticosteroids or the immunomodulators [azathioprine (AZA), 6-mercaptopurine (6-MP) or methotrexate (MTX)];

  OR

- Demonstrated corticosteroid dependence;

  OR

- Required repeated (>3 per year) courses of corticosteroids.

Participants with prior exposure to biologic anti-tumor necrosis factor alpha (TNFα) agents will be ineligible for participation.

The following concomitant medications for UC are allowed in this study: 5-aminosalicylates (5-ASAs), corticosteroids (including budesonide and beclomethasone dipropionate), and immunomodulators (ie, 6-MP, AZA, MTX). For participants receiving concomitant therapy with 5-ASAs and/or corticosteroids for UC, the dosage of these medications must be stable for a specified period of time before screening as described in the protocol.

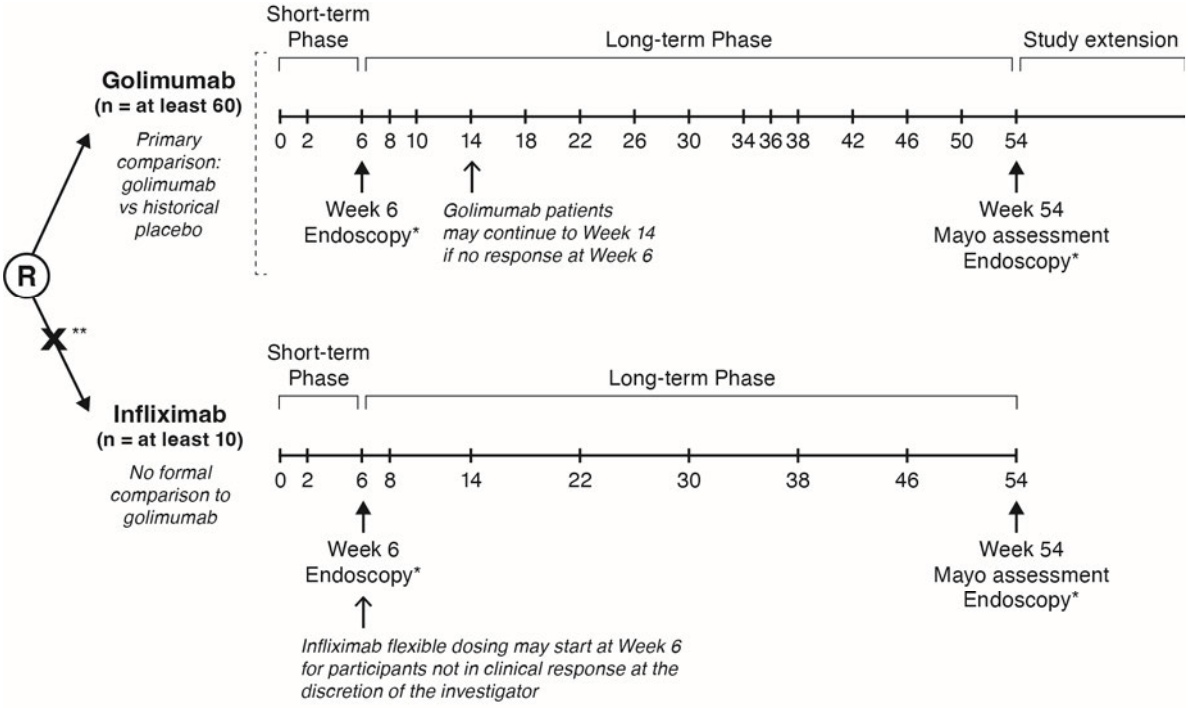
Between Week 0 and Week 6, concomitant medications for UC (ie, 5-ASAs, corticosteroids, and/or immunomodulators) should not be initiated or their dose increased. For participants receiving 5-ASAs at baseline, the dose must remain stable through Week 54 (except for weight-based adjustments). For participants receiving immunomodulators at baseline, the dose should not be increased (except for weight-based adjustments). For participants receiving immunomodulators (ie, 6-MP, AZA, or MTX) or corticosteroids (including budesonide and beclomethasone dipropionate), at baseline, the immunomodulators may be discontinued at any time during the study, and corticosteroids may be tapered beginning at Week 0.

The primary endpoint is clinical remission at Week 6 based on the Mayo score. In this study, the remission rate of golimumab in pediatric participants will be formally compared with a historical placebo remission rate derived from a meta-analysis of adult Phase 2/3 UC studies with golimumab and Phase 3 UC studies of other products approved in this indication utilizing similar populations and endpoints.

This study also includes an infliximab arm. Upon implementation of Protocol Amendment 4, no additional participants will be randomized to the infliximab arm; all newly enrolled participants will receive golimumab. No formal comparisons between golimumab and infliximab will be performed.

As this study is an open-label study, it will remain unblinded after randomization. An overview of the study design is presented in Figure 1.

Figure 1: Study schema for CNTO148UCO3003



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

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This 54-week study will consist of a 6-week Short-Term Phase (Weeks 0-6) and a 48-week Long-Term Phase (Weeks 6-54) followed by a study extension (for eligible golimumab-treated participants only).

Prior to Protocol Amendment 4, approximately 125 participants who satisfy inclusion/exclusion criteria were to be included in the study at sites located globally, including in North and South America, Asia, and Europe. At least 24 golimumab participants with body weight <45 kg, and at least 5 golimumab participants with body weight <30 kg were planned to be included.

In order to ensure that at least 5 participants with body weight <30 kg receive golimumab, participants who weigh <30 kg were to only be allocated to the golimumab treatment arm. The remaining 120 participants were to be randomized in a 3:1 ratio to golimumab or infliximab, respectively.

Upon implementation of Protocol Amendment 4, no additional participants will be randomized to infliximab; all newly enrolled participants will receive golimumab.

Upon implementation of Amendment 5, approximately 70 participants will participate in this study (at least 60 participants will receive golimumab, at least 10 participants will receive infliximab). Of the 60 golimumab participants, at least 15 will have a body weight <45 kg and at least 5 will have a body weight <30 kg.

The participants will be dosed as follows during the Short-Term Phase:

- Participants enrolled or randomized to golimumab subcutaneous (SC) will receive doses at Weeks 0 and 2
  - Participants with body weight ≥45 kg will receive fixed induction doses of 200 mg at Week 0 and 100 mg at Week 2.
  - Participants with body weight <45 kg will receive body-surface area (BSA)-adjusted induction doses of 120 mg/m^2 (up to a maximum of 200 mg) at Week 0 and 60 mg/m^2 (up to a maximum of 100 mg) at Week 2.
- Participants randomized to infliximab 5 mg/kg IV will receive doses at Weeks 0 and 2.

Upon implementation of Amendment 4, no additional participants will be randomized to infliximab; all newly enrolled participants will receive golimumab.

At Week 6, golimumab and infliximab-treated participants will undergo sigmoidoscopy (or colonoscopy at the investigator's discretion) and will be evaluated for clinical response as determined by the interactive web response system (IWRS). The Mayo Score will be determined using local endoscopy.

- Participants in clinical response to golimumab will continue to receive SC golimumab 100 mg or 60 mg/m^2 every 4 weeks (q4w) through Week 50. Participants not in clinical response at Week 6 may receive 2 additional doses of golimumab (ie, at Week 6 and Week 10). Of these participants, those who are partial Mayo responders at Week 14 (defined as a decrease from the Week 0 partial Mayo score of ≥3 points) will continue to receive SC golimumab 100 mg or 60 mg/m^2 q4w through Week 50. Participants who are not in partial Mayo response at Week 14 will be withdrawn from further study intervention administrations and complete a final safety follow-up period of 16 weeks following the last administration of study intervention.
- Participants in clinical response to infliximab will continue to receive IV infliximab 5 mg/kg administered q8w through Week 46. Participants not in clinical response at Week 6 may be considered for an increased dose of infliximab (to 10 mg/kg [capped at 1 g] at Week 6 and q8w thereafter or 5 mg/kg at Weeks 6 and 8, and 10 mg/kg (capped at 1 g) at Week 14 and q8w thereafter, respectively). Participants who have achieved a partial Mayo response at Week 14 should continue receiving infliximab at 10 mg/kg q8w through Week 46. Participants not in partial Mayo response at Week 14 may be considered for an additional dose escalation to 10 mg/kg q4w (capped at 1g), or may be withdrawn from further study intervention administrations and complete a final safety follow-up period of 8 weeks following the last administration of study intervention. At Week 22, those participants who received an

escalation in their infliximab dosing to 10 mg/kg q4w will need to demonstrate a partial Mayo response to continue in the study. Participants in partial Mayo response will continue receiving open-label infliximab 10 mg/kg (capped at 1g) q4w through Week 50. Participants who are not in partial Mayo response at Week 22 will have study intervention discontinued and should complete a final safety follow-up at least 8 weeks following the last administration of infliximab.

Participants in clinical response at Week 6 as determined by the IWRS receiving infliximab will also be assessed for clinical flare based on the partial Mayo score at every visit after Week 6 to determine a loss of response. If a clinical flare is confirmed, the participant may be eligible for rescue medication. See the protocol for further details. A clinical flare in UC is defined as an increase from the start of the Long-Term Phase ([Week 6] in the partial Mayo score of at least 2 points **and** an absolute partial Mayo score ≥4; **or** an absolute partial Mayo score ≥7 points. Participants who experience a flare in their UC disease from Week 6 onward may initiate this step-wise dose escalation at any time to the maximum of 10 mg/kg (capped at 1g) q4w. Participants who dose-escalate in response to a UC flare will be reassessed after two administrations at the final escalated dose. Participants in partial Mayo response (ie, a decrease from flare baseline of ≥2 in the partial Mayo score) will continue receiving open-label infliximab through Week 46 at the escalated dose. A more complete definition of a clinical flare can be found in protocol Section 6.5.3. Participants who have not achieved a partial Mayo response will be discontinued from study intervention administration and should return for a final safety visit at least 8 weeks after their last infliximab administration.

Following Amendment 4, after the Week 8 visit and before the Week 54 visit, participants in the infliximab arm will only require study visits on treatment days. All other nontreatment visits during this time period will be optional. All participants must have the Week 54 or Early Termination visit.

Assessments during the Long-Term Phase for both groups include efficacy, PK, and safety.

After the Week 54 evaluations,

- For participants receiving golimumab, at the discretion of the investigator, if participants receiving golimumab are able to benefit from continued SC golimumab, the participants will continue to receive SC golimumab q4w starting at Week 54 under this protocol's study extension until marketing authorization is obtained for golimumab for the treatment of pediatric participants 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 pediatric UC population, whichever occurs first. Participants who continue golimumab treatment as part of the study extension will be intermittently evaluated per the protocol for efficacy, PK, and safety.
- For participants receiving infliximab, these participants will be withdrawn from study participation and transition to local standard of care which may include continued commercially available infliximab at the discretion of their physician.

Beginning with the Week 54 evaluations, participants in those regions where the adult maintenance posology is weight based (eg, 50 mg q4w for those weighing ≤80 kg and 100 mg q4w for those weighing >80 kg) may make a one-time reduction in their golimumab dose to 50 mg q4w. Participants may return to the golimumab 100 mg q4w dosing at the discretion of the investigator, but then no additional changes in dosing can be made for the duration of the study extension.

Beginning at Week 58, participants who are eligible to continue receiving golimumab in the study extension will be offered the option for self-administration (at least 12 years old) or caregiver-administration (any age). If a pediatric participant or caregiver elects against self- or caregiver-administration, the health care professional will continue to administer injections in this study.

At select sites, participants entering the study extension who elect to administer the study intervention at home will have the option to be enrolled in a Usability Assessment Substudy. Approximately 10 participants will be enrolled in the Usability Assessment Substudy at Week 58. The objective of the Substudy is to provide supportive data that the Prefilled Syringe with UltraSafe (PFS-U) and Prefilled Pen (PFP-V) as designed, together with the appropriate training and written instructions for use, are suitable for at home administration (AHA) by pediatric participants or their caregivers.

An internal data monitoring committee (DMC) will be commissioned for this study (See Section 3.2). For further details see DMC SAP. Database locks (DBLs) are planned at Week 54 and at the end of study. Additional DBLs other than the 2 specified above may be performed.

1.3. Statistical Hypotheses for Trial Objectives

The primary endpoint is clinical remission at Week 6.

The primary hypothesis is that golimumab is an effective therapy in pediatric UC relative to a historical placebo control as assessed by clinical remission at Week 6 based on the Mayo score. The historical placebo control is based on a meta-analysis of 2 Phase 2/3 adult UC studies of golimumab (C0524T16 and C0524T17), and 5 Phase 3 adult UC studies including infliximab (C0168T37 and C0168T46), adalimumab (ULTRA 1 and ULTRA 2), and vedolizumab (GEMINI 1).

1.4. Criteria for Success

The success of the study will ultimately be based on the totality of evidence. The primary analysis will be based on the proportion of golimumab pediatric participants in clinical remission at Week 6 based on the Mayo score and its associated 90% confidence interval (CI). The criteria for the primary analysis will have been met if the lower limit of the two-sided 90% CI for the proportion of golimumab participants in clinical remission at Week 6 is >10.0% (ie, the upper limit of the 95% CI for the proportion of placebo participants in clinical remission at Week 6 derived from a meta-analysis of 2 Phase 2/3 adult UC studies of golimumab and 5 Phase 3 adult UC studies of other products approved in this indication [Section 5.2.1.3]). Identification of the studies used in the meta-analysis can be found in Attachment 3. Details of the meta-analysis, which uses a fixed-effects model can be found in Attachment 4.

1.5. Sample Size Justification

Sample size calculations were based on the need to have a sufficient number of participants assigned to the golimumab treatment arm to achieve the criteria defined in Section 1.4. A sample size of 60 participants in the golimumab arm will ensure that the lower bound of the 90% CI for the pediatric golimumab remission rate is above 10.0% (ie, the upper bound of the 95% CI for the historical placebo control) as long as the observed remission rate is at least 18.3%. The probability of observing a remission rate of ≥18.3%, given different assumptions for the true rate of clinical remission is shown in Table 2.

With 60 golimumab-treated participants, the probability of observing a remission rate of ≥18.3% ranges from 50% (if the golimumab adult UC remission rate of 17.8% is assumed) to greater than 99% (if the remission rate of 42.9% from the first golimumab study in pediatric UC is assumed). It is reasonable to assume that the true remission rate in pediatric UC participants is greater than the remission rate observed in the adult UC study, as the remission rate in the first golimumab pediatric UC study was at least twice that observed in the adult UC study. If we assume the remission rate to be 22.5%, then the probability of observing a remission rate of ≥18.3% is at least 80% (Table 2).

Table 2: Probability of observing a clinical remission rate of ≥18.3% with differing assumptions for the true remission rate

Clinical Remission as assessed by the Mayo Score	Probability of observing ≥18.3%
17.8% (observed adult remission rate; C0524T17)	50%
20.0%	68%
22.5%	82%
25.0%	91%
42.9% (observed pediatric remission rate; CNTO148UCO1001)	>99.9%

The precision (ie, half width of the CI) based on this sample size of 60 golimumab participants is 8.1% (assuming a clinical remission rate of 17.8% at Week 6) and 10.5% (assuming a clinical remission rate at Week 6 of 42.9%).

Furthermore, the Fisher Information Matrix-based optimal design analysis indicates that PK data from a total of 60 participants (including 45 participants in the ≥45 kg subgroup and 15 participants in the <45 kg subgroup) would be sufficient to adequately characterize the PK of golimumab in pediatric participants with UC.

Upon implementation of Amendment 4, no additional participants were randomized to infliximab; all newly enrolled participants received golimumab.

1.6. Randomization and Blinding

Randomization

Prior to Protocol Amendment 4, central randomization was to be implemented in this study. Participants weighing ≥30 kg were randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision

of the sponsor. Participants were to be randomized in a 3:1 ratio to golimumab or infliximab. Based on this randomization code, the study intervention will be packaged and labeled for each participant.

Permuted block randomization was to be used. The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study agent kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Participants <30 kg were not to be randomized and offered only golimumab. This was implemented to ensure that at least 5 participants who weigh <30 kg will receive golimumab treatment, as specified in discussions with health authorities in the United States and Europe.

Upon implementation of Protocol Amendment 4, no additional participants will be randomized to infliximab; all newly enrolled participants will receive golimumab.

Blinding

This is an open-label study, and therefore blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Unless otherwise specified, actual scheduled visits will be used for the summaries and listings over time with no visit windows applied. The study visits scheduled after randomization should occur at the time delineated in the protocol Schedule of Activities.

A visit number will be assigned to scheduled visits except for the early termination visit. If the early termination visit falls in the protocol-specified window of a scheduled visit and there are not already data for the scheduled visit, the scheduled visit number will be assigned to the early termination visit. If there are already data for the same scheduled visit, those data will be used in lieu of the early termination visit data.

2.2. Pooling Algorithm for Analysis Centers

Data from all investigational centers/sites will be pooled for analyses.

2.3. Analysis Sets

Participants in this study include the randomized participants, participants who weigh <30 kg who were not randomized and golimumab participants after implementation of Protocol Amendment 4 who were not randomized. Enrolled participants include both the randomized and non-randomized participants.

2.3.1. Efficacy Analysis Set(s)

2.3.1.1. Full Golimumab Analysis Set 1

The ***Full Golimumab Analysis Set 1*** (FGAS1) includes all enrolled participants who received at least 1 dose (complete or partial) of golimumab during the Short-Term Phase (Weeks 0-6). This analysis set will be used for the efficacy analyses of the endpoints through Week 6, unless otherwise specified.

2.3.1.2. Full Golimumab Analysis Set 2

The ***Full Golimumab Analysis Set 2*** (FGAS2) includes participants who are 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 Long-Term Phase. This analysis set will be used for the efficacy analyses of the endpoints during the Long-Term Phase through Week 54, unless otherwise specified.

2.3.1.3. Full Golimumab Analysis Set 3

Some prespecified efficacy analyses during the Long-Term Phase (Weeks 6 through Week 54) will also be conducted using the ***Full Golimumab Analysis Set 3*** (FGAS3). This analysis set includes:

- Participants who are in clinical response at Week 6 to golimumab (determined by the IWRS), as assessed by the Mayo score (local reader)
- Participants who are in partial Mayo response at Week 14 for participants receiving golimumab

and who received at least 1 dose (complete or partial) of golimumab during the Long-Term Phase.

2.3.1.4. Full Infliximab Analysis Set 1

The ***Full Infliximab Analysis Set 1*** (FIAS1) includes all enrolled participants who received at least 1 dose (complete or partial) of infliximab during the Short-Term Phase. This analysis set will be used for the efficacy analyses of the endpoints through Week 6, unless otherwise specified.

2.3.1.5. Full Infliximab Analysis Set 2

The ***Full Infliximab Analysis Set 2*** (FIAS2) includes participants who are in clinical response at Week 6 to infliximab (determined by the IWRS) as assessed by the Mayo score (local reader) and who received at least 1 dose (complete or partial) of infliximab during the Long-Term Phase. This analysis set will be used for the efficacy analyses of the endpoints during the Long-Term Phase through Week 54, unless otherwise specified.

2.3.1.6. Randomized Analysis Set

The ***Randomized Analysis Set*** will primarily be used for the randomization listing. It includes only randomized participants. It will not include participants who weigh <30 kg as these participants were not randomized and golimumab participants after implementation of Protocol Amendment 4 who were not randomized.

2.3.2. Safety Golimumab Analysis Set

The ***Safety Golimumab Analysis Set*** includes all enrolled participants who received at least 1 dose (complete or partial) of golimumab. Enrolled participants confirmed not to have taken any golimumab will not be included in the safety analysis set.

The ***Safety Golimumab Analysis Set During the Short-Term Phase*** includes all enrolled participants who received at least 1 dose (complete or partial) of golimumab during the Short-Term Phase. Enrolled participants confirmed not to have taken any golimumab during the Short-Term Phase will not be included in the Safety Analysis Set During the Short-Term Phase.

The ***Safety Golimumab Analysis Set During the Long-Term Phase*** includes all enrolled participants who received at least 1 dose (complete or partial) of golimumab during the Long-Term Phase. Enrolled participants confirmed not to have taken any golimumab during the Long-Term Phase will not be included in this safety analysis set. Selected safety analyses during the Long-Term Phase will also be provided for the ***Safety Analysis Set who are in Clinical Response at Week 6*** to golimumab as determined by the IWRS at Week 6.

The ***Safety Infliximab Analysis Set*** includes all enrolled participants who received at least 1 dose (complete or partial) of infliximab. Enrolled participants confirmed not to have taken any infliximab will not be included in the safety analysis set.

The ***Safety Infliximab Analysis Set During the Short-Term Phase*** includes all enrolled participants who received at least 1 dose (complete or partial) of infliximab during the Short-Term Phase.

The ***Safety Infliximab Analysis Set During the Long-Term Phase*** includes all enrolled participants who received at least 1 dose (complete or partial) of infliximab during the Long-Term Phase. Enrolled participants confirmed not to have taken any infliximab during the Long-Term Phase will not be included in this safety analysis set.

2.3.3. PK Golimumab Analysis Set

The ***PK Evaluable Golimumab Analysis Set*** includes 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.

The ***PK Evaluable Golimumab Analysis Set During the Short-Term Phase*** includes 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 Short-Term Phase.

The ***PK Evaluable Golimumab Analysis Set During the Long-Term Phase*** includes all participants who have received at least one dose of golimumab (complete or partial) during the Long-Term Phase and have at least one valid blood sample drawn for PK analysis during the Long-Term Phase. Selected PK analyses during the Long-Term Phase will also be provided for the ***PK Evaluable Golimumab Analysis Set who are in Clinical Response at Week 6*** to golimumab as determined by the IWRS at Week 6.

The ***PK Evaluable Infliximab Analysis Set*** includes all participants who have received at least one dose of infliximab (complete or partial) and have at least one valid blood sample drawn for PK analysis.

The ***PK Evaluable Infliximab Analysis Set During the Short-Term Phase*** includes all participants who have received at least one dose of infliximab (complete or partial) and have at least one valid blood sample drawn for PK analysis during the Short-Term Phase.

The ***PK Evaluable Infliximab Analysis Set During the Long-Term Phase*** includes all participants who have received at least one dose of infliximab (complete or partial) during the Long-Term Phase and have at least one valid blood sample drawn for PK analysis during the Long-Term Phase.

2.3.4. Immunogenicity Golimumab Analysis Sets

The ***Immunogenicity Golimumab Analysis Set*** includes all participants who received at least one dose (partial or complete) of golimumab and have appropriate samples for detection of antibodies to golimumab.

The ***Immunogenicity Golimumab Analysis Set During the Short-Term Phase*** includes 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 Short-Term Phase.

The ***Immunogenicity Golimumab Analysis Set During the Long-Term Phase*** includes 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 Long-Term Phase.

The ***Immunogenicity Infliximab Analysis Set*** includes all participants who received at least one dose (partial or complete) of infliximab and have appropriate samples for detection of antibodies to infliximab.

The ***Immunogenicity Infliximab Analysis Set During the Short-Term Phase*** includes all participants who received at least one dose (partial or complete) of infliximab and have appropriate samples for detection of antibodies to infliximab during the Short-Term Phase.

The ***Immunogenicity Infliximab Analysis Set During the Long-Term Phase*** includes all participants who received at least one dose (partial or complete) of infliximab during the Long-Term Phase and have appropriate samples for detection of antibodies to infliximab during the Long-Term Phase.

2.4. Definition of Subgroups

The consistency of clinical remission at Week 6 as measured by the Mayo score (using local endoscopy sub-score) will be evaluated for subgroups based on demographics, UC disease characteristics, UC-related concomitant medication usage and UC-related medication history.

The following subsections define the subgroup analyses that will be performed.

2.4.1. Demographics at Week 0

a. Age (2 - <12 yrs, 12 - <18 yrs)

b. Sex (male, female)

c. Race (White, non-White)

d. Weight (<45 kg, ≥45 kg)

e. Center location (North America [United States], Europe [Belgium, Poland, France, Italy, Spain, and Netherlands], Asia (Taiwan, Korea), Rest of World (South America [Brazil], Israel)

2.4.2. Clinical Disease Characteristics at Week 0:

a. UC disease duration (≤1 years, >1 year)

b. Extent of disease (limited to left side of colon, extensive)

c. Severity of UC disease by Mayo score (Moderate: 6≤ Mayo score ≤10, Severe: Mayo score >10)

d. Severity of UC disease by PUCAI score (No or mild disease ≤34, Moderate or Severe: >34)

e. CRP (≤3 mg/L, >3 mg/L)

f. Fecal calprotectin (≤250 mg/kg, >250 mg/kg)

2.4.3. Concomitant Medication Use at Week 0:

a. Parenteral or oral corticosteroids, including budesonide and beclomethasone dipropionate (yes, no)

b. 5-ASA compounds (yes, no)

c. 6-MP/AZA/MTX (yes, no)

2.4.4. UC-related Medication History

a. Participants with biologic failure

- Primary nonresponse, secondary nonresponse, or intolerance to vedolizumab (yes, no)

2.5. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration or enrollment date if participant was never dosed. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥ date of Day 1
- Visit date - (date of Study Day 1), if visit date < date of Day 1

There is no 'Day 0'.

2.6. Baseline

Unless otherwise stated, baseline is defined as the last observation prior to the start of the first study treatment administration.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Interim Analysis

No interim analysis is planned for this study.

3.2. Data Monitoring Committee Review

An independent internal DMC (consisting of Sponsor members [a gastroenterologist, a clinician and a statistician at a minimum] outside of the study team), will be established to monitor safety data (for both golimumab and infliximab treatments arms) on an ongoing basis until all participants reach the Week 54 visit or terminate the study prior to the Week 54 visit.

The major function of the DMC is to monitor the safety of the study intervention by reviewing the interim study safety data every 3 months. The first DMC meeting will occur approximately 4 months after the first participant is dosed with study intervention.

In addition, during the study, the sponsor's study responsible physician (or designee) will regularly review safety data from the sites and notify the DMC and appropriate Sponsor personnel of any issues.

The DMC roles and responsibilities, and the general procedures of the DMC review are defined and documented in the DMC Charter. Information about scope of the data, analysis sets, planned analyses, and the statistical methods for the planned DMC safety data packages through the Week 54 DBL are defined in the DMC SAP. Additionally, a dedicated DMC Data Presentation Specifications (DPS) document details output and programming specifications.

4. PARTICIPANT INFORMATION

Participant information will be based on FGAS1 for golimumab and FIAS1 for infliximab, unless otherwise noted.

In addition, the distribution of participants by region, country, and site will be presented.

4.1. Demographics and Baseline Characteristics

Table 3 presents a list of the demographic variables that will be summarized separately for golimumab and infliximab.

Age will be the age in years at the time of the signing of the informed consent.

BSA (m^2) will be calculated as sqrt (height [cm] x weight [kg]/3600).

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and interquartile [IQ] range).
Weight (kg)	
Height (cm)	
BSA (m^2)	
Categorical Variables	
Age (2 - <12, including 2 - <6 yrs and 6 - <12 yrs, 12 - <18)	Frequency distribution with the number and percentage of participants in each category.
Weight (<45, including <30 and ≥30 - 45, ≥45)	
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Not reported)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported)	
Center location (North America [United States], Europe [Belgium, Poland, France, Italy, Spain, and Netherlands], Asia (Taiwan, Korea), Rest of World (South America [Brazil], Israel)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 4 presents a list of the baseline disease characteristics variables that will be summarized separately for golimumab and infliximab.

Table 4: Baseline Disease Characteristics Variables

Continuous Variables:	**Summary Type**
UC disease duration (years)	Descriptive statistics (N, mean, SD, median and range [minimum and maximum], and IQ range).
UC symptoms duration prior to diagnosis (months)	
Mayo Score	
PUCAI Score	
CRP	
IMPACT III	
Fecal calprotectin concentrations	
TUMMY UC and Observer Tummy-UC	
Categorical Variables	
Extent of disease (Limited to left side of colon, Extensive)	Frequency distribution with the number and percentage of participants in each category.
Severity of disease by Mayo Score (No or mild disease: <6, Moderate: ≥6 - ≤10, Severe: >10)	
Severity of disease by PUCAI Score (no or mild disease: ≤34, moderate: >34 - <65, Severe: ≥65)	
Abnormal CRP (>3 mg/L)	
Abnormal fecal calprotectin (>250 mg/kg)	

Past medical history and current diagnoses, opioid usage and tobacco/nicotine status (nonsmoker, prior smoker, current smoker) will be summarized separately for golimumab and infliximab.

In addition, summaries by age (2-<12 yrs, including 2-<6 yrs and 6-<12 yrs, 12-<18 yrs), and weight (<45 kg, including <30 kg and ≥30-<45 kg, ≥45 kg) will be provided separately for golimumab and infliximab for demographics and baseline disease characteristics.

A listing of all demographic variables will also be presented.

4.2. Disposition Information

The number of participants in the following disposition categories will be summarized throughout the study separately for golimumab and infliximab:

- Participants who received study agent
- Participants who discontinued study agent
    - Reasons for discontinuation of study intervention (including discontinuation due to COVID-19 related reasons)
- Participants who terminated study prematurely
    - Reasons for termination of study (including termination due to COVID-19 related reasons)

A listing of participants from Week 0 through Week 54 will be provided for the following category:

- Participants who discontinued study agent (including discontinuation due to COVID-19 related reasons)
- Participants who terminated study prematurely (including termination due to COVID-19 related reasons)

4.3. Treatment Compliance

Distribution of participants by study agent lot up to Week 6 will be provided for the Safety Analysis Set During the Short-Term Phase and Safety Infliximab Analysis Set During the Short-Term Phase. These will also be summarized during the Long-Term Phase up to Week 54 for the Safety Analysis Set During the Long-Term Phase and Safety Infliximab Analysis Set During the Long-Term Phase.

In addition to the summary tables a listing will be provided for study agent batch lot number.

4.4. Extent of Exposure

Participants (%) who received study intervention at each visit up to Week 6 will be summarized for the Safety Analysis Set During the Short-Term Phase and Safety Infliximab Analysis Set During the Short-Term Phase. These will also be summarized during the Long-Term Phase up to Week 54 for the Safety Analysis Set During the Long-Term Phase and Safety Infliximab Analysis Set During the Long-Term Phase.

In addition, a table and a listing will be provided separately for golimumab and infliximab subjects for:

- Participants who dose adjusted along with the reason for dose adjustment
- Participants who missed doses due to COVID-19 reasons

The average follow-up time (weeks) and average exposure (number of administrations) will be summarized in the adverse event (AE) tables from Week 0 through Week 6 (before dosing), during

the Long-Term Phase from Week 6 (after dosing) through Week 54, and from Week 0 through the Final Safety Visit.

4.5. Protocol Deviations

Protocol deviations will be summarized separately for golimumab and infliximab from Week 0 through Week 54 for:

- Major protocol deviations
- Participants who entered the study but did not meet the inclusion/exclusion criteria by category
- Protocol deviations in study agent administration.

In these summaries a participant can be included in more than 1 deviation category.

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Received additional dose of study agent
- Other (e.g. missed visits for reasons other than AEs, actions deemed as major deviations by the study team)

Participants who entered the study but did not meet the inclusion/exclusion selection will be grouped into the following 5 categories: UC disease criteria, medication criteria, laboratory criteria, medical history criteria, and other.

Protocol deviations in study agent administrations includes: missing doses, additional dose of study agent, incorrect doses (+/-10mg for Golimumab and +/-10% of planned dose for Infliximab), incorrect treatment and treatments administrated out of dosing windows. In addition, duration of administration less than 1.5 hours will also be summarized for infliximab participants. Protocol deviations in study agent administrations will be derived from the study drug administration data.

In addition to the summary tables, the following listings will be provided from Week 0 through Week 54:

- List of participants with major protocol deviations
- List of participants who did not meet study selection criteria by category
- List of participants who had a protocol deviation in study agent administration

4.6. Prior and Concomitant Medications

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continued on after the first dose of study agent.

Summaries of UC medication history (participants who took medications for UC and their length of exposure prior to Week 0) will be provided separately for golimumab and infliximab.

UC disease-specific concomitant medications at baseline (oral 5-ASAs, immunomodulators [6-MP/AZA/MTX], and oral corticosteroids (including budesonide and beclomethasone dipropionate) will be summarized separately for golimumab and infliximab. Summaries by age (2-<12 yrs, including 2-<6 yrs and 6-<12 yrs, 12-<18 yrs), and weight (<45 kg, including <30 kg and 30-45 kg, ≥45 kg) will also be provided separately for golimumab and infliximab.

In addition, summaries of UC-related non-biologic medication history (history of response to or tolerance of 6-MP/AZA/MTX and history of response to, tolerance of or dependence on corticosteroids) and UC-related biologic medication history (vedolizumab) will be summarized separately for golimumab and infliximab.

5. EFFICACY

Efficacy endpoints through Week 6 and during the Long-Term Phase through Week 54 will be summarized in Sections 5.2 to 5.5 for golimumab. For endpoints through Week 6, analyses will be provided for participants in FGAS1. For endpoints beyond Week 6, analyses will be provided for participants in FGAS2 (subjects in clinical response at Week 6 as determined by IWRS), unless otherwise specified. Infliximab endpoints will be summarized in Section 5.6. Efficacy endpoints during the study extension will be summarized in Section 8.

A formal comparison is planned for the primary endpoint with a historical placebo control. Summary statistics will be provided for all efficacy endpoints. No comparisons of infliximab to golimumab will be performed. Unless otherwise specified, all endpoints that involve the Mayo endoscopy subscore will be based on the subscore assigned by the local endoscopist.

Upon implementation of Protocol Amendment 4, participants will not be randomized to the infliximab arm. However, summary statistics will still be provided for the infliximab group.

5.1. Analysis Specifications

5.1.1. Level of Significance

The primary endpoint utilized a 90% confidence level.

5.1.2. Data Handling Rules

5.1.2.1. Treatment Failure Rules

For all efficacy endpoints through Week 54, treatment failure rules will be applied. For dichotomous endpoints, participants who met any treatment failure criteria are considered as not achieving the respective endpoints. For continuous endpoints, participants who met any treatment failure criteria have their baseline values (at Week 0) carried forward from the time of the treatment failure onwards. Participants who have any of the following events through Week 54 will be considered to be a treatment failure from the time of event onward.

Participants who have any of the following events will be considered to be a treatment failure:

- Had a colectomy (partial or full) or ostomy,

OR

- Discontinued study intervention due to lack of efficacy or an AE of worsening of UC,

OR

- Use of a rescue medication after a clinical flare as defined below (Week 6 onwards)

OR

- Had a prohibited change in UC medication as defined below:

Corticosteroids:

1. Increase above baseline in the prednisone equivalent dosage of oral or parenteral (subcutaneous, intramuscular, or intravenous) corticosteroids (excluding budesonide and beclomethasone dipropionate) due to worsening ulcerative colitis.
2. Increase above baseline in the dosage of oral budesonide or oral beclomethasone dipropionate due to worsening ulcerative colitis.
3. No oral or parenteral corticosteroids (excluding budesonide and beclomethasone dipropionate) at baseline and initiation of oral or parenteral corticosteroids (excluding budesonide and beclomethasone dipropionate) after baseline due to worsening ulcerative colitis.
4. No oral budesonide or oral beclomethasone dipropionate at baseline and initiation of oral budesonide or oral beclomethasone dipropionate due to worsening ulcerative colitis.
5. An initiation of rectal corticosteroids (foam or enema; excludes suppositories) after baseline due to worsening ulcerative colitis.
6. An increase of rectal corticosteroids (foam or enema; excludes suppositories) after baseline due to worsening ulcerative colitis.
7. Any switch among oral budesonide/oral beclomethasone dipropionate to another oral or parenteral corticosteroids due to worsening of disease.

5-ASA compounds:

1. Increase above baseline in the dosage of oral 5-ASA compounds (sulfasalazine, mesalamine, olsalazine, or balsalazide) due to worsening ulcerative colitis.
2. No oral 5-ASA compounds at baseline and initiation of oral 5-ASA compounds after baseline due to worsening ulcerative colitis.
3. Initiation of rectal 5-ASAs (foam, enema, or suppositories) after baseline due to worsening ulcerative colitis.
4. Increase above baseline in the dosage of rectal 5-ASAs (foam, enema, or suppositories) due to worsening ulcerative colitis.
5. Switch between one 5-ASA compound to another 5-ASA compound due to worsening ulcerative colitis.

Immunomodulator agents:

1. Increase above baseline in the dosage of AZA/6-MP or MTX due to worsening ulcerative colitis.
2. No AZA, 6-MP, or MTX at baseline and initiation of AZA, 6-MP, or MTX after baseline due to worsening ulcerative colitis.
3. Switch between AZA/6-MP and MTX due to worsening ulcerative colitis.

Protocol-prohibited medications:

Initiation of any of the following immunomodulatory agents after baseline:

1. Immunomodulatory agents other than 6-MP, AZA, or MTX (including, but not limited to, 6-TG, cyclosporine, MMF, tacrolimus, and sirolimus)
2. Immunomodulatory biologic agents (including, but not limited to, TNFα antagonists (eg, etanercept, adalimumab), ustekinumab, abatacept, anakinra, rituximab, alemtuzumab, vedolizumab, natalizumab, and visilizumab)
3. Thalidomide or related agents
4. Investigational drugs

Definition of rescue medication:
- Following a clinical flare, initiation due to worsening ulcerative colitis of 6-MP/AZA/MTX, oral budesonide, oral beclomethasone dipropionate, or oral steroids will be considered a rescue medication.
- Following a clinical flare, oral corticosteroids (prednisone equivalent) increase above the dose received at baseline due to worsening ulcerative colitis will be considered a rescue medication.

Any participant who uses rescue medication after a clinical flare will be considered a treatment failure from the time of the use of rescue medication onwards.

5.1.2.2. Discontinuation Due To COVID-19

For subjects who discontinue study intervention due to COVID-19, their data will be used as available.

5.1.2.3. Missing Data Rules

For all analyses, participants with insufficient data for binary endpoints will be considered to not have achieved their respective endpoint; for participants with insufficient data for continuous endpoints, the last available value will be carried forward.

Note that treatment failure rules override missing data rules. This means that if a participant has an event of treatment failure, baseline values will be assigned from the point of treatment failure onward for continuous endpoints, and participants will be considered as not achieving the respective endpoints for dichotomous endpoints, regardless of whether the data were observed or missing.

5.2. Primary Efficacy Endpoint(s)

The primary endpoint is clinical remission at Week 6, which is derived from the Mayo score using local endoscopies. Note that the analysis will target a composite estimand which incorporates treatment failure rules into the endpoint in order to address the intercurrent events related to treatment failure.

5.2.1. Definition

5.2.1.1. Mayo Score/Partial Mayo score

The Mayo score[4] was developed from the criteria of Truelove and Witts[5] for mild, moderate, and severe UC; and from the criteria of Baron et al[1] for grading the mucosal appearance. The Mayo score consists of the following 4 subscores:

- Stool frequency
- Rectal bleeding
- Findings of endoscopy
- Physician's global assessment

Each subscore is rated on a scale from 0 to 3, indicating normal to severe activity.

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 endoscopy. Thus, the Mayo score may take on values in the range of 0 to 12. **The partial Mayo score**, which is the Mayo score without taking into account the findings of endoscopy, is calculated as the sum of the stool frequency, rectal bleeding, and physician's global assessment subscores, and may take on values from 0 to 9. **The modified Mayo score,** which is the Mayo score without the PGA subscore, is calculated as the sum of the stool frequency, rectal bleeding, and endoscopy subscores, and may take on values from 0 to 9.

Since one of the main objectives of the Simponi pediatric UC development program is to compare back to the adult Simponi UC results, it is important to maintain consistency with the data handling rules used for the key endpoints at Week 6 in the adult study (C0524T17). Therefore, the Mayo score at Week 6 will be calculated if at least 1 of the 4 subscores is available at Week 6. Likewise, the partial Mayo score will be calculated if at least 1 of the 3 subscores is available from the visit at which the partial Mayo score is measured. If the Mayo score/partial Mayo score cannot be calculated, it will be considered missing (insufficient data) for that visit. In case of partially missing data (ie, 1-3 of the subscores is missing, but not all 4 subscores), the last value for the missing subscore (including endoscopy at Week 6) will be carried forward in order to calculate the full Mayo score or partial Mayo score at Week 6. For a missing endoscopy subscore, this would mean that the baseline value for the endoscopy (ie, a score of 2 or 3) will be carried forward to Week 6. Even though we will carry forward the endoscopy subscore, the participant will not meet the criteria for clinical remission (ie, Mayo score ≤2 with no subscore >1) and will also not have achieved endoscopic healing. The participant could potentially achieve clinical response.

Due to the potential for a substantial number of missing endoscopies at Week 54 in this pediatric study, different missing data rules (than those used in the C0524T18 study) will be applied for the Week 54 calculation of the Mayo score. Since the first major secondary endpoint (ie, symptomatic remission at Week 54) does not include the endoscopy subscore, the extrapolation back to the adult study for the Week 54 endpoint should be preserved. The following rules will be applied to calculate the Mayo score and partial Mayo score in case of partially missing data (ie, 1-3 of the subscores is missing, but not all 4 subscores) during the Long-Term Phase. If the endoscopy subscore is not missing at Week 54, then for missing subscores for the other Mayo subscores, the last available subscore value will be carried forward to calculate the Mayo score. **If the endoscopy subscore is missing at Week 54, then the Mayo score cannot be calculated and will be considered missing (insufficient data) for that visit.** Thus, participants with missing endoscopy at Week 54 will be considered not to be in clinical response or clinical remission, and not to have endoscopic healing at Week 54. For missing subscores for the partial Mayo score, the last available subscore value will be carried forward to calculate the score. If the partial Mayo score cannot be calculated, it will be considered missing (insufficient data) for that visit.

The modified Mayo score will be calculated in a similar fashion.

The baseline Mayo score is defined as the Mayo score calculated just prior to the first administration of study agent at Week 0 (using the screening endoscopy).

Stool Frequency and Rectal Bleeding Subscores

The electronic case report forms (eCRFs) capture seven days of rectal bleeding data and the number of stools per day prior to each visit at which the partial Mayo score or Mayo score is collected. Sites are instructed to check the boxes next to the 3 days which are used to calculate stool frequency and rectal bleeding subscores. **Absolute stool number** is the average of the daily stool number over the three days, and the rectal bleeding subscore is calculated using the average rectal bleeding number for the three days based on the criteria in Attachment 1. At the screening visit, each person indicates the number of stools he/she passed in a 24-hour period when in

remission or before his/her UC diagnosis. The stool frequency subscore will be calculated based on the criteria in Attachment 1 by subtracting the number of stools when in remission or prior to UC from the absolute stool number.

Sites are directed to use the most recent 3 consecutive days within the week prior to the visit and are directed to exclude the following:

- The day medications were taken for constipation, diarrhea or irregularity
- The day of a procedure or preparation for procedure (e.g. enema, other laxatives, or clear liquid diet) that would affect stool frequency and/or blood content of the stool
- The 48 hours after the use of antimotility agents (i.e. diphenoxylate hydrochloride with atropine sulfate or loperamide)
- The 48 hours immediately following a colonoscopy

If three consecutive days are not available, the sites are instructed to choose two consecutive days and the closest nonconsecutive day. If two consecutive days are not available, then three nonconsecutive days closest to the visit should be chosen. If 3 days (within the week prior to the indicated visit) that meet the criteria defined above are not available, then the absolute stool number, stool frequency subscore and rectal bleeding subscore cannot be calculated and will be missing in the eCRF.

Endoscopy Subscore

The endoscopic findings will be based on the criteria of the Mayo endoscopy subscore described in Attachment 1. The endoscopic subscore will be assessed by the investigator (i.e., local endoscopist) during the endoscopy procedure and by a central reader reviewing a video of the endoscopy. The central readers will be blinded to local endoscopist scores, treatment assignment and study visit.

The central reader will perform a friability assessment for each endoscopy (sigmoidoscopy or colonoscopy) received by providing a response to the following question: “Is hemorrhage detected with incidental trauma caused by the endoscopic procedure?” If friability is present, the central reader will also provide a confidence level (High or Low) when evaluating friability. Further details are provided in the Imaging Charter.

Further details regarding video acquisition, standardization, reading, and data transfer are provided in the Imaging Charter.

The analysis of endpoints related to the endoscopy subscore, including the Mayo score, will be based on the locally read endoscopic subscore. The local endoscopy reader is used to maintain consistency in methodology for endoscopic data used in the comparisons with the historical placebo control for the primary efficacy endpoints and other efficacy endpoints with the adult Simponi data.

The analyses of endpoints based on central read of endoscopy is described in Section 5.5.

Physician's Global Assessment Subscore

The physician's global assessment acknowledges the 3 other Mayo subscores, the patient's recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

5.2.1.2. Clinical Remission

Clinical remission as measured by the Mayo score is defined as a Mayo score ≤2 points, with no individual subscore >1 (based on Mayo endoscopy subscore assigned by the local endoscopist).

5.2.1.3. Analysis Methods

The primary analysis population will be based on FGAS1. The primary analysis population includes all participants (including the smallest weight cohort [<30 kg]) who were treated with golimumab. The success of the study will ultimately be based on the totality of evidence.

The primary analysis will be based on the proportion of pediatric participants who received golimumab and who were in clinical remission at Week 6 based on the Mayo score (endoscopy subscore 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 will have been met if the lower limit of the two-sided 90% CI for the proportion of pediatric golimumab participants in clinical remission at Week 6 is 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 (see Attachment 4 for more details).

5.2.2. Subgroup Analyses

The consistency of treatment effect for the golimumab participants for the primary endpoint will be summarized using counts and percentages for the subgroups defined in Section 2.4.

5.2.3. Sensitivity Analysis

To examine the robustness of the primary endpoint analysis for golimumab, the following sensitivity analyses will be performed:

1. Sensitivity Analysis 1 (Observed case): excludes participants who have missing data (Mayo Score cannot be calculated) at Week 6 and have not had an event of treatment failure prior to Week 6.
2. Sensitivity Analysis 2 (Last Observation Carried Forward [LOCF] for missing data): For participants with missing data at Week 6, the last available value for each subscore will be carried forward to impute missing data.
3. Sensitivity Analysis 3: Participants with missing data for any of the Mayo subscores at Week 6 are considered not to be in clinical remission.
4. Sensitivity Analysis 4 (Multiple Imputation): After treatment failure rules are applied, participants with missing data for any of the Mayo subscores will have the missing data imputed by Multiple Imputation assuming the data is missing at random.

5. Sensitivity Analysis 5 (Historical placebo control based on random effects model and inverse-variance weighting method): Comparisons of the lower limit of the 90% confidence interval for clinical remission at Week 6 to the upper bound of the 95% CI for the historical adult placebo remission rate (ie, 10.8%; see Attachment 3 and Attachment 4 for more details).
6. Sensitivity Analysis 6 (Historical placebo control based on fixed effects model and sample-size weighting method): Comparisons of the lower limit of the 90% confidence interval for clinical remission at Week 6 to the upper bound of the 95% CI for the historical adult placebo remission rate (ie, 10.8%; see Attachment 3 and Attachment 4 for more details).
7. Sensitivity Analysis 7 (Historical placebo control based on random effects model and sample-size weighting method): Comparisons of the lower limit of the 90% confidence interval for clinical remission at Week 6 to the upper bound of the 95% CI for the historical adult placebo remission rate (ie, 11.2%; see Attachment 3 and Attachment 4 for more details).
8. Sensitivity Analysis 8 (Historical placebo control based on random effects model and sample-size weighting method): Comparisons of the lower limit of the 90% confidence interval for clinical remission at Week 6 to the upper bound of the 95% CI for the historical adult placebo remission rate, estimated with a meta-analysis considering studies with "any route of administration" (i.e., 11.0%; see Attachment 3 and Attachment 4 for more details).

5.2.4. Supportive Analyses

5.2.4.1. Supportive Analysis 1

The historical proportion of adults on placebo in clinical remission at Week 6 will be estimated using participant-level data of the of 2 Phase 2/3 adult UC studies of golimumab (C0524T16 and C0524T17), and 2 Phase 3 adult UC studies of infliximab (C0168T37 and C0168T46). A logistic regression model will be fitted with the clinical remission status at Week 6 as the dependent variable and the following variables as covariates: baseline Mayo score, baseline CRP (≤3 mg/L, >3 mg/L), study (C0524T16, C0524T17, C0168T37, C0168T46) and baseline oral corticosteroids (receiving, not receiving). Using baseline Mayo score, baseline oral corticosteroids (receiving, not receiving) and baseline CRP (≤3 mg/L, >3 mg/L) covariate data from the pediatric participants, the predicted clinical remission status at Week 6 for a "pediatric covariate adjusted placebo intervention group" will be calculated based on covariate parameters from the adult logistic regression model. The estimate and the corresponding 95% CI for the proportion of participants in clinical remission in the pediatric covariate-adjusted placebo intervention group will be constructed. This will be descriptively compared with the 90% CI of the proportion of golimumab pediatric participants who are in clinical remission at Week 6 in the FGAS1.

5.2.4.2. Supportive Analysis 2

A Bayesian approach will be used to compare the proportion of pediatric participants on golimumab in clinical remission at Week 6 and a historical proportion of adults on placebo in clinical remission at Week 6. A Bayesian logistic model will be used to obtain the covariate adjusted placebo remission rate to account for potential differences in the participants of the current CNTO148UCO3003 pediatric study and in the C0524T16, C0524T17, C0168T37 and C0168T46 adult studies (ie, participants who received placebo). The following covariates will be used if they are significantly associated with the outcome measure in the adult studies: baseline Mayo score, baseline CRP (≤3 mg/L, >3 mg/L), and baseline oral corticosteroids (receiving, not receiving). The

adult placebo proportion in clinical remission will be modeled using the weighted average of the covariate-adjusted remission rate based on the participant-level data of the golimumab (C0524T16, C0524T17), and infliximab (C0168T37 and C0168T46) studies and the study-level data of the adalimumab (ULTRA 1 and ULTRA 2), and vedolizumab (GEMINI 1) studies. The posterior distribution of the difference in outcome measures between the treatment groups and its corresponding 90% credible interval (CrI) will be constructed to make inference. If the lower bound of the CrI is greater than 0, then it is assumed that the proportion of pediatric participants on golimumab in clinical remission at Week 6 is higher than that of adult participants on placebo intervention. Details are in Attachment 5.

5.3. Major Secondary Endpoints

The following major secondary endpoints will be summarized for golimumab. Efficacy endpoints through Week 6 will be summarized based on the FGAS1. Efficacy endpoints during the Long-Term Phase through Week 54 will be summarized based on the FGAS2 (subjects in clinical response at Week 6 as determined by IWRS).

1. Symptomatic remission at Week 54.
2. Clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
3. Clinical remission at Week 54, as assessed by the PUCAI score.
4. Clinical remission at Week 6, as assessed by the PUCAI score.
5. Clinical response at Week 6, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
6. Endoscopic healing at Week 6 (based on Mayo endoscopy subscore assigned by the local endoscopist).
7. Endoscopic healing at Week 54 (based on Mayo endoscopy subscore assigned by the local endoscopist).
8. Clinical remission at Week 54, as assessed by the Mayo score, for participants who are in clinical remission at Week 6 (based on Mayo endoscopy subscore assigned by the local endoscopist).
9. Participants who were not receiving corticosteroids for at least 12 Weeks prior to Week 54 and in clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).

5.3.1. Sensitivity Analysis for Clinical Remission at Week 54

The following sensitivity analysis will be performed for clinical remission at Week 54 for golimumab subjects:
Historical placebo control based on random effects meta-analysis with sample-size weighting method: comparison of the lower limit of the 90% confidence interval for clinical remission at Week 54 to the upper bound of the 95% CI for the historical adult placebo remission rate (see Attachment 3 and Attachment 4 for more details). Clinical Remission at Week 54 will be summarized based on the FGAS2 (subjects in clinical response at Week 6 as determined by IWRS).

5.3.2. Supportive Analysis for Clinical Remission at Week 54

The following supportive analysis will be performed for clinical remission at Week 54 for all enrolled subjects at Week 0 for golimumab:

Historical placebo control based on random effects meta-analysis with sample-size weighting method: comparison of the lower limit of the 90% confidence interval for clinical remission at Week 54 to the upper bound of the 95% CI for the historical adult placebo remission rate (see Attachment 3 and Attachment 4 for more details). Clinical Remission at Week 54 will be summarized based on the FGAS1.

5.3.3. Definitions

5.3.3.1. PUCAI

The PUCAI[6], a noninvasive measure of UC disease activity, consists of the following 6 subscores:

- Abdominal Pain
- Rectal Bleeding
- Stool consistency of most stools
- Number of stools per 24 hours
- Nocturnal bowel movement (any diarrhea episode causing wakening)
- Activity level

The PUCAI score is calculated as the sum of the 6 subscores of abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal bowel movement, and activity level. The PUCAI score may take on values in the range of 0 to 85.

The PUCAI score will be calculated if at least 3 of the 6 subscores are available from the visit at which the PUCAI score is measured. For missing PUCAI subscores, the last available subscore value will be carried forward to calculate the score. If the PUCAI score cannot be calculated, it will be considered missing (insufficient data) for that visit.

The baseline PUCAI score is defined as the PUCAI score calculated just prior to the first administration of study agent at Week 0.

5.3.3.2. Symptomatic Remission

Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

5.3.3.3. Endoscopic Healing

Endoscopic healing is determined from the endoscopy subscore of the Mayo score. Endoscopic healing is defined as an endoscopy subscore of 0 or 1.

5.3.3.4. Clinical Response

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.

5.3.3.5. Clinical Remission

Clinical remission as measured by the PUCAI score is a PUCAI score <10.

5.3.4. Analysis Methods

Treatment failure rules will be applied as specified in Section 5.1.2.1. These rules will override the response status based on the Mayo, PUCAI, and endoscopy score.

Participants who do not have sufficient data to calculate their Mayo Score at Week 6 or Week 54 will be considered to not have achieved clinical response or clinical remission (based on the Mayo Score) at these timepoints. Participants who do not have sufficient data to calculate their stool frequency and rectal bleeding subscores at Week 54 will be considered to not have achieved symptomatic remission at Week 54. Participants who do not return for evaluation or have insufficient data to calculate their PUCAI Score at Week 6 or Week 54 will be considered to not have achieved clinical remission (based on the PUCAI Score) at these timepoints. Participants who do not return for endoscopy evaluation at Week 6 or at Week 54 will be considered to not have endoscopic healing at these timepoints.

In addition to summarizing the proportion of golimumab participants who meet each of the major secondary endpoints, 90% CIs using the asymptotic formula based on the normal approximation to the binomial distribution will be provided for each major secondary endpoint.

Additional exploratory analysis using confidence intervals based on other confidence levels (e.g., 80% or 95% instead of 90%) may also be performed.

5.3.4.1. US-specific Analysis for Symptomatic Remission at Week 54

To accommodate a request for demonstration of long-term efficacy, a US-specific analysis of the first major secondary endpoint of symptomatic remission at Week 54 will be provided to support submission in the United States. Symptomatic remission at Week 54 will be based on the proportion of pediatric participants who received golimumab and who were in clinical response at Week 6. The proportion of golimumab pediatric participants in symptomatic remission at Week 54 will be summarized overall, and the associated 90% CI will be provided for participants who are clinical responders at Week 6 to golimumab as determined by the IWRS using local endoscopy. This will be descriptively compared to the proportion of adult participants who were in symptomatic remission at Week 54 in the historical placebo control in the C0524T18 study and its associated 95% CI. Note that the analysis will target a composite estimand which incorporates treatment failure rules into the endpoint in order to address the intercurrent events related to treatment failure.

5.4. Other Efficacy Endpoints

Endpoints in this section will be summarized for golimumab-treated subjects. Efficacy endpoints through Week 6 will be summarized based on the FGAS1. Efficacy endpoints during the Long-Term Phase through Week 54 will be summarized based on the FGAS2 (subjects in clinical response at Week 6 as determined by IWRS).

5.4.1. Remission

1. Symptomatic remission at Week 6.
2. Clinical remission at Week 30, as assessed by the PUCAI score, for participants who are in clinical remission at Week 6.
3. Clinical remission at Week 54, as assessed by the PUCAI score, for participants who are in clinical remission at Week 6.
4. Symptomatic remission at Week 54, for participants who are in symptomatic remission at Week 6.
5. Corticosteroid-free clinical remission at Week 54, as assessed by the PUCAI score.
6. Corticosteroid-free clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
7. Corticosteroid-free symptomatic remission at Week 54.
8. Remission at Week 6 based on Mayo score less than or equal to 2, with no individual subscore greater than 1, a stool frequency subscore of 0, and a rectal bleeding subscore of 0.
9. Partial Mayo remission at Week 6.
10. Partial Mayo remission at Week 54.
11. Participants who were not receiving corticosteroids for at least 12 weeks prior to Week 54 and in symptomatic remission at Week 54.
12. Participants who were not receiving corticosteroids for at least 12 Weeks prior to Week 54 and in clinical remission at Week 54, as assessed by the PUCAI score.
13. Corticosteroid-free clinical remission at Week 54 among subjects who were receiving corticosteroids at Week 0, as assessed by the PUCAI score.
14. Corticosteroid-free clinical remission at Week 54 among subjects who were receiving corticosteroids at Week 0, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
15. Corticosteroid-free symptomatic remission at Week 54 among subjects who were receiving corticosteroids at Week 0.

5.4.2. Other Clinical Efficacy Endpoints

1. Clinical response at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
2. Baseline and postbaseline values and the change from baseline in the Mayo score at Week 6 and at Week 54 (based on Mayo endoscopy subscore assigned by the local endoscopist).

3. Baseline and postbaseline values in the Mayo subscores at Week 6 and at Week 54 (based on Mayo endoscopy subscore assigned by the local endoscopist).
4. Baseline and postbaseline values and the change from baseline in the PUCAI score through Week 6 and during the Long-Term Phase through Week 54.
5. Baseline and postbaseline values and the change from baseline in the Partial Mayo score through Week 6 and during the Long-Term Phase through Week 54.
6. Clinically important change at Week 6 as assessed by the PUCAI score.
7. Clinically important change at Week 30 as assessed by the PUCAI score.
8. Clinically important change at Week 54 as assessed by the PUCAI score.
9. Baseline and postbaseline values and the change from baseline in the average daily corticosteroid use Week 0 through Week 6.
10. Baseline and postbaseline values and the change from baseline in the average daily corticosteroid use after Week 6 through Week 54.
11. Endoscopic normalization (based on Mayo endoscopy subscore assigned by the local endoscopist) at Week 6 and at Week 54.

5.4.3. CRP and Fecal Marker Endpoints

1. Baseline and postbaseline values and the change from baseline in CRP through Week 6 and during the Long-Term Phase through Week 54.
2. Baseline and postbaseline values and the change from baseline in fecal calprotectin concentrations through Week 6 and during the Long-Term Phase through Week 54.
3. Normalization of CRP concentration (≤3 mg/L) through Week 6 and during the Long-Term Phase through Week 54 among participants with abnormal CRP concentration (>3 mg/L) at baseline.
4. Normalization of fecal calprotectin concentration (≤250 mg/kg) through Week 6 and during the Long-Term Phase through Week 54 among participants with abnormal fecal calprotectin concentration (>250 mg/kg) at baseline.

5.4.4. Key Efficacy Endpoints by Age and Weight Subgroups

Key efficacy endpoints (primary and major secondary endpoints) will be summarized for golimumab by:

- baseline age (2-<12, including 2-<6 and 6-<12, 12-<18)
- baseline weight (<45 kg, including <30 kg and 30-45 kg, ≥45 kg)

Efficacy endpoints through Week 6 will be summarized based on the FGAS1. Efficacy endpoints during the Long-Term Phase through Week 54 will be summarized based on the FGAS2.

5.4.5. Quality of Life

Baseline and postbaseline values and the change from baseline in IMPACT III through Week 6 and during the Long-Term Phase through Week 54 will be summarized for golimumab participants ≥10 years at Week 0.

5.4.6. Efficacy Analyses Based on All Golimumab Participants Including Partial Mayo Responders at Week 14

The following endpoints will be summarized for golimumab participants based on FGAS3**:**

1. Clinical remission at Week 54, as assessed by the PUCAI score.
2. Clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
3. Symptomatic remission at Week 54.
4. Partial Mayo remission at Week 54.
5. Endoscopic healing at Week 54 (based on Mayo endoscopy subscore assigned by the local endoscopist).
6. Corticosteroid-free clinical remission at Week 54, as assessed by the PUCAI score.
7. Corticosteroid-free symptomatic remission at Week 54.
8. Corticosteroid-free clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
9. Clinically important change during the Long-Term Phase at Weeks 30 as assessed by the PUCAI score.
10. Clinically important change during the Long-Term Phase at Weeks 54 as assessed by the PUCAI score.
11. Clinical response at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).

5.4.7. UC-related Hospitalization and Surgery

The following endpoints will be summarized for golimumab participants:

1. UC-related hospitalization through Week 54
2. UC-related surgery through Week 54

5.4.8. Supplementary Analyses Due to COVID-19

The following will be summarized for golimumab participants.

5.4.8.1. Week 6

Due to the COVID-19 pandemic, the Sponsor has expanded the week 6 endoscopy window to week 5 to week 8, if the endoscopies cannot be obtained at Week 6 for reasons related to COVID-19.

The following additional sensitivity analyses will be performed for all primary and major secondary endpoints at Week 6 that include an endoscopy component:

1. All participants who could not have an endoscopy at Week 6 due to COVID-19 related reasons will be excluded from the clinical response, clinical remission, and endoscopic healing analysis.

2. Missing endoscopy subscore outcomes at Week 6 due to COVID-19 will be imputed using Multiple Imputation assuming the data is missing at random.

Note that participants who have had an event of treatment failure prior to Week 6 will be considered to be a nonresponder in these analyses, regardless of whether they are missing the endoscopy at Week 6.

5.4.8.2. Week 54

Due to COVID-19, the Sponsor has expanded the Week 54 endoscopy window from Week 40 to anytime after week 54, as long as it is prior to the planned Week 54 database lock. The participants need to be receiving golimumab at the time of the endoscopy.

The following analysis will be performed for all major secondary endpoints at Week 54:

1. Missing endoscopy subscore outcomes at Week 54 due to COVID-19 will be imputed using Multiple Imputation, assuming the data is missing at random.

Note that participants who have had an event of treatment failure prior to Week 54 will be considered to be a nonresponder in these analyses, regardless of whether they are missing the endoscopy at Week 54.

5.4.9. Definition

5.4.9.1. Partial Mayo remission

Partial Mayo score remission is defined as partial Mayo score ≤2.

5.4.9.2. IMPACT III

Quality of life measures will be assessed in participants 10 to 17 years of age at Week 0 using the IMPACT-III questionnaire (Protocol Appendix 7 [Section 10.7]). The questionnaire comprises 35 questions on a variety of topics, from mood, self-image, and school absences to self-perceptions of weight and height. It has been validated in many studies and is applicable for children 10 to 17 years of age with UC or Crohn's disease. The score ranges from 35 to 175.[3]

5.4.9.3. Clinically Important Change

A decrease in the PUCAI score of 20 points (from baseline) is considered a minimally clinically important change.[6]

5.4.9.4. CRP and Fecal Biomarkers:

- ***Normalization of CRP concentration:*** CRP concentration ≤3 mg/L.
- ***Normalization of fecal calprotectin concentration:*** fecal calprotectin concentration ≤250 mg/kg.

5.4.9.5. Average daily prednisone-equivalent corticosteroid dose

For corticosteroid medication (excluding budesonide and beclomethasone dipropionate) use at specific time point, the average daily prednisone-equivalent corticosteroid dose is calculated using the corticosteroid dosage levels from the 6 days prior to the day before the visit.

Subjects who have a treatment failure (see Section 5.1.2.1) will have their baseline corticosteroid use (average daily dose) carried forward, starting from the time of the treatment failure, regardless of the actual data.

5.4.9.6. Endoscopic Normalization

Endoscopic normalization is determined from the endoscopy subscore of the Mayo score. Endoscopic normalization is defined as an endoscopy subscore of 0.

5.4.10. Analysis Methods

Treatment failure rules and missing data rules will be applied as specified in Section 5.1.2.1 and 5.1.2.2, respectively. For continuous endpoints (ie, PUCAI score, Mayo score, partial Mayo score, fecal markers and CRP), the same treatment failure rules that will be applied for the dichotomous efficacy endpoints will also be applied to these endpoints. The baseline value will be carried forward from the time the treatment failure occurs onward. For subjects without a corticosteroid information at a visit, the last available value will be carried forward.

Participants who do not return for evaluation or have insufficient data for dichotomous endpoints will be considered as not having the event. For participants who do not return for evaluation or have insufficient data for continuous endpoints, the last available value will be carried forward.

Descriptive statistics will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables.

5.5. Exploratory Endpoints

The following exploratory endpoints will be summarized for participants receiving golimumab. Efficacy endpoints through Week 6 will be summarized based on the FGAS1. Efficacy endpoints during the Long-Term Phase through Week 54 will be summarized based on the FGAS2 (subjects in clinical response at Week 6 as determined by IWRS).

- Response at Week 6 by an alternative response definition as defined in Section 5.5.1.1.
- Remission at Week 6 by three alternative remission definitions as defined in Section 5.5.1.2.
- Analysis related to friability present on endoscopy are defined in Section 5.5.2.
- Analyses of different approaches to addressing missing endoscopy scores at Week 54 are defined in Section 5.5.3.

- Analyses of comparison of pediatric participants with adult participants are defined in Section 5.5.4
- Baseline and postbaseline values and the change from baseline in TUMMY UC/Observer Tummy UC over time through Week 54 by age (<8 yrs, ≥8yrs).
- Primary and major secondary endpoints using centrally read endoscopy scores.

5.5.1. Alternative Definitions of Response and Remission

5.5.1.1. Alternative Response Definition

1. **Alternative response definition:** A decrease in the modified Mayo score (ie, Mayo score without the PGA subscore) of ≥2 points and ≥***30***% and either a decrease in rectal bleeding subscore of ≥1 or a rectal bleeding score of 0 or 1.

5.5.1.2. Alternative Remission Definitions

1. **Alternative remission definition 1:** A stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
2. **Alternative remission definition 2:** A stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1, where the stool frequency subscore has not increased from induction baseline.
3. **Alternative remission definition 3:** An absolute stool number ≤3, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.

5.5.2. Analyses Related to Friability Present on Endoscopy

Summaries of the following endpoints will be provided in which participants with friability present on endoscopy will be considered nonresponders. These endpoints will be based on centrally read endoscopy scores.

5.5.2.1. Endpoints at Week 6

1. Endoscopic healing at Week 6.
2. Remission at Week 6 based on the Mayo score ≤2 points, with no individual subscore >1.
3. Remission at Week 6 based on the Full Mayo score (Mayo score ≤2 with no subscore >1), with the additional criteria of a stool frequency subscore of 0 and a rectal bleeding subscore of 0.
4. Remission at Week 6 based on a stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
5. Remission at Week 6 based on a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
6. Remission at Week 6 based on an absolute stool number ≤3, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
7. Endoscopic normalization.

5.5.2.2. Endpoints at Week 54

1. Endoscopic healing at Week 54.
2. Remission at Week 54 based on the Mayo score ≤2 points, with no individual subscore >1.
3. Remission at Week 54 based on the Full Mayo score (Mayo score ≤2 with no subscore >1), with the additional criteria of a stool frequency subscore of 0 and a rectal bleeding subscore of 0.
4. Remission at Week 54 based on a stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
5. Remission at Week 54 based on a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
6. Remission at Week 54 based on an absolute stool number ≤3, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
7. Endoscopic normalization.

5.5.3. Analyses of Missing Endoscopy Score at Week 54

There is a high risk of missing endoscopy scores at Week 54, therefore sensitivity analysis with different approaches to the missing data are proposed. In case of missing data, caution should be exercised for interpreting endpoints beyond Week 6 that involve endoscopy at Week 54, particularly if a large number of participants did not have a Week 54 endoscopy performed.

Sensitivity analyses, with differing approaches to handling missing endoscopies at Week 54, will be performed for the following endpoints:

1. Endoscopic healing at Week 54.
2. Clinical remission at Week 54, as assessed by the Mayo score.
3. Clinical response at Week 54, as assessed by the Mayo score.

In addition, endoscopies not performed at Week 6 or Week 54 will be summarized by reason why it was not done.

1. Sensitivity Analysis 1 (Observed case): Excludes participants who have missing endoscopy data at Week 54 and have not had an event of treatment failure prior to Week 54.
2. Sensitivity Analysis 2 (LOCF): Participants with missing endoscopy data at Week 54 and have at least 1 other subscore for the Mayo score will have their last endoscopy subscore carried forward in determining clinical remission or clinical response.
3. Sensitivity Analysis 3: Participants with missing endoscopy data at Week 54 due to "lack of efficacy" are considered not to be in endoscopic healing, clinical remission or clinical response. For reasons other than "lack of efficacy", Week 6 endoscopy scores will be carried forward.

Additional sensitivity analysis may be performed if a significant number of endoscopies are missing at Week 54.

5.5.4. Comparison of Pediatric Participants With Adult Participants

5.5.4.1. Comparison of Pediatric Remission Rates With Adult Remission Rates

A descriptive comparison of the remission rate in pediatric participants to the remission rate achieved by adults (Simponi trials: C0524T17, C0524T18) on both active treatment and placebo will be conducted.

This analysis will be conducted for the following endpoints:

- Clinical remission at Week 6, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
- Clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
- Clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist) among participants who achieved clinical remission at Week 6.
- Corticosteroid-free remission at Week 54.

5.5.4.2. Ratio of Pediatric Participants to Adult Participants

Ratio of the proportion of pediatric participants in clinical remission at Week 6 over the proportion of adult participants in clinical remission at Week 6 in the golimumab 200 mg intervention group from study C0524T17 will be summarized.

5.5.5. TUMMY-UC

TUMMY-UC/Observer TUMMY UC is a noninvasive participant-reported outcome (PRO) for the measure of signs and symptoms for pediatric UC similar to the PUCAI index, which is undergoing validation.[2] The total TUMMY score is derived by adding the score of each of the 8 components, and it ranges from 0 to 114. The TUMMY-UC is for participants ≥8 years, while.the Observer Tummy UC is similar to the TUMMY-UC but used for participants under age 8. The Observer Tummy UC is completed by caregivers. The version used at the Week 0 assessment will be used at all subsequent assessments regardless if participant age changes.

5.5.6. Analysis Methods

Descriptive statistics (mean, SD, median, IQ range, minimum and maximum) will be provided for continuous variables. Counts and percentages will be provided for categorical variables.

Treatment failure and missing data rules will be applied as specified in Section 5.1.2.1 and 5.1.2.2 to all endpoints other than the analysis for TUMMY-UC and Observer Tummy. No treatment failure or missing data rules will be applied for the summaries for TUMMY-UC or Observer Tummy. For endpoints involving endoscopy, participants with missing friability or a friability that cannot be determined will be considered not to have friability. For subjects without a corticosteroid information at a visit, the last available value will be carried forward. No imputation will be

performed for missing UC disease-related hospitalizations and surgeries, the missing values will remain as missing. In addition, no treatment failure rules will be applied.

In addition to summarizing the proportion of golimumab participants who meet each remission endpoint, 90% CIs using the asymptotic formula based on the normal approximation to the binomial distribution will be provided for comparison of remission rates with adults (Section 5.5.4.1). Descriptive comparisons of the remission rates in pediatric participants to the remission rates achieved by adult participants on both active treatment and placebo estimated from relevant Simponi trials (C0524T17, C0524T18) will be conducted.

Additional exploratory analysis using confidence intervals based on other confidence levels (e.g., 80% or 95% instead of 90%) may also be performed for selected endpoints.

5.6. Efficacy Summaries in Infliximab Participants

Endpoints in this section will be summarized for infliximab-treated subjects. Efficacy endpoints through Week 6 will be summarized based on the FIAS1. Efficacy endpoints during the Long-Term Phase through Week 54 will be summarized based on the FIAS2 (subjects in clinical response at Week 6 as determined by IWRS).

1. Clinical remission at Week 6, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
2. Symptomatic remission at Week 54 for participants in clinical response to infliximab.
3. Clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist) for participants in clinical response to infliximab.
4. Clinical remission at Week 54, as assessed by the PUCAI score for participants in clinical response to infliximab.
5. Clinical remission at Week 6, as assessed by the PUCAI score.
6. Clinical response at Week 6, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist).
7. Endoscopic healing at Week 6 (based on Mayo endoscopy subscore assigned by the local endoscopist).
8. Endoscopic healing at Week 54 (based on Mayo endoscopy subscore assigned by the local endoscopist) for participants in clinical response to infliximab.
9. Clinical remission at Week 54, as assessed by the Mayo score, for participants who are in clinical remission at Week 6 (based on Mayo endoscopy subscore assigned by the local endoscopist).
10. Participants who were not receiving corticosteroids for at least 12 Weeks prior to Week 54 and in clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist) for participants in clinical response to infliximab.

5.6.1. Analysis Methods

Treatment failure rules will be applied as specified in Section 5.1.2.1. These rules will override the response status based on the Mayo, PUCAI, and endoscopy score. For subjects without a corticosteroid information at a visit, the last available value will be carried forward.

Participants who do not have sufficient data to calculate their Mayo Score at Week 6 or Week 54 will be considered to not have achieved clinical response or clinical remission (based on the Mayo Score) at these timepoints. Participants who do not have sufficient data to calculate their stool frequency and rectal bleeding subscores at Week 54 will be considered to not have achieved symptomatic remission at Week 54. Participants who do not return for evaluation or have insufficient data to calculate their PUCAI Score at Week 6 or Week 54 will be considered to not have achieved clinical remission (based on the PUCAI Score) at these timepoints. Participants who do not return for endoscopy evaluation at Week 6 or at Week 54 will be considered to not have endoscopic healing at these timepoints.

6. SAFETY

Safety through Week 6 and during the Long-Term Phase through Week 54 and through FSV for participants that did not enter the Study Extension, will be summarized separately for golimumab and infliximab participants.

Selected safety analysis during the Long-Term Phase through Week 54 will also be summarized for Safety Analysis Set who are in Clinical Response at Week 6 as determined by the IWRS for golimumab participants.

Safety will be assessed by summarizing the frequency and type of AEs, and laboratory parameters (hematology and chemistry).

6.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent is considered to be treatment emergent adverse event (TEAE). If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported TEAEs will be included in the analysis. For each AE, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized through Week 6 and during the Long-Term Phase through Week 54. AE tables will also be presented from Week 0 through the Final Safety Visit. TEAEs will be tabulated by descending frequency in the total column of the System Organ Class (SOC) and then by preferred term within the SOC.

Adverse Events will be summarized separately for golimumab and infliximab-treated participants. Summaries include:

- All AEs
- Serious AEs
- AEs leading to discontinuation of study agent
- AEs of severe intensity
- AEs reasonably related to study agent
- Infections
- Serious infections and infections requiring oral or parenteral antimicrobial treatment.
- Injection-site reactions (for golimumab participants)
- AEs within 1 hour of infusion (for infliximab participants)

SAEs, serious infections and AES leading to discontinuation of study agent will be summarized for golimumab participants during the Long-Term Phase through Week 54 for:

- Safety Analysis Set who are in Clinical Response at Week 6 as determined by the IWRS

A summary of key safety events (death, discontinued study agent because of 1 or more adverse events, AEs, SAEs, infections, serious infections, neoplasms [malignant], AEs during or within 1 hour of an infusion (infliximab), infection site reactions [golimumab]) through Week 6, during the Long-Term Phase through Week 54 and from Week 0 through the Final Safety Visit for participants that did not enter the Study Extension will be provided separately for golimumab and for infliximab.

Key safety events through Week 6 will also be summarized by Safety Analysis Set during the Short-Term Phase and from Week 0 through the Final Safety Visit for participants that did not enter the Study Extension for golimumab participants by:

- baseline age [2-<12 years, 12-<18 years]
- baseline weight (<45 kg, including <30 kg and 30-45 kg, ≥45 kg)
- baseline immunomodulator status
- baseline corticosteroid status
- clinical response status at Week 6 as determined by the IWRS.

Key safety events during the Long-Term Phase through Week 54 will be summarized by Safety Analysis Set for golimumab participants by:

- baseline age [2-<12 years, 12-<18 years]
- baseline weight (<45 kg, including <30 kg and 30-45 kg, ≥45 kg)
- clinical response status at Week 6 as determined by the IWRS.

AEs, SAEs, serious infections and AES leading to discontinuation of study agent will also be summarized from Week 0 through Week 54 for the Safety Analysis Set.

In addition to the summary tables, the following listings will also be provided from Week 0 through the final safety visit separately for golimumab and infliximab participants:

- Serious TEAEs
- TEAEs leading to discontinuation of study agent
- Any deaths
- Possible anaphylaxis and possible delayed hypersensitivity reactions
- TEAEs associated with COVID-19

A reasonably related AE is defined as any event with the relationship to study agent as 'very likely', 'probable', or 'possible' on the AE eCRF page or if the relationship to study agent is missing.

AEs leading to discontinuation of study agent are defined as events with action taken as 'Drug Withdrawn' or events that lead to discontinuation from the study due to the AE event.

AEs within 1 hour of infusion is defined as an AE that occurs during or within 1 hour following the infusion of study agent, with the exception of laboratory abnormalities. If the AE onset time is missing and the AE onset date is the same as the date of infusion, an AE will be considered as an infusion reaction only if the question on the AE eCRF page 'Was this an infusion related reaction' = 'Yes'.

An injection site reaction is defined as an AE with the question on the AE eCRF page 'Was this an injection site reaction' = 'Yes'.

An infection is defined as any AE that was characterized by the investigator as an infection on the eCRF.

Since safety should be assessed relative to exposure and follow-up, all AE summary tables will summarize the average weeks of follow-up and average exposure (number of administrations) separately for golimumab and infliximab.

All product quality complaints (PQC) device and device-related AEs will be collected and investigated and summarized in a separate technical report. Further details can be found in the protocol.

6.2. Clinical Laboratory Tests

Routine laboratory data from clinical chemistry, and hematology, will be collected at screening and at Visits according to the Schedule of Activities in the study protocol. The laboratory data to be summarized are as follows:

- Clinical Blood Chemistry: Chemistry panel including sodium, potassium, chloride. blood urea nitrogen (BUN), creatinine, AST, ALT, total and direct bilirubin, alkaline phosphatase, calcium, phosphate, albumin, total protein, gamma glutamyl transferase (GGT)
- Hematology: hemoglobin, hematocrit, platelet count, white blood cell (WBC) total and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils).

Descriptive statistics for selected clinical laboratory analyte and for change from baseline at each scheduled post-baseline visit will be provided through Week 6 and during the Long-Term Phase through Week 54. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0) will be used in the summary of laboratory data (Grade 0-4). The proportion of participants with post-baseline values by maximum toxicity grade for clinical laboratory tests will be summarized separately for golimumab and infliximab. Participants with toxicity grades ≥2 will be listed. The laboratory tests not included in Attachment 2 will not be presented in the corresponding toxicity tables or listings. Summaries of maximum toxicity grade will also be provided during the Long-Term Phase through Week 54.

Proportion of participants with maximum postbaseline ALT/AST will be provided for the categories, separately through Week 6 and during the Long-Term Phase through Week 54:

- >1 to <3 x ULN
- ≥3 to <5 x ULN
- ≥5 to <8 x ULN
- ≥8 x ULN

In addition, the proportion of participants with maximum postbaseline total bilirubin relative to ULN will be provided for the categories, separately through Week 6 and during the Long-Term Phase through Week 54:

- Subjects within normal range (≤1x ULN total bilirubin)
- Subjects with abnormalities (>1x ULN total bilirubin)
  - >1 to <2 x ULN
  - ≥2 x ULN

Change from baseline is defined to be the assessment at the postbaseline visit minus the assessment at baseline. Summaries of laboratory data will be completed using all the available laboratory data at the time point of interest without imputing missing data.

6.2.1. Antinuclear Antibodies and Double-Stranded DNA Antibodies

Blood samples will be collected as per the protocol Schedule of Activities to determine the presence of ANA and anti-dsDNA antibodies.

The ANA test is positive if the ANA titer ≥1:160. All samples will be tested for ANA and all samples will be analyzed for anti-dsDNA positivity using a multiplex bead immunoassay (via the AtheNA Multi-Lyte test). Anti-dsDNA positivity is defined as >120 IU/ml.

The analyses are as follows:

- The proportion of participants with a positive ANA titer at any time through Week 6 and during the Long-Term Phase through Week 54 will be summarized.
- The proportion of participants with a positive anti-dsDNA antibody titer at any time after Week 0 through Week 6 and during the Long-Term Phase through Week 54 for those participants who are ANA positive will be summarized.

A listing of participants with a postbaseline ANA titer ≥1:160 from after Week 0 through the final safety visit will be provided.

6.3. Vital Signs and Physical Examination Findings

Summaries will not be provided for vital signs and physical examination findings. Abnormalities considered clinically relevant by the investigator will be reported as AEs.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Blood samples for the determination of the serum golimumab concentrations will be drawn according to the protocol Schedule of Activities. Serum samples will be used to evaluate various PK parameters. All PK evaluations will be based on the participants who receive any golimumab or infliximab.

Descriptive statistics (N, mean, SD, median, range, and IQ range) will be used to summarize serum golimumab and infliximab concentrations at each scheduled sampling time point by treatment group. PK data may be displayed graphically, such as mean +/- SD PK concentrations over time by treatment group.

Serum concentrations will be summarized through Week 6 and during the Long-Term Phase through Week 54 separately for golimumab and infliximab. In addition, serum golimumab concentrations from Week 0 through Week 54 will also be summarized for the PK evaluable analysis set who are in clinical response. For summary statistics of serum golimumab concentrations, concentration values below the limit of quantification will be treated as zero. No imputation for missing concentration data will be performed. The proportion of participants with concentration below the lowest quantifiable concentrations at each visit will also be summarized through Week 6 and during the long term-phase through Week 54 separately for the golimumab and infliximab group.

Once a participant meets one of the following dosing deviation criteria, the participant's data will be excluded from the by-visit data analyses from that point onwards.

Dosing deviation criteria for participants treated with golimumab:

- Received an incorrect SC dose.
- Missed an administration.

- Received an additional SC dose.
- Received commercial golimumab.

Dosing deviation criteria for participants treated with infliximab:

- Received an incomplete/incorrect infusion.
- Missed an administration.
- Received an additional infusion.

In addition, PK samples taken outside the scheduled visit window (±4 days) will be excluded from the summary tables at that visit. After the Week 6 visit, if the PK sampling time deviates more than 10 days, the PK concentration at this visit will be excluded from the by-visit data analyses.

Serum golimumab concentrations will also be summarized for golimumab participants through week 6 by:

- Baseline age [2-<12 years, 12-<18 years]
- Baseline weight (<45 kg, including <30 kg and 30-45 kg, ≥45 kg)
- Clinical response status as determined by the IWRS
- Baseline immunomodulator status
- Study (C0524T17 [200/100 mg induction dosing], CNTO148UC03003)

In addition to the summary tables the following plots will also be provided for golimumab participants:

- Plot of serum golimumab concentrations over time through Week 6 by weight (<45 kg, ≥45 kg)
- Plot of serum golimumab concentrations over time through Week 6 for all treated participants by study (C0524T17 [200/100 mg induction dosing], CNTO148UC03003).

A population PK analysis approach will be used to determine golimumab PK parameters. Relevant covariates will be evaluated for their effect on golimumab PK where appropriate. Additional PK data from other studies may be used to supplement the population PK analysis in pediatric participants with UC. The results of the population PK analysis will be provided in a separate report from the clinical study report.

7.1.1. Pharmacokinetics and Efficacy

To determine the influence of golimumab concentration on the efficacy of golimumab, the primary and major secondary endpoints will be summarized by golimumab concentrations at Week 6 and at steady state trough, as appropriate (< 1st quartile, ≥ 1st quartile and < 2nd quartile, ≥ 2nd quartile and < 3rd quartile, and ≥ 3rd quartile).

Further, the primary and major secondary endpoints by golimumab concentrations using medians or tertiles may be explored.

In addition to the tables, the following plots will also be provided for PK evaluable analysis set.

- Bar chart of median improvement from baseline in the Mayo scores at Week 6 will be summarized by golimumab concentration quartiles (micrograms/mL) at Week 6 by study (C0524T17 [200/100 mg induction dosing], CNTO148UC03003).
- Bar chart of clinical response at Week 54 will be summarized by golimumab concentration quartiles (micrograms/mL) at Week 54 by study (C0524T18 [100 mg dosing], CNTO148UC03003).
- Bar chart of clinical remission at Week 54 will be summarized by golimumab concentration quartiles (micrograms/mL) at Week 54 by study (C0524T18 [100 mg dosing], CNTO148UC03003).

7.2. Immunogenicity

Antibodies to golimumab and antibodies to infliximab will be evaluated using drug tolerant enzyme immunoassays in serum samples collected from all participants according to the protocol Schedule of Activities. These samples will be tested by the Sponsor or Sponsor's designee.

Sample and participant status (positive/negative) will be provided by the bioanalytical group. Participants with anti-drug antibody (ADA) positive samples at baseline are classified as “positive” if titer increases at least 2-fold following treatment. If titer remains the same after treatment or if ADA titer reduces or ADA disappears, the participant is classified as “negative”. Participants with unavailable status following treatment will be classified as “participants with baseline samples only”.

The anti-golimumab and anti-infliximab antibodies summarization and analysis will be based on the observed data; therefore no imputation of missing data will be performed. Note: participant status is through each database lock time point, thus, participant status and peak titers may change as the study progresses over time. For example, if a study has a lock at Week 54, datasets through Week 54 will have a certain participant level status (e.g., negative) but at a future lock, say Week 256, they may have developed ADA and thus participant status may change (e.g., from negative to positive) from the interim to the end DBL. Peak titers can also change if a higher titer occurs after an initial DBL.

The summary of participants with baseline positive samples is taken from the sample status at baseline. There is no participant level status at baseline.

Incidence of antibody (positive, negative) status and neutralizing antibodies (NAb) to golimumab or infliximab will be summarized separately for all participants in the PK analysis set who receive any golimumab or infliximab and have appropriate samples for the detection of antibodies to golimumab or antibodies to infliximab (ie, participants with at least 1 sample obtained after their first administration of golimumab or infliximab). Serum samples will be screened for antibodies binding to golimumab or infliximab and the titer of confirmed positive samples will be reported.

The analysis of antibodies to golimumab or infliximab, irrespective of dose adjustment includes the following:

- Summary of antibody to golimumab status (positive/negative) through Week 6.
- Summary of antibody to infliximab status (positive/negative) through Week 6.
- Summary of antibody to golimumab status (positive/negative) from Week 0 through Week 54 for the Immunogenicity Golimumab Analysis Set.
- Summary of antibody to infliximab status (positive/negative) from Week 0 through Week 54 for the Immunogenicity Infliximab Analysis Set.
- Antibody to golimumab status (positive/negative) through Week 6 will also be summarized by study (CNTO148UCO3003 and those who received 200/100 mg induction dosing in the SIMPONI adult UC study C0524T17).

Further, antibody to golimumab status (positive/negative) through Week 6 by clinical response status may be explored if sufficient number of golimumab participants are positive. Other relationships between antibody to golimumab status, and safety and efficacy may also be explored if sufficient number of golimumab participants are positive.

The analysis of neutralizing antibodies to golimumab or antibodies to infliximab includes the following:

- The proportion of participants with a positive neutralizing antibody to golimumab status at any time through Week 6
- The proportion of participants with a positive neutralizing antibody to infliximab status at any time through Week 6
- The proportion of participants with a positive neutralizing antibody to golimumab status at any time from Week 0 through Week 54 will be summarized for participants who entered the Long-Term Phase
- The proportion of participants with a positive neutralizing antibody to infliximab status at any time from Week 0 through Week 54 will be summarized for participants who entered the Long-Term Phase

In addition to the summary tables, listings from Week 0 through Week 54 of participants positive for anti-golimumab or anti-infliximab will be provided separately. The neutralizing antibody status will be included in the antibody to golimumab or antibody to infliximab listing.

7.3. Pharmacodynamics

Blood, fecal and mucosal biopsy samples will be collected at visits indicated in Schedule of Activities of the protocol. Changes in the concentration of individual serum markers from baseline to the selected post treatment time points will be summarized. Differential expression of RNA in whole blood and mucosal biopsies and microbiome analysis will be performed. Biomarker analyses are considered exploratory and will be summarized in separate technical reports.

7.4. Histologic and Immunohistochemical

The biopsy samples collected will also be used for the histologic and immunohistochemical assessment of disease and healing. This may be further investigated and summarized in a separate technical report.

8. STUDY EXTENSION

For all golimumab participants who are eligible to enter the study extension at Week 54 and continue receiving study extension doses of SC golimumab q4w, the following analyses will be performed:

- Summary of the number of participants who discontinued study agent.
- Summary of the number of participants who terminated study participation.
- Tabulations of the number of participants by the study agent lot(s).

The study visit window during the Study Extension after Week 54 will be ±14 days. Limited efficacy, PK, and safety analyses will be performed on participants who enter the study extension.

8.1. Efficacy

All participants who are entering the study extension and received at least 1 administration of study agent during the study extension will be included in the ***Study Extension Full Analysis Set***.

During the study extension, efficacy endpoints will include the PUCAI. Treatment failure rules will be applied for all efficacy endpoints during the study extension unless otherwise specified. In such a case, baseline values (at Week 0) will be assigned from the point of treatment failure onward, regardless of the observed data, for continuous endpoints, and participants will be considered as not achieving the respective endpoints for dichotomous endpoints. Treatment failure rules override other data handling rules.

Participants who have any of the following events will be considered to be a treatment failure during the study extension:

- Had a colectomy (partial or full) or ostomy,

  OR

- Discontinued study intervention due to lack of efficacy or an AE of worsening of UC,

  OR

- Initiated a prohibited medication.

For all analyses, participants who have not turned 18 at the time of the assessment and have insufficient data for binary endpoints will be considered to not have achieved their respective endpoint; for participants with insufficient data for continuous endpoints, the last available value will be carried forward. For participants who have turned 18 at the time of the assessment and have insufficient data, their last value will be carried forward.

The following summaries of efficacy data will be performed from the study-extension through the end of the study:

- The proportion of participants in clinical remission, based on the PUCAI score
- The change from study-extension baseline (Week 54) in PUCAI scores

In addition, these efficacy analyses will also be summarized based on observed data without missing data imputation or data handling rules.

8.2. PK/ Immunogenicity

PK/ immunogenicity summaries entering the study extension and who received at least 1 dose (complete or partial) of study treatment of study agent during the study extension and have at least one valid blood sample drawn for PK analysis during the study extension phase will be included in the ***Study Extension PK/Immunogenicity Evaluable Analysis Set***.

PK summaries include serum golimumab concentration during the study extension, number of participants without a detectable serum golimumab concentration during the study extension, antibody to golimumab status through the study extension and neutralizing antibody to golimumab.

8.3. Safety

The ***Study Extension Safety Analysis Set*** includes golimumab-treated participants who are entering the study extension and who received at least 1 dose (complete or partial) of study treatment during the study extension. The average follow-up time (weeks) and average exposure (number of administrations) will also be summarized in the AE safety tables. The following will be summarized:

- The frequency and type of AEs observed during the study extension
- Summary of maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade for postbaseline laboratory values during the study extension
- Summary of maximum postbaseline measurement during the study extension for ALT, AST and alkaline phosphatase relative to ULN
- Summary of maximum postbaseline total bilirubin during the study extension relative to ULN.

Listings of SAEs, AEs leading to discontinuation of study agent, and possible anaphylaxis and possible delayed hypersensitivity reactions will be provided. Any deaths will also be presented in a listing. In addition, listings of participants with any abnormal postbaseline laboratory values of CTCAE grade ≥2 will also be provided.

8.4. At Home Administration

Participants who elect to have at home administration in the study extension will be included in the ***Study Extension AHA***. The following will be summarized:

- Baseline demographics and baseline disease characteristics
- Number of injections at home
- The frequency and type of AEs
- Serum Concentrations

8.5. Usability Assessment Substudy

Participants entering the study extension who choose AHA will be included in an *Usability Substudy Analysis Set*. The objective of the Substudy is to provide supportive data that the Prefilled Syringe with UltraSafe (PFS-U) and Prefilled Pen (PFP-V) as designed, together with the appropriate training and written instructions for use, is suitable for at home administration (AHA) by pediatric participants or their caregivers.

The Usability Assessment Substudy data will also be included in the Week 54 DBL. The PFS Usability questionnaire will be completed at Week 62 and Week 66. The questionnaire consists of 5 questions. Each question will be descriptively summarized based on observed data without missing data imputation or other data handling rules.

REFERENCES

1. Baron JH, Connell AM, Lennard-Jones JE. Variation Between Observers in Describing Mucosal Appearances in Proctocolitis. Br Med J. 1964;1(5375):89-92.
2. Marcovitch L, Nissan A, Mack D, Otley A, Hussey S, Mclean B, Lewis M, Croft N, Barakat, Farah M, Griffiths A, Turner, D. Item Generation And Reduction Toward Developing A Patient-Reported Outcome For Pediatric Ulcerative Colitis (TUMMY-UC). Journal of Pediatric Gastroenterology and Nutrition. 2017; 64(3): 373–377.
3. Otley A, Smith C, Nicholas D, et al. The IMPACT Questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2002;35(4):557-563.
4. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625-1629.
5. Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. Brit Med J. 1955; 2:1041-1048.
6. Turner D, Otley AR, Mack D, et al. Development, validation and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007;133:423-32.
7. Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. Journal of Statistical Software.2010; 36(3), 1-48. http://www.jstatsoft.org/v36/i03/ accessed Feb 28, 2024

ATTACHMENTS

ATTACHMENT 1: MAYO SCORE

Mayo scoring system for assessment of ulcerative colitis activity

Stool frequency[a]
0 = Normal number of stools for this patient
1 = 1-2 stools more than normal
2 = 3-4 stools more than normal
3 = 5 or more stools more than normal

Rectal bleeding[b]
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed

Findings of endoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment[c]
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

[a] At the screening visit, each person indicates the number of stools he/she passed in a 24-hour period when in remission or before his/her UC diagnosis, thereby serving as his/her own control to establish the degree of abnormality of stool frequency.
[b] The daily bleeding score represents the most severe bleeding of the day.
[c] The physician's global assessment acknowledges the 3 other criteria, the patient's recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

ATTACHMENT 2: LABORATORY TOXICITY GRADING

The grading scale use for lab assessments is based on CTCAE v5.0.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Hematology Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Hemoglobin (g/dL)	Increase	>0 - 2 x ULN	>2 - 4 x ULN	>4 x ULN	
Hemoglobin (g/dL)	Decrease	<LLN - 10.0	<10.0 - 8.0	<8.0	
Lymphocytes (/mm3)	Increase		>4000 - 20,000	>20,000	
Lymphocytes (/mm3)	Decrease	<LLN - 800	<800 - 500	<500 - 200	<200
Neutrophils (/mm3)	Decrease	<LLN - 1500	<1500 - 1000	<1000 - 500	<500
Platelets (/mm3)	Decrease	<LLN - 75,000	<75,000 - 50,000	<50,000 - 25,000	<25,000
Total WBC count (/mm3)	Increase			>100,000	
Total WBC count (/mm3)	Decrease	<LLN - 3000	<3000 - 2000	<2000 - 1000	<1000
Chemistry Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
ALT	Increase	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
AST	Increase	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Albumin (g/L)	Decrease	≥30 - <LLN	≥20 - <30	<20	
Alkaline Phosphatase	Increase	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin (total)	Increase	>ULN - 1.5 x ULN if	>1.5 - 3.0 x ULN if	>3.0 - 10.0 x ULN if	>10.0 x ULN if baseline

		baseline was normal; >1.0 - 1.5 x baseline if baseline was abnormal	baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	was normal; >10.0 x baseline if baseline was abnormal
Corrected Calcium (mmol/L)	Increase	>ULN - ≤2.9	>2.9 - ≤3.1	>3.1 - ≤3.4	>3.4
Corrected Calcium (mmol/L)	Decrease	≥2.0 - <LLN	<2.0 - ≥1.75	<1.75 - ≥1.5	<1.5
Creatinine	Increase	>ULN - ≤1.5 xULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 xULN
Glucose (mmol/L)	Decrease	<LLN - 3.0	<3.0 - 2.2	<2.2 - 1.7	<1.7
Potassium (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - 6.0	>6.0 - 7.0	>7.0
Potassium (mmol/L)	Decrease	<LLN - 3.0		<3.0 - 2.5	<2.5
Sodium (mmol/L)	Increase	>ULN - 150	>150 - 155	>155 - 160	>160
Sodium (mmol/L)	Decrease	<LLN - 130	129 - 125	124 - 120	<120

ATTACHMENT 3: META-ANALYSIS FOR THE PLACEBO RESPONSE

3.1 Meta-analysis Clinical Remission at Week 6

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

Studies considered, but not incorporated in this meta-analysis included:

- Phase 3 data for approved biologics from UC sub-populations with prior use of anti-TNF agents were not included in the meta-analysis (e.g. Gemini 1 (Vedolizumab) anti-TNF exposed subpopulation). In addition, data from Phase 3 studies in UC for unapproved biologic agents were not included in the meta-analysis (e.g. Abatacept IP1 and IP2).
- Phase 3 studies supporting registration of tofacitinib in UC. As tofacitinib is not a biologic agent (and was not approved for use in participants in UC at the time of determining which studies to include), and due to concerns that the fundamentally different route of administration (daily oral vs intermittent biologic), as well as methodologic differences in endpoint assessment (central reading rather than local), could present significant confounding effects, these studies were not included.
- Phase 2 studies were excluded from the meta-analysis (ie, Phase 2 studies of biologic therapies in participants with UC).
- Phase 2 or Phase 3 studies conducted in participants with UC with unapproved products (at the time of determining which studies to include in the analysis) including JAK inhibitors (other than tofacitinib) and other agents. As they may have potential confounding effects that could be introduced by differences in study design and conduct, patient populations, route of administration, and other factors, Phase 2 and 3 studies of nonbiologic agents were excluded from the meta-analysis.
- RINVOQ (Upadacitinib) is now approved in UC but was not approved at the time the original criteria were created, and thus excluded from the original meta-analysis.

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 5 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 5) to estimate the historical placebo rate.

3.1.1 Sensitivity Analysis

For the analysis described in Section 5.2.3 (sensitivity analysis 8), similar criteria as in Attachment 3.1 were used for study identification, except for criteria 4 (to include now studies with any route of administration). Studies considered but not incorporated in this meta-analysis included Phase 3 studies with oral route of administration as they had a different definition for primary efficacy endpoint or with endpoint later than 6 Weeks after study start (e.g., Week 10 or Week 12). Thus, only one additional study fulfilled the criteria described above (UNIFI, which was not available at the time the original analysis was performed). A summary of all studies is presented in Table 5.

Table 5: 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)

Table 5: 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
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)

* Studies included for comparison with the primary endpoint.
$ Studies included for Sensitivity Analysis.

3.2 Meta-analysis Clinical Remission at Week 54

The meta-analysis for Clinical Remission at Week 6 is based on the original study design. Based on recent regulatory precedence, a meta-analysis with revised criteria was added for clinical remission at Week 54 to be more inclusive of additional studies. Clinical remission at Week 54 is provided in Section 5.3.1 and Section 5.3.2.

For the purpose of the meta-analyses for the placebo rate to be descriptively compared with the **Clinical Remission at Week 54**, studies were chosen that met the following criteria:

1. Studies that had a similar adult patient population
2. Phase 3, global clinical studies
3. Studies with endpoint ~54 weeks after study start
4. Studies that had a randomized withdrawal design or a treat through design
5. Studies with similar definition for clinical remission from Week 0 to Week 54
6. Studies with population naïve or non-naïve to TNF
7. Studies that used central or local endoscopic assessment

8. Studies that defined the clinical remission with the Full Mayo score (Mayo score <=2 with no individual subscore >=1) or Full Mayo score without PGA.

3.2.1 Sensitivity Analysis for Clinical Remission at Week 54

A sensitivity analysis will be performed for clinical remission at Week 54 for golimumab participants who are in clinical response at Week 6 as determined by the IWRS.
This analysis includes eight Phase 3 studies with randomized withdrawal design: golimumab [PURSUIT-M], ustekinumab [UNIFI-M], vedolizumab [GEMINI 1, MLN0002/CCT-101M (Japan), VISIBLE 1], ozanimod [TRUE NORTH], tofacitinib [OCTAVE SUSTAIN] and Upadacitinib [U-ACHIEVE] (see Table 6).

3.2.2 Supportive Analysis for Clinical Remission at Week 54

A supportive analysis will be performed for clinical remission at Week 54 for all enrolled subjects at Week 0 for golimumab participants.

This analysis includes five Phase 3 studies with treat through design: infliximab [C0168T37 and C0168T46], adalimumab [ULTRA 2 and M10-447 (Japan)] and estrasimod [ELEVATE UC 52]. All studies calculate clinical remission for Week 52 or Week 54, except for C0168T46 where remission is obtained until Week 30 only (see Table 6).

Table 6: Characteristics of Past Ulcerative Colitis Studies in Adult Participants with Moderately to Severely Active Ulcerative Colitis, timing of clinical remission endpoint ~54 weeks after study start

Study	Population	Endoscopic Assessment	Trial Design	Timing of Clinical Remission Endpoint	Clinical Remission Definition	Placebo Point Estimate	Point Estimate for Active Labeled Dose
REMICADE ACT 1 (C0168T37)	Naïve to TNF	Local	Treat Through	Week 54	Full Mayo score	16.5% (n=121)	34.7% for 5mg (n=121) 34.4% for 10mg (n=122)
Adalimumab – ULTRA 2	Non-naïve to TNF	Local	Treat Through	Week 52	Full Mayo score	8.5% (n=246)	17.3% (n=248)
Adalimumab - M10-447 (Japan)	Naïve to TNF	Local	Treat Through	Week 52	Full Mayo score	7.3% (n=96)	12.9% (n=177)
Etrasimod – ELEVATE UC 52	Non-naïve to TNF	Central	Treat Through	Week 52	Full Mayo score without PGA	6.7% (n=135)	32.1% (n=274)
REMICADE ACT 2 (C0168T46)	Naïve to TNF	Local	Treat Through	Week 30	Full Mayo score	10.6% (n=123)	25.6% for 5mg (n=121) 35.8% for 10mg (n=120)
Golimumab – PURSUIT-M	Naïve to TNF	Local	Randomized Withdrawal	Week 54	Full Mayo score	22.1% (n=154)	33.1% for 50mg (n=151)

Table 6: Characteristics of Past Ulcerative Colitis Studies in Adult Participants with Moderately to Severely Active Ulcerative Colitis, timing of clinical remission endpoint ~54 weeks after study start

Study	Population	Endoscopic Assessment	Trial Design	Timing of Clinical Remission Endpoint	Clinical Remission Definition	Placebo Point Estimate	Point Estimate for Active Labeled Dose
							33.8% for 100mg (n=151)
Ustekinumab – UNIFI-M	Non-naïve to TNF	Central	Randomized Withdrawal	Week 52	Full Mayo score	24.0% (n=175)	38.4% for 90mg every 12 weeks (n=172) 43.8% for 90mg every 8 weeks (n=176)
Vedolizumab – GEMINI 1	Non-naïve to TNF	Local	Randomized Withdrawal	Week 52	Full Mayo score	15.9% (n=126)	41.8% for every 8 weeks (n=122) 44.8% for every 4 weeks (n=125)
Vedolizumab – MLN0002/CCT-101M (Japan)	Non-naive to TNF	Local	Randomized Withdrawal	Week 60	Full Mayo score	30.9% (n=42)	56.1% (n=41)
Vedolizumab – VISIBLE 1	Non-naïve to TNF	Central	Randomized Withdrawal	Week 52	Full Mayo score	14.3% (n=56)	46.2% for SC (n=106) 42.6% for IV (n=54)
Ozanimod – TRUE NORTH	Non-naïve to TNF	Central	Randomized Withdrawal	Week 52	Full Mayo score without PGA	18.5% (n=227)	37% (n=230)
Tofacitinib – OCTAVE SUSTAIN	Non-naïve to TNF	Central	Randomized Withdrawal	Week 60	Full Mayo score	11.1% (n=198)	34.3% for 5mg (n=198) 40.6% for 10mg (n=197)
Upadacitinib – U-ACHIEVE	Non-naïve to TNF	Central	Randomized Withdrawal	Week 60	Full Mayo score without PGA	12.1% (n=149)	42% for 15mg (n=148) 52% for 30mg (n=154)

ATTACHMENT 4: META-ANALYSIS STATISTICAL DETAILS AND RESULTS

The meta-analysis for the historical placebo control used the 'metafor' package in R[7]. The meta-analytic models were fitted with the rma.uni() function.

For a set of i = 1, 2, …k independent studies, the fixed-effects model (method="FE") with no covariates (mods=~1) was fitted to the data using the rma.uni() function with:

rma(yi=p,sei=se,mods=~1,method="FE")

Weighted estimation (with inverse-variance weights) is the default and was used where

$$\bar{\theta}_w = \sum_{i=1}^{k}(w_i\theta i)/\sum_{i=1}^{k} wi$$

$\overline{\theta_w}$ is the weighted average of the true outcomes in the set of k studies, with weights equal to $w_i = 1/v_i$ (the 'inverse-variance' method). Alternatively, $\overline{\theta_w}$ can also be estimated with weights equal to the sample sizes n_i of each study. In this case, the meta-analysis is performed with a sample-size weighting method with:

rma(yi=p,sei=se,mods=~1,method="FE",weights=n)

Similarly, the random-effects model was fitted using DerSimonian-Laird (DL) random-effects model using the rma.uni ( ) function with:

rma(yi=p,sei=se,mods=~1,method="DL")

or with the below for sample-size weighting:

rma(yi=p,sei=se,mods=~1,method="DL",weights=n).

The meta-analysis for the placebo point estimate for the fixed effects and random effects model are included in Table 7. Sensitivity analyses using sample-size weighting method are also provided.

Table 7: Placebo Remission Rate Based on Meta-analysis

Study (Naive TNF Population)	**Total (n)**	**Participants in Clinical Remission (n)**	**Placebo Point Estimate for Clinical Remission Based on Meta-analysis (95% CI) Inverse-variance Weighting**		**Placebo Point Estimate for Clinical Remission Based on Meta-analysis (95% CI) Sample-size Weighting**	
			Fixed Effects	Random Effects	Fixed Effects	Random Effects
Week 6 Studies for comparison with the primary endpoint	988	89	8.3% [6.6%,10.0%]	8.6% [6.5%,10.8%] Q=8.39; p-value=0.211; I^2=28.47	9.0% [7.2%,10.8%]	9.0% [6.8%,11.2%] Q=8.39; p-value=0.211; I^2=28.47
Week 6 Studies for Sensitivity	1139	104	8.5% [6.9%,10.1%]	8.7% [6.8%,10.6%]	9.1% [7.5%,10.8%]	9.1% [7.2%,11.0%]

Table 7: Placebo Remission Rate Based on Meta-analysis

Study (Naive TNF Population)	**Total (n)**	**Participants in Clinical Remission (n)**	**Placebo Point Estimate for Clinical Remission Based on Meta-analysis (95% CI) Inverse-variance Weighting**		**Placebo Point Estimate for Clinical Remission Based on Meta-analysis (95% CI) Sample-size Weighting**	
			Fixed Effects	Random Effects	Fixed Effects	Random Effects
Analysis				Q=8.76; p-value=0.271; I^2=20.06		Q=8.76; p-value=0.271; I^2=20.06
Week 54 Studies for Sensitivity Analysis	1127	199	16.4% [14.3%,18.6%]	17.5% [13.6%,21.5%] Q=21.70; p-value=0.003; I^2=67.74	17.7% [15.5%,19.9%]	17.7% [13.6%,21.8%] Q=21.70; p-value=0.003; I^2=67.74
Week 54 Studies for Supportive Analysis	721	70	9.0% [6.9%,11.0%]	9.3% [6.5%,12.1%] Q=6.90; p-value=0.141; I^2=42.05	9.7% [7.6%,11.9%]	9.7% [6.8%,12.6%] Q=6.90; p-value=0.141; I^2=42.05

ATTACHMENT 5: BAYESIAN MODEL

This Attachment describes the Bayesian model used for the Primary Endpoint.

5.1 Adult Placebo Patient Level data

Let Y_{AUi} be the primary outcome measure of patient i in study j, where r_{AUij} is the response rate of the placebo group.

$$Y_{AUij} \sim Bernoulli\left(r_{AUij}\right) and\ i = 1, \dots, n; j = 1, \dots, m$$

The response rate is modelled via a logit scale with baseline covariates from study j:

$$\theta_{AUij} = \log\left(\frac{r_{AUij}}{1 - r_{AUij}}\right) and\ i = 1, \dots, n; j = 1, \cdots, m$$

$$\theta_{AUij} = \beta_{0j} + \beta_{1j} x_{1AUij} + \cdots + \beta_{cj} x_{cAUij}$$

$$\beta_{kj} \sim N(\mu_k, \tau_k) \quad and\ k = 0,1, \cdots, c$$

where

$$\mu_k \sim N(0, \tau), \qquad \tau_k \sim Gamma(a, b), \quad and\ k = 0,1, \cdots, c$$

and the hyperparameters are set to be non-informative priors, i.e. $\tau = 0.001, a = 0.001, b = 0.001$. $N(\mu, \tau)$ represents the normal distribution with mean μ and variance $1/\tau$.

The following four studies are included in the model: C0524T16 (PURSUIT IV study); C0524T17(PURSUIT SC study); C0168T37(ACT 1 study) and C0168T46 (ACT 2 study).

5.2 Covariate Adjusted Response Rate

Based on the model described in Attachment 5.1, a covariate adjusted response rate can be obtained to match the population of CNTO148UCO3003 by using the average value for each covariate.

If the overall proportion of patients on placebo from the studies with patient level data r_{AUp} is given as $\bar{X}_{kP}$, the population level model described in Attachment 5.1 for calculating the covariate adjusted response rate r_{AUp} is given by:

$$\theta_{AUP} = \log\left(\frac{r_{AUp}}{1 - r_{AUp}}\right)$$

$$\theta_{AUP} = \mu_0 + \mu_1 \bar{X}_{1P} + \cdots + \mu_c \bar{X}_{cP}$$

5.3 Adult Placebo Study Level data

Let r_{AVj} be the proportion of patients on placebo in clinical remission from study j with study level data. Thus:

$$Y_{AVj} \sim Bin\left(n_{AVj},\ r_{AVj}\right) and\ j = 1, \ldots, m$$

$$\theta_{AVj} = log\left(\frac{r_{AVj}}{1 - r_{AVj}}\right)$$

$$\theta_{AVj} \sim N(\mu_{AV}, \tau_{AV})$$

where

$$\mu_{AV} \sim N(0, \tau),\ \ \tau_{AV} \sim Gamma(a, b)$$

and the hyperparameters are set to non-information priors, i.e. $\tau = 0.001, a = 0.001, b = 0.001$.

The following three studies are included in the model: ULTRA 1, ULTRA 2 and GEMINI 1. The overall proportion of patients on placebo from the studies with study level data r_{AV} is given by

$$\mu_{AV} = \log\left(\frac{r_{AV}}{1 - r_{AV}}\right).$$

5.4 Joint Adult Placebo Model

The joint adult model incorporates both r_{AUp} and r_{AV} with a weight of w, such that:

$$r_{AJ} = \ (1 - w)r_{AV} + w\, r_{AUp}$$

where

$$w \ \in [0, 1].$$

5.5 Pediatric Model

Let Y_{Pi} be the primary outcome measure of pediatric patient i, where r_P is response rate in the CNTO148UCO3003 study. Thus

$$Y_{Pi} \sim Bernoulli\ (r_P)$$

$$\theta_p = log\left(\frac{r_p}{1 - r_p}\right)$$

where parameter θ_p is set to be a non-informative prior: i.e. $\theta_p \sim N(0, 0.001)$.

5.6 Posterior estimate

The posterior distribution of the difference in outcome measures between the treatment groups, i.e. $r_p - r_{AJ}$, and its corresponding 90% credible interval will be constructed.