Janssen Research & Development*

Clinical Protocol

A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

UNIFI

Protocol CNTO1275UCO3001; Phase 3
AMENDMENT 2

Ustekinumab (CNTO1275)

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	17 March 2015
Amendment 1	14 July 2015
Amendment 2	20 April 2016

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (20 April 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To address health authority requests for additional data collection as well as to address investigator feedback and to provide further clarifications on the protocol.

Rationale: The text was corrected to clarify that the US-specific definition of clinical remission will be used to support the US submission only, and a line was added to indicate that each definition will be applied to all subjects in the analysis population.

Synopsis; 9.2.2, Endpoints	• The following **US-specific definition** of clinical remission will be used in the United States: an absolute stool number ≤3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. Each definition of clinical remission will be applied to all subjects in the analysis population.
11.3.1.2, (Induction) Primary Analysis	The primary endpoint is clinical remission at Week 8. The definition of clinical remission (as well as the testing procedure) will be different for countries outside the United States and for the United States, as described below. Each definition of clinical remission will be based on all randomized subjects.
11.3.2.2, (Maintenance) Primary Analysis	The primary endpoint is clinical remission at Week 44. The definition of clinical remission is different for countries outside the United States and for the United States, as described below. Each definition of clinical remission will be based on the primary population.

Rationale: At the request of a health authority, collection of stool consistency data using the Bristol Stool Form Scale has been added as an exploratory analysis.

Synopsis (Objectives and Hypotheses); 2.1.3, Exploratory Objectives	An exploratory objective for the Bristol Stool Form Scale was added: • To evaluate the data based on the Bristol Stool Form Scale score in the induction study.
Synopsis (Efficacy Evaluations/Endpoints); 9.2.1, Evaluations	The Bristol Stool Form Scale was added to the bulleted list of efficacy evaluations in the Synopsis and at the start of Section 9.2.1, and a paragraph describing it was added to the text following the bullets in Section 9.2.1: The Bristol Stool Form Scale is a medical aid to classify the form (or consistency) of human feces into 7 categories.[22] It has been used as a research tool to evaluate the effectiveness of treatments for various diseases of the bowel (eg, irritable bowel syndrome [IBS]).[12] The daily average of the same 3-day period used to calculate the stool frequency and rectal bleeding subscores of the Mayo score will be used to calculate the average Bristol Stool Form Scale score for the visit.

Table 1, Time and Events Schedule: Induction Study	The Bristol Stool Form Scale was added to the Time and Events Schedule: Induction, under the Efficacy assessments subhead, with data collection at Weeks I-0, I-2, I-4, I-8, and I-16.
9.1.2, Screening Phase	Text about the Bristol Stool Form Scale was added to the Screening Phase subsection: Bristol Stool Form Scale diaries will also be provided to subjects to classify the form (or consistency) of their stools during the induction study (Section 9.2.1). Subjects will be instructed to complete Mayo diary cards and Bristol Stool Form Scale diaries 7 days immediately before each visit and bring them to every visit for data collection and review by the investigator/study coordinator. Bristol Stool Form Scale diaries are required only during the induction study.
9.2.2.3, Exploratory Endpoints	The section was updated to include an exploratory endpoint based on data collected using the Bristol Stool Form Scale (only in the induction study): • Average Bristol Stool Form Scale score over time in induction.
11.3.3, Exploratory Analyses	A sentence about the Bristol Stool Form Scale was added to the Exploratory Analyses section: Analyses of the average Bristol Stool Form Scale score over time in the induction study will be conducted.
References	Two references for the Bristol Stool Form Scale (Dove et al 2013 and Lewis/Heaton 1997) were added to the References and other references were renumbered accordingly.

Rationale: Because an exploratory objective was added for the Bristol Stool Form Scale evaluation in induction, the wording for the header and the existing objective was changed.

Synopsis (Objectives and Hypotheses); 2.1.3, Exploratory Objectives	**(2.1.3) Exploratory Objectives** • To evaluate response using the Mayo score without the physician's global assessment (PGA) subscore in both induction and maintenance. • To evaluate the performance of the Bristol Stool Form Scale score in the induction study.
9.2.2.3, Exploratory Endpoints	**9.2.2.3. Exploratory Endpoints** • Response using the Mayo score without the PGA subscore in both induction and maintenance. • Average Bristol Stool Form Scale score over time in induction.

Rationale: If tuberculin is unavailable for the skin test, this method of testing will be considered not required for Ukrainian study centers. QuantiFERON-TB Gold and chest radiograph must still be done if tuberculosis (TB) is suspected, along with referral to a TB specialist if possible.

Table 1, Time and Events Schedule: Induction, footnote h	h. All subjects will undergo QuantiFERON-TB Gold testing. In countries where the QuantiFERON-TB Gold test is not registered/approved, TB skin testing will also be required (recommended but not required for study centers in Ukraine if tuberculin is not available).
Table 1, Time and Events Schedule: Induction, and Table 3, Time and Events Schedule: Long-Term Extension, footnote m; Table 2, Time and Events Schedule: Maintenance Study, footnote k	The following footnote was revised in each of the three Time and Events Schedules: If TB is suspected at any time, a chest radiograph and QuantiFERON-TB Gold test should be performed. In countries where the QuantiFERON-TB Gold test is not registered/approved, TB skin testing should also be performed (recommended but not required for study centers in Ukraine if tuberculin is not available).

4.1, Inclusion Criteria, 10d	The following sentence was added at the end of Inclusion Criterion 10d: A tuberculin skin test is recommended but not required for study centers in Ukraine if tuberculin is not available.
9.1.2, Screening Phase	The following paragraph was revised: Subjects with a negative QuantiFERON-TB Gold test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with prerandomization procedures. A tuberculin skin test is recommended but not required for study centers in Ukraine if tuberculin is not available. Subjects with a newly identified positive QuantiFERON-TB Gold (or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed, or the subject will be excluded from the study.
9.7 Safety Evaluations, Early Detection of Active Tuberculosis	The last paragraph was revised as follows: Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB Gold test, a repeat tuberculin skin test (Attachment 4) in countries in which the QuantiFERON-TB Gold test is not approved/registered or tuberculin skin testing is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. A tuberculin skin test is recommended but not required for study centers in Ukraine if tuberculin is not available. If the QuantiFERON-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2. Subjects should be encouraged to return for all subsequent scheduled study visits as specified in the Time and Events Schedules.
10.2, Discontinuation of Study Agent	– A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result (and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities [recommended but not required for study centers in Ukraine if tuberculin is not available]), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated before the next administration of study agent and continued to completion. Indeterminate QuantiFERON-TB Gold test results should be handled as described in Section 9.1.2. Subjects with persistently indeterminate QuantiFERON-TB Gold test results may continue without treatment for latent TB, if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.
Attachment 3, QuantiFERON-TB Gold Testing: Adherence to Local Guidelines	A sentence was added to the second (and final) paragraph: In countries in which the QuantiFERON®-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required. In Ukraine, the tuberculin skin test is recommended but not required if tuberculin is not available.

Attachment 4, Tuberculin Skin Testing: Treatment of Latent Tuberculosis	The following sentence was added as the second (and final) paragraph: In Ukraine, the tuberculin skin test is recommended but not required if tuberculin is not available.

Rationale: To be consistent with Table 2 (Time and Events Schedule: Maintenance), in which study agent administrations at Weeks 20 and 28 were removed with Protocol Amendment 1, the corresponding marks for those administrations were deleted from Figure 1.

3.1 (Figure 1)	Study agent administration marks were deleted for Weeks 20 and 28 of the maintenance study.

Rationale: Respiratory rate was added in the appropriate footnotes in each of the Time and Events Schedules and in text to clarify that it is among the vital signs to be collected during the study.

Table 1, footnote n; Table 2, footnote i; Table 3, footnote k	Temperature, pulse/heart rate, respiratory rate, and blood pressure.
9.7, Safety Evaluations	**Vital Signs** Vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained…

Rationale: The order of the third and fourth secondary objectives/major secondary endpoints in the maintenance study has been reversed. In addition, the analysis population for the objective/endpoint of corticosteroid-free remission at Week 44 (now the third secondary objective/major secondary endpoint) has been updated to include all subjects randomized into the maintenance study regardless of corticosteroid use at the M-0 visit (instead of being limited to only subjects who were receiving corticosteroids at the M-0 visit). This analysis will thereby evaluate the overall impact of ustekinumab maintenance therapy on achieving clinical remission while either eliminating or preventing the use of corticosteroids in subjects induced into clinical response with ustekinumab. The previous endpoint of corticosteroid-free remission at Week 44 in subjects induced into clinical response with ustekinumab and receiving corticosteroids at Week 0 of maintenance has been moved to the Other Secondary Endpoints section.

Maintaining clinical remission in subjects induced into clinical remission with ustekinumab (now the fourth secondary objective/major secondary endpoint) has been retained, reflecting its significance as a desired treatment effect. In recognition of this objective/endpoint as a subgroup analysis, however, it has been moved to follow the corticosteroid-free remission objective/endpoint discussed above.

Synopsis (Maintenance Study, Secondary Objectives); 2.1.2.2, Secondary Objectives (Maintenance Study)	**(2.1.2.2) Secondary Objectives** • To evaluate the efficacy of ustekinumab in maintaining clinical response in subjects induced into clinical response with ustekinumab. • To evaluate endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) in subjects induced into clinical response with ustekinumab. • To evaluate the efficacy of ustekinumab in achieving corticosteroid-free clinical remission in subjects induced into clinical response with ustekinumab. • To evaluate the efficacy of ustekinumab in maintaining clinical remission in subjects induced into clinical remission with ustekinumab. … (additional secondary objectives)
Synopsis (Maintenance Endpoints)	The following are the **major secondary endpoints** in the maintenance study, presented in the order in which they will be tested: maintenance of clinical response through Week 44; endoscopic healing at Week 44; clinical remission and not receiving concomitant corticosteroids at Week 44; and maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline.

3.1.2, Maintenance Study

The primary endpoint of the maintenance study is clinical remission at Week 44 among subjects who were responders to IV ustekinumab induction. The major secondary endpoints of the maintenance study are maintenance of clinical response through Week 44; endoscopic healing at Week 44; clinical remission and not receiving concomitant corticosteroids at Week 44; and maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline.

9.2.2.2.2, Major Secondary Endpoints

The following are the major secondary endpoints, which are presented in the order in which they will be tested:

- Maintenance of clinical response through Week 44.
- Endoscopic healing at Week 44.
- Clinical remission and not receiving concomitant corticosteroids at Week 44.
- Maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline.

9.2.2.2.3, Other Secondary Endpoints; 11.3.2.4, Other Planned Analyses

The previous major secondary endpoint of corticosteroid-free remission in subjects induced into clinical response with ustekinumab and receiving corticosteroids at Week 0 of maintenance was moved to the subsection of Other Secondary Endpoints:

… (first 13 other secondary endpoints/10 other planned analyses)

- Clinical remission and not receiving concomitant corticosteroids at Week 44 among the subjects receiving concomitant corticosteroids at maintenance baseline.

11.2.2, Table 7

The order of the third and fourth major secondary endpoints in the power calculations shown in Table 7 was revised. The power to detect a treatment effect for the (new) third major secondary endpoint (corticosteroid-free remission at Week 44) also changed because of the revision of the analysis population for the endpoint to include all subjects randomized into the maintenance study, regardless of corticosteroid use at the M-0 visit:

Table 7: Power for detecting a treatment effect for each of the major secondary endpoints with 327 subjects in the primary population (109 in each treatment group)

Major secondary endpoints	Proportion of subjects achieving the endpoint		Power[a] (%)
	Placebo	Ustekinumab	
Maintenance of clinical response through Week 44	25	50	97
Endoscopic healing at Week 44	25	45	88
Clinical remission and not receiving concomitant corticosteroids at Week 44	15	30	76
Maintenance of clinical remission through Week 44 *among the subjects who had achieved clinical remission at maintenance baseline (both global and US definitions)* [b]	25	50	65

a: Based on testing the SC ustekinumab 90 mg q8w group versus placebo at α=0.05 (2-sided).
b: It is estimated that about 37% of subjects in the primary population (40 subjects per treatment group) will be in clinical remission at Week 0 of maintenance.

Synopsis (Statistical Methods)

Maintenance: Except for the fourth major secondary endpoint of maintenance of clinical remission, analyses of major secondary endpoints will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the IWRS) and induction treatment. For the fourth major secondary endpoint, a 2-sided CMH chi-square test stratified by induction treatment will be used.

11.3.2.3, Major Secondary Endpoint Analyses	Except for the fourth major secondary endpoint of maintenance of clinical remission, analyses of major secondary endpoints will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the IWRS) and induction treatment. For the fourth major secondary endpoint, a 2-sided CMH chi-square test stratified by induction treatment will be used. Note that, for the United States, for the fourth major secondary endpoint of maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline, the US-specific definition of clinical remission should also be used to determine whether or not a subject had achieved clinical remission at maintenance baseline.

Rationale: Text was added to clarify procedures to determine clinical flare and loss of response.

Table 2, Time and Events Schedule: Maintenance, footnote b	b. Subjects in clinical flare who have not previously met the criteria for loss of clinical response (ie, are in clinical flare for the first time or have flared previously and not met the criteria for loss of response) should complete all visit assessments indicated for the M-44 visit (including an endoscopy, which need only be a sigmoidoscopy) during their scheduled visit or at any unscheduled visit. Subjects with subsequent clinical flares after loss of clinical response should complete all assessments indicated for the visit at which the clinical flare occurred.
Table 2, Time and Events Schedule: Maintenance, footnote l	l. A subject who meets the criteria for clinical flare but has not previously met the criteria of loss of clinical response (ie, is in clinical flare for the first time or flared previously and not met the criteria for loss of response) should undergo an additional endoscopy (which need only be a sigmoidoscopy) to determine loss of response based on the Mayo score. An endoscopy is not required if the subject has a subsequent clinical flare after loss of response criteria were met for the previous clinical flare.
3.1.2.1, Management of Clinical Flare and Loss of Response	In paragraph 2, sigmoidoscopy was added as an acceptable type of endoscopy required to establish loss of response: Subjects in clinical flare who have not previously met the criteria for loss of clinical response in the maintenance study (ie, are in clinical flare for the first time or have flared previously and not met the criteria for loss of response) should undergo endoscopy, which need only be a sigmoidoscopy, and be evaluated for loss of clinical response… New text was added as paragraph 6: Subjects will be strongly encouraged to undergo endoscopy at the time of first clinical flare to establish if loss of clinical response criteria were met. A subject who declines to undergo an endoscopy on initial clinical flare will be assessed for partial Mayo response 16 weeks after the initial flare.
9.1.4.1, Management of Clinical Flare and Loss of Response	A sentence was added at the end of paragraph 2: Subjects who meet the criteria for clinical flare and who have not previously met the criteria for loss of clinical response in the maintenance study (ie, are in clinical flare for the first time or have flared previously and not met the criteria for loss of response) should undergo an endoscopy to assess the Mayo endoscopy subscore, as well as the safety and efficacy evaluations specified for the M-44 visit (Table 2) during their scheduled visit or at any unscheduled visit. The endoscopy at the time of clinical flare need only be a sigmoidoscopy. The Mayo score should be calculated from the partial Mayo obtained at the assessment for clinical flare and the subsequent Mayo endoscopy subscore as assigned by the local endoscopist.

	New text was added as the second-to-last paragraph: Subjects will be strongly encouraged to undergo endoscopy at the time of first clinical flare to establish if loss of clinical response criteria were met. A subject who declines to undergo an endoscopy on initial clinical flare will be assessed for partial Mayo response 16 weeks after the initial flare.

Rationale: Beclomethasone dipropionate was added to Inclusion Criterion 6e because this extended-release formulation is approved for the treatment of UC in some regions where this study is being conducted. (Renumbered as 6.e.1.)

4.1, Inclusion Criteria, 6e	e. If receiving budesonide or beclomethasone dipropionate, the dose must have been stable for at least 2 weeks.

Rationale: Specific reference to budesonide as a corticosteroid was deleted from selected Inclusion Criteria and in text because use of the term "corticosteroids" includes prednisone-like corticosteroids as well as corticosteroids that have been developed for targeted delivery to the colon (ie, budesonide and beclomethasone dipropionate) and are approved for the treatment of UC in some regions where this study is being conducted.

4.1, Inclusion Criteria, 6f	f. If oral 5-ASA compounds or oral corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks. (Renumbered as 6.f.1.)
4.1, Inclusion Criteria, 7e	e. Rectal corticosteroids (ie, corticosteroids administered to the rectum or sigmoid colon via foam or enema or suppository) for at least 2 weeks. (Renumbered as 7.e.1.)
8.1.1, Induction Study	• Oral corticosteroids.
8.1.1.1.1, Restricted Medications/Therapies	• Rectal corticosteroids (ie, corticosteroids administered to the rectum or sigmoid colon via foam, enema, or suppository).
8.1.2.3, Corticosteroids	Oral corticosteroids for UC **should not be initiated or have the dose increased** during the maintenance study, unless corticosteroids are used as rescue medication for loss of response (Section 3.1.2.1). For subjects who are receiving oral corticosteroids on entry into the maintenance study, the investigator should begin tapering the daily dose of corticosteroids beginning at Week 0 of the maintenance study.
9.1.4, Maintenance Study	All subjects enrolled in the maintenance study will be responders to study agent administered in the induction study (ie, have received study agent at Week 0 in the induction study and been in clinical response at Week 8, or at Week 16 in subjects who were not responders at Week 8). **Subjects who initiated or increased their dose of UC medications (ie, oral 5-ASAs, oral corticosteroids, or the immunomodulators AZA, 6-MP, or MTX) or initiated a restricted or prohibited medication during the induction study are not eligible to enter maintenance.**

Rationale: The word "full" was added to Inclusion Criteria 8 and 9 to clarify the extent of the colonoscopy that satisfies these criteria. Corresponding changes were made in Table 1 and in Section 9.1.2.

4.1, Inclusion Criteria, 8	8. A subject ≥45 years of age must either have had a full colonoscopy to assess for the presence of adenomatous polyps within 5 years before the first administration of study agent or a full colonoscopy to assess for the presence of adenomatous polyps at the screening visit. The adenomatous polyps must be removed before the first administration of study agent. (Renumbered as 8.1.)
4.1, Inclusion Criteria, 9	9. A subject who has had extensive colitis for ≥8 years, or disease limited to the left side of the colon for ≥10 years, must either have had a full colonoscopy to assess for the presence of dysplasia within 1 year before the first administration of study agent or a full colonoscopy to assess for the presence of malignancy at the screening visit. (Renumbered as 9.1.)

Table 1, Time and Events Schedule: Induction, footnote p	p. The screening endoscopy must be performed within 2 weeks before the I-0 visit. The interval from the endoscopy procedure to the availability of the Mayo endoscopy subscore as assessed by the central reader is approximately 4 days; therefore, the screening endoscopy must be performed at least 4 days before the baseline (I-0) visit. The Mayo endoscopy subscore assessed by the central reader will be used to determine eligibility (ie, Mayo endoscopy subscore ≥2) and to calculate the baseline Mayo score. A full colonoscopy will replace a sigmoidoscopy if screening for polyps or dysplasia is required. At least 48 hours must elapse between a colonoscopy with polypectomy and the I-0 visit.
9.1.2, Screening Phase	**The screening endoscopy must be performed within 2 weeks (and at least 4 days) before the induction Week 0/baseline (I-0) visit.** Subjects who are identified as being at increased risk for colon cancer (Inclusion Criterion 9) or for adenomatous polyps (Inclusion Criterion 8) will undergo a full colonoscopy instead of a sigmoidoscopy to allow screening for dysplasia or to assess for the presence of adenomatous polyps, respectively. Any screening colonoscopy for malignancy should include surveillance biopsies consistent with local practice. At least 48 hours must elapse between a colonoscopy with polypectomy and the I-0 visit.

Rationale: International System of Units (SI) equivalents were added to the specified results for screening laboratory tests in Inclusion Criterion 15 for clarity.

4.1, Inclusion Criteria, 15	15. Has screening laboratory test results within the following parameters: a. Hemoglobin ≥8.0 g/dL (SI: ≥80.0 g/L) b. White blood cell count (WBC) ≥3 × 10^3 cells/µL (SI: ≥3.0 × 10^9 cells/L) c. Neutrophils ≥1.5 × 10^3 cells /µL (SI: ≥1.5 × 10^9 cells/L) d. Platelets ≥100 × 10^3 cells /µL (SI: ≥100 × 10^9 cells/L) e. Serum creatinine ≤1.5 mg/dL (SI: ≤133 µmol/L) f. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations must be within 2 times the upper limit of the normal range (ULN) for the laboratory conducting the test.

Rationale: An additional method of apheresis that has a similar mechanism of action was added to Exclusion Criterion 12e. (Renumbered as 12.e.1.)

4.2, Exclusion Criteria, 12e	e. Apheresis (eg, Adacolumn or Cellsorba apheresis) within 2 weeks before the first administration of study agent.

Rationale: Exclusion Criterion 17 was updated to reflect the availability of highly effective antiviral therapy with HCV clearance (as measured by HCV RNA) leading to patients who remain seropositive but are considered to be clinically cured of their hepatitis C. (Renumbered as 17.1.)

4.2, Exclusion Criteria, 17	17. Are seropositive for antibodies to hepatitis C virus (HCV) without a history of successful treatment, defined as being negative for HCV RNA at least 24 weeks after completing antiviral treatment.

Rationale: Exclusion Criterion 29 was updated to reference the most current (5th) edition of the *Diagnostic and Statistical Manual of Mental Disorders*. (Renumbered as 29.1.)

4.2, Exclusion Criteria, 29	29. Has a history of drug or alcohol abuse according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-V), within 1 year before screening.

Rationale: The recommendation for tapering budesonide has been revised and tapering for beclomethasone dipropionate has been incorporated. These revisions reflect the current approved doses and the absence of general tapering guidelines for these specific corticosteroids.

8.1.2.3, Corticosteroids	Recommended tapering schedule for oral prednisone-equivalent corticosteroids: • Subjects receiving >20 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until 0 mg/day. • Subjects receiving ≤20 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day. Tapering of budesonide or beclomethasone dipropionate should follow local clinical practice.

Rationale: Text was added to clarify unblinding related to the futility analysis and the third database lock during induction.

5, Treatment Allocation and Blinding	In the Blinding subsection, the following text was added to paragraph 6: In the induction study, at the first DBL for the futility analysis, the induction treatment assignment information will be unblinded for the first 30% of randomized subjects in the study and released for analysis to an external statistical support group (the sponsor will remain blinded). The induction treatment assignment for the remaining subjects and the maintenance treatment assignment information for all subjects will remain blinded at that time. Further details about unblinding for the futility analysis will be provided in the Interim Analysis Plan (IAP). At the second DBL when all randomized subjects in the induction study have either completed the I-8 visit or have terminated study participation before Week 8, the induction treatment assignment information will be unblinded for all subjects and released to selected sponsor personnel for analysis. The maintenance treatment assignment information for all subjects will remain blinded at that time. At the third DBL when all randomized subjects in the induction study have entered the maintenance study, or have completed their final safety visit (20 weeks after the last administration of study agent) for those not participating in the maintenance study, or have terminated their study participation, data will be released to selected sponsor personnel for analysis. The maintenance treatment assignment information for all subjects will continue to remain blinded at that time. Identification of sponsor personnel who will have access to the unblinded subject-level data at the time of each DBL will be documented before unblinding.

Rationale: Guidance was added about what to do if a subject's screening procedures cannot be completed within the specified 8-week window.

9.1.2, Screening Phase	Completion of screening and randomization procedures within the specified 8-week window is required. If a subject is approaching the completion of that period, the medical monitor can be contacted to discuss eligibility. If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph, stool analysis), the subject will be considered a screen failure because he/she will not meet eligibility criteria, and the expired assessments (along with the non-time-specific laboratory tests) will have to be repeated on rescreening.

Rationale: Text was revised to explicitly state the visit that represents the first opportunity for dose adjustment in the LTE.

9.1.5.1, Dose Adjustment During the LTE	During the LTE, if a subject's UC disease activity worsens (in the investigator's judgment), the subject may be eligible for a dose adjustment, as described in Section 3.1.3. These subjects will be allowed 1 dose adjustment during the LTE. The IWRS will ensure that a subject is eligible for a dose adjustment and, if he or she is eligible, that SC ustekinumab is not administered more frequently than q8w. The first opportunity for dose adjustment in the LTE is at the Week 56 visit.

Rationale: To clarify which endoscopy score will be used to determine subject eligibility at baseline and for the primary and major secondary endpoints involving the endoscopy subscore.

9.2.1, Evaluations	The Mayo score (Attachment 5) was developed from the criteria of Truelove and Witts[34] for mild, moderate, and severe UC and from the criteria of Baron et al[3] for grading endoscopic appearance. The Mayo score is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, PGA, and endoscopy findings) and ranges from 0 to 12 points. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severe disease. The endoscopic findings will be assessed by the investigator (ie, local endoscopist) during the endoscopy procedure and by the central reader reviewing a video of the endoscopy. Subject eligibility at baseline will be based on the final reported endoscopic subscore as determined by the following process: • If the local endoscopist and the central reader agree on the endoscopic subscore, the agreed score will be the final reported endoscopic subscore. • If there is a discrepancy between the local endoscopist and the central reader subscores, the video endoscopy will be submitted to a second central reader (designated for adjudication). The median score of the 3 completed reads (ie, local read, central read 1, and central read 2 designated for adjudication) will be the final reported endoscopic subscore. Specific details will be provided in the imaging charter. A subject's clinical response status at Week 8 (or Week 16) of the induction study, or loss of response status in the maintenance study, to determine subsequent treatment, will be based on the endoscopy subscore assigned by the local endoscopist.
9.2.2, Endpoints	The second paragraph was revised to cross-reference the new text in Section 9.2.1 described above: For the primary and major secondary endpoints involving the endoscopy subscore of the Mayo score (eg, clinical remission, clinical response, endoscopic healing), the final reported endoscopic subscore will be used, as described in Section 9.2.1.

Rationale: The Statistical Methods section was revised to specify that a fixed-sequence testing procedure will be used for the United States.

Synopsis (Statistical Methods: Primary Efficacy Analysis)	Maintenance: The primary analysis is based on the primary population (ie, subjects who are in clinical response to IV ustekinumab induction). The primary endpoint is clinical remission at Week 44. The definition of clinical remission is different for countries outside of the United States and the United States. For both definitions of clinical remission, the comparisons between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the interactive web response system [IWRS]) and induction treatment. For countries outside the United States, a fixed-sequence testing procedure (ustekinumab 90 mg SC q8w will first be tested; if positive, then ustekinumab 90 mg SC q12w will be tested) will be used to control the overall Type I error rate at the 0.05 level for the primary endpoint. For the United States, a fixed-sequence testing procedure will be employed to strongly control the overall Type 1 error rate at the 0.05 level across the primary and all 4 major secondary endpoints and across the 2 ustekinumab doses, starting with the high maintenance dose group of the primary endpoint.

11.2.2, Maintenance Study	The second paragraph was revised: A fixed-sequence testing procedure, starting with the high dose group (q8w), will be used to control the overall Type I error rate at the 0.05 level (2-sided). As such, sample size/power calculations were based on the chi-square test to detect a significant difference between subjects receiving SC ustekinumab 90 mg q8w and those receiving placebo.
11.3.2.2, Primary Analysis	Text was added to the subsection for countries outside the United States: A fixed-sequence testing procedure will be used to control the overall Type I error rate at the 0.05 level for the primary endpoint. Specifically, the high maintenance dose group (ustekinumab 90 mg SC q8w) will first be compared with the placebo maintenance dose group at the 2-sided 0.05 level of significance. Only if this test is positive will the low maintenance dose group (ustekinumab 90 mg SC q12w) be compared with the placebo maintenance dose group at the 2-sided 0.05 level of significance. The study will be considered positive if the test involving the high maintenance dose group (ustekinumab 90 mg SC q8w) is positive, regardless of the result of the test for the low maintenance dose group (ustekinumab 90 mg SC q12w). Text was added to the subsection for the United States and the paragraph about Type I error control was deleted: A fixed-sequence testing procedure will be employed for the United States to strongly control the overall Type 1 error rate at the 0.05 level across the primary and all 4 major secondary endpoints and across the 2 ustekinumab doses, starting with the high maintenance dose group (ustekinumab 90 mg SC q8w) of the primary endpoint. The exact testing procedure will be detailed in the SAP before the Week 44 DBL in the maintenance study. The study will be considered positive if the test involving the high maintenance dose group is positive.
11.3.4.2, Maintenance Study	The last phrase of the first paragraph was deleted: The maintenance study will be considered positive if the test involving the high maintenance dose group (ustekinumab 90 mg SC q8w) shows a statistically significant difference versus placebo for the maintenance primary endpoint, clinical remission at Week 44 (global definition for the countries outside the United States and US-specific definition for the United States).

Rationale: In Attachment 1, "approved biosimilars" were added as TNF antagonist therapies to which definitions of inadequate initial response, loss of response, or intolerance can be applied to identify a subject as a biologic failure. Similar changes were made where applicable in the body of the protocol.

Attachment 1	Title changed: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNF Antagonist Therapies (Infliximab, Adalimumab, Golimumab, or Approved Biosimilars for Infliximab or Adalimumab) or Vedolizumab Item I was revised as follows; similar changes were made in Items II and III: I. Inadequate initial response to at least 8 weeks of therapy with infliximab, adalimumab, or golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab (primary nonresponse) Eligible subjects must satisfy criteria A, B, and C. A. Have received induction doses of: • REMICADE (infliximab; 3 intravenous [IV] doses ≥5 mg/kg) at Weeks 0, 2, and 6 (or approved biosimilar for infliximab) OR

	• Humira (adalimumab; subcutaneous [SC] doses of 160 mg at Week 0 and ≥80 mg at Week 2 followed by a dose ≥40 mg every 2 weeks) or approved biosimilar for adalimumab … B. Did not initially respond to these induction doses of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab, as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of ulcerative colitis (UC), as assessed by a treating physician: … These signs and symptoms of UC must have occurred ≥2 weeks after receiving the last induction dose of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab and are offered only as a benchmark of the minimally acceptable criteria required to designate a subject as having had an inadequate initial response to infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab. … C. Have documentation available to the investigator that meets the following 2 requirements: • Provides the dates and doses of the failed infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab induction therapy. • Documents that the subject had persistence of disease activity following infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab induction therapy.
4.1, Inclusion Criteria, 7b	7. The following medications/therapies must have been discontinued before first administration of study agent: b. TNF-antagonist therapy (eg, infliximab, etanercept, certolizumab, adalimumab, golimumab [or approved biosimilars for these therapies]) for at least 8 weeks. (Renumbered as 7.b.1.)

Rationale: In Attachment 2, the corticosteroid text has been updated to include approved extended-release corticosteroids such as budesonide and beclomethasone dipropionate for the treatment of UC, and to clarify the definition of corticosteroid dependence.

Attachment 2, Definition of Inadequate Response to or Intolerance of Corticosteroids or AZA/6-MP and Corticosteroid Dependence	Text under the Corticosteroids subhead was revised as follows: **Subjects have failed to respond to corticosteroids if** they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving at least 0.75 mg/kg/day or ≥40 mg/day of prednisone (or corticosteroid equivalent, given orally or intravenously) for 2 weeks; or ≥9 mg/day of budesonide or ≥5 mg/day of beclomethasone dipropionate given orally for at least 4 weeks. **Subjects are intolerant of corticosteroids if**: • They have developed clinically significant adverse events (eg, osteonecrosis or osteoporosis, psychosis, uncontrolled diabetes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of corticosteroids to treat ulcerative colitis (UC). **OR** • They have a medical condition that precludes the use of corticosteroids as a treatment for UC. **Subjects are corticosteroid dependent if** they have failed to successfully taper their corticosteroid (ie, had a flare of disease) within 3 months of starting therapy, or if a relapse occurs within 3 months after stopping corticosteroids or if they are unable to discontinue these agents without flare within 3 months after starting them.

Rationale: Attachment 6, Anticipated Events, was added and text in Section 12.1.1, Adverse Event Definitions, and Section 12.3.1 was revised to comply with current protocol template requirements.	
12.1.1, Adverse Event Definitions (Adverse Events Associated with the Study Population)	**Adverse Events Associated with the Study Population** Anticipated events are events that are considered common for the study population defined in this protocol and, when determined to be serious, should be reported by the investigator as described in Section 12.3.2. Anticipated events will be recorded and reported as described in Attachment 6.
12.3.1, All Adverse Events	The following sentence was added as the second paragraph: Anticipated events will be recorded and reported as described in Attachment 6.
Attachment 6	Added to protocol; includes a revised list of events deleted from Section 12.1.1.
Rationale: The estimated patient-years of exposure for ustekinumab was updated.	
1.1, Background	Paragraph 3: Considerable data available from other completed or ongoing clinical studies of ustekinumab in additional indications (including Crohn's disease, multiple sclerosis, primary biliary cirrhosis, sarcoidosis, and rheumatoid arthritis), together with extensive postmarketing data based on an estimated 551,966 person-years of exposure through 31 December 2015, also support the safety profile of ustekinumab.
1.2, Overall Rationale for the Study	Paragraph 6, last sentence: Finally, ustekinumab provides a novel mechanism of action in the treatment of UC, with a documented long-term safety profile in excess of 5 years of clinical data, which is complemented by postmarketing data representing 551,966 person-years of exposure.
Rationale: Minor errors were noted and corrected.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (14 July 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To address health authority feedback and provide additional clarifications.

Applicable Section(s)	Description of Change(s)
Rationale: At the request of a health authority, a sample collection for antibodies to ustekinumab has been moved during induction and another sample collection has been added during maintenance.	
Table 1, Time and Events Schedule: Induction Study	The sample collection for antibodies to ustekinumab was moved from the Week 2 visit to the Week 4 visit in induction.
Table 2, Time and Events Schedule: Maintenance Study	A sample collection for antibodies to ustekinumab was added at the Week 4 visit in maintenance.
Rationale: Study agent administrations at Week 20 and Week 28 have been deleted from the Time and Events Schedule for Maintenance because both administrations, for placebo only, are not required to maintain the study blind for either maintenance dose regimen.	
Table 2, Time and Events Schedule: Maintenance Study	In the Study agent administration row of the schedule, notations were deleted at Week 20 and Week 28.
Synopsis; 3.1.2, Maintenance Study; 5, Treatment Allocation and Blinding; 9.1.4, Maintenance Study	Because the Week 20 and 28 administrations were deleted, text indicating that study agent would be administered every 4 weeks in maintenance was revised throughout the protocol as follows: All subjects will receive their assigned dose of SC study agent at maintenance Week 0. Thereafter, to maintain the blind, all subjects will receive study agent at all scheduled study agent administration visits specified in the Time and Events Schedule for maintenance.
Rationale: The first dose of study agent in the long-term extension (LTE) will be at Week 48, not Week 44; therefore, the Week 44 column has been deleted from the Time and Events Schedule for the LTE. Language was added to an existing footnote to clarify the timing of the first LTE dose and note that study agent will not be administered at Week 52, because only placebo would be given at that visit and therefore is not required to maintain the blind.	
Table 3, Time and Events Schedule: Long-Term Extension	The Week 44 column was deleted, along with footnote c, which was only applicable if study agent was administered at Week 44. Footnote c (previously footnote d) was revised as follows: c. The first study agent administration in the LTE will occur at Week 48; no study agent will be administered at Week 52. After the study is unblinded to the investigative sites, subjects receiving placebo will be terminated from study participation and subjects receiving ustekinumab will continue to receive ustekinumab, but will have study visits scheduled to coincide with their dose regimen (ie, either every 8 or every 12 weeks).
Table 2, Time and Events Schedule: Maintenance Study	Footnote h was deleted because it referenced study agent administration at Week 44 of the LTE.

Applicable Section(s)	Description of Change(s)
3.1.3, Long-Term Extension, 2nd paragraph; 9.1.5, Long-Term Extension, 1st paragraph	Text in the body of the protocol was edited to indicate that the first dose of study agent in the LTE will occur at Week 48, not Week 44.
Rationale: A notation was added in the Time and Events Schedule for the LTE to clarify the timing of the last potential dose of study agent during the LTE.	
Table 3, Time and Events Schedule: Long-Term Extension	A study agent administration was added at Week 200 (ie, final efficacy visit) on the Time and Events Schedule for the LTE for the last dose of study agent.
Rationale: Text was added to clarify the first visit at which a subject is eligible for dose adjustment in the LTE.	
3.1.3, Long-Term Extension, 4th paragraph; 9.1.5.1, Dose Adjustment During the LTE	Text was added to indicate that Week 56 is the first visit at which a subject is eligible for dose adjustment in the LTE. The first visit at which a subject can be considered for a dose adjustment is at Week 56. Subjects will be allowed 1 dose adjustment during the LTE. During the LTE, if a subject's UC disease activity worsens (in the investigator's judgment), the subject may be eligible for a dose adjustment, beginning at Week 56, as described in Section 3.1.3.
Rationale: The Common Terminology Criteria for Adverse Events (CTCAE) defines a grade 1 AE for "white blood cell decreased" (ie, below the lower limit of normal) as $<3 \times 10^9$/L (or 3.0×10^3/µL); therefore, for inclusion in the study, the permissible lower limit for a subject's white blood cell count has been increased to at least 3×10^3/µL.	
4.1, Inclusion Criteria, 15b	15. Has screening laboratory test results within the following parameters: b. White blood cell count (WBC) $\geq 3 \times 10^3$/µL
Rationale: To clarify that eligible subjects should have a serum creatinine level that is not higher than 1.5 mg/dL.	
4.1, Inclusion Criteria, 15e	15. Has screening laboratory test results within the following parameters: e. Serum creatinine ≤1.5 mg/dL
Rationale: Additional information about the Mayo score has been incorporated, including a Mayo Score attachment. Reference to the modified Mayo score was removed; it will be described in the SAP.	
9.2.1, Evaluations	The **Mayo score** (Attachment 5) was developed from the criteria of Truelove and Witts[34] for mild, moderate, and severe UC and from the criteria of Baron et al[3] for grading endoscopic appearance. The Mayo score is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, PGA, and endoscopy findings) and ranges from 0 to 12 points. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severe disease. The endoscopic findings will be assessed by the investigator (ie, local endoscopist) during the endoscopy procedure and by the central reader reviewing a video of the endoscopy. Subject eligibility at baseline will be based on the endoscopy subscores assigned by the central reader. Specific details will be provided in the imaging charter. A subject's clinical response status at Week 8 (or Week 16) of the induction study, or loss of response status in the maintenance study, to determine subsequent treatment, will be based on the endoscopy subscore assigned by the local endoscopist.

Applicable Section(s)	Description of Change(s)
Rationale: Text was added to clarify that the global definition of clinical remission will also be used to stratify subjects randomized into the maintenance study.	
9.2.2, Endpoints	A sentence was added to the global definition of clinical remission: • The following **global definition of clinical remission** will be used for countries outside the United States: a Mayo score ≤2 points, with no individual subscore >1. This definition will also be used to stratify subjects by clinical remission status at maintenance baseline for the maintenance study.
Rationale: A discontinuation criterion has been revised to include an absolute minimum value for blood pressure so that the subjects meeting symptomatic hypotension applying either of the 2 criteria (ie, based on a change in systolic blood pressure or a minimum blood pressure) are not permitted to receive additional study drug.	
9.7, Safety Evaluations: Allergic Reactions; 10.2, Discontinuation of Study Agent	Subjects who experience reactions after an injection or infusion that result in bronchospasm with wheezing and/or dyspnea that requires ventilatory support **OR** that result in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg will not be permitted to receive additional study agent. • A serious adverse reaction related to an injection or an infusion, including an injection site or infusion reaction, resulting in bronchospasm with wheezing and/or dyspnea that requires ventilatory support **OR** that results in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg.
Rationale: As recommended by a Health Authority, the Cochran-Mantel-Haenszel test (rather than the logistic regression model) will be used for the primary and major secondary efficacy analyses for both the induction and maintenance studies.	
11.3.1.2, Statistical Methods: Induction: Primary Analysis	The third and sixth paragraphs have been revised as follows: The comparison between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided Cochran-Mantel-Haenszel (CMH) chi-square test stratified by biologic failure status (yes or no) and region (Eastern Europe, Asia, or rest of world). The Bonferroni method will be used to control the overall Type I error rate at the 0.05 level (2 sided) for comparisons of the 2 ustekinumab induction treatment groups with placebo, with each comparison being tested at the 0.025 level (2-sided). The comparison between each ustekinumab treatment group and the placebo group will be based on a 2-sided CMH chi-square test stratified by biologic failure status and region at the 0.025 level of significance.
Synopsis, Primary Efficacy Analysis: Induction	The corresponding section of the Synopsis has been revised as follows: <u>Induction</u>: The primary analysis is based on all randomized subjects. The primary endpoint is clinical remission at Week 8. The definition of clinical remission (as well as the testing procedure) will be different for countries outside of the United States and for the United States. For the <u>global definition</u> of clinical remission, a step-up Hochberg testing procedure will be employed to control the Type 1 error. For the <u>US-specific definition</u>, the Bonferroni method will be used to control the overall Type I error rate at the 0.05 level (2-sided) for comparisons of the 2 ustekinumab induction treatment groups with placebo, with each comparison being tested at the 0.025 level (2-sided). For both definitions of clinical remission, the comparisons between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided Cochran-Mantel-Haenszel (CMH) chi-square test stratified by biologic failure status and region.

Applicable Section(s)	Description of Change(s)
11.3.1.3, Statistical Methods: Induction: Major Secondary Endpoint Analyses	The first paragraph has been revised as follows: The major secondary endpoint analyses in the induction study will be based on all randomized subjects. The major secondary endpoints of endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) at Week 8 and clinical response at Week 8 will be compared between each ustekinumab treatment group and the placebo group using a 2-sided CMH chi-square test stratified by biologic failure status and region. For the major secondary endpoint of change from induction baseline in the IBDQ score at Week 8, the treatment groups will be compared using ANCOVA on the van der Waerden normal scores with induction baseline IBDQ score, biologic failure status, region, and treatment group as covariates.
Synopsis, Major Secondary Efficacy Analyses: Induction	The corresponding section of the Synopsis has been revised as follows: Induction: For the major secondary endpoints of endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) at Week 8 and clinical response at Week 8, the treatment groups will be compared using a 2-sided CMH chi-square test stratified by biologic failure status and region. For the major secondary endpoint of change from induction baseline in the IBDQ score at Week 8, the treatment groups will be compared using analysis of covariance (ANCOVA) on the van der Waerden normal scores with induction baseline IBDQ score, biologic failure status, region, and treatment group as covariates.
11.3.2.2, Statistical Methods: Maintenance: Primary Analysis	The third and fifth paragraphs have been revised as follows: The comparisons between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (yes/no as determined by the IWRS) and induction treatment (placebo IV [I-0] → ustekinumab ~6 mg/kg IV [I-8], ustekinumab 130 mg IV [I-0], or ustekinumab ~6 mg/kg IV [I-0]). The comparison between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status (as determined by the IWRS) at maintenance baseline and induction treatment.
Synopsis, Primary Efficacy Analysis: Maintenance	The corresponding section of the Synopsis has been revised as follows: Maintenance: The primary analysis is based on the primary population (ie, subjects who are in clinical response to IV ustekinumab induction). The primary endpoint is clinical remission at Week 44. The definition of clinical remission is different for countries outside of the United States and for the United States. For both definitions of clinical remission, the comparisons between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the interactive web response system [IWRS]) and induction treatment. A fixed-sequence testing procedure (ustekinumab 90 mg SC q8w will first be tested; if positive, then ustekinumab 90 mg SC q12w will be tested) will be used to control the overall Type I error rate at the 0.05 level for the primary endpoint.
11.3.2.3, Statistical Methods: Maintenance: Major Secondary Endpoint Analyses	The first 3 paragraphs have been revised into 2 paragraphs, as follows: The major secondary endpoint analyses will be based on the primary population. Except for the third major secondary endpoint of maintenance of clinical remission, analyses of major secondary endpoints will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the IWRS) and induction treatment. For the third major secondary endpoint, a 2-sided CMH chi-square test stratified by induction treatment will be used. Note that, for the United States, for the third major secondary endpoint of maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline, the US-specific definition of clinical remission should also be used to determine whether or not a subject had achieved clinical

Applicable Section(s)	Description of Change(s)
	remission at maintenance baseline.
Synopsis, Major Secondary Efficacy Analyses: Maintenance	The corresponding section of the Synopsis has been revised as follows: Maintenance: Except for the third major secondary endpoint of maintenance of clinical remission, analyses of major secondary endpoints will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the IWRS) and induction treatment. For the third major secondary endpoint, a 2-sided CMH chi-square test stratified by induction treatment will be used.
Rationale: Details were clarified about the futility analysis and the roles of the DMC and the sponsor.	
3.1, Overview of Study Design;	An independent Data Monitoring Committee (DMC) will assess the safety of subjects participating in the induction and maintenance studies, participate in the futility interim analysis (Section 11.11.1), and make recommendations to the sponsor about continuation of the studies. Refer to Section 11.12 for details.
3.1.1, Induction Study;	An interim analysis to assess for futility is planned when the first 30% of subjects either complete the induction Week 8 (I-8) visit or terminate study participation before Week 8. This analysis will be based on clinical remission at Week 8. The whole study may be stopped for futility when the conditional power (ie, the probability of success at the end of the study, given the data at the interim analysis) on **both** ustekinumab doses is less than a prespecified cutoff. Refer to Section 11.11 for details.
5, Treatment Allocation and Blinding;	In the induction study, at the first DBL for the futility analysis, the induction treatment assignment information will be unblinded for the first 30% of randomized subjects in the study and released for analysis to an external statistical support group (the sponsor will remain blinded).
11.11.1 Interim Analysis: Induction Study;	A futility analysis based on the primary endpoint of clinical remission (global definition) at Week 8 will be conducted when 30% of randomized subjects have either completed the I-8 visit or have terminated study participation before Week 8. The whole study may be stopped for futility when the conditional power (ie, the probability of success at the end of the study, given the data at the interim analysis) on **both** ustekinumab doses is less than a prespecified cutoff. The DMC will review the interim analysis results and form a recommendation on whether or not to stop the trial for futility. The sponsor decision committee will then review the DMC's recommendation and make a final decision.
11.12, Data Monitoring Committee	A DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this protocol. The committee will meet periodically to review safety data. After the review, the DMC will make recommendations regarding the continuation of the study. The same DMC will also review the interim analysis results from the induction study and form a recommendation to the sponsor on whether or not to stop the trial for futility. Details will be provided in a separate DMC charter.
Rationale: The definition of failure to respond to corticosteroids was clarified in Attachment 2.	
Attachment 2	**Subjects have failed to respond to corticosteroids if** they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving at least 0.75 mg/kg/day or ≥40 mg/day of prednisone (or corticosteroid equivalent, given orally or intravenously) for 2 weeks.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Protocol Number: **CNTO1275UCO3001**

EudraCT Number: **2014-005606-38**

Ustekinumab (STELARA®) is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human interleukin (IL)-12/23p40 that binds with high affinity to human IL-12 and IL-23. Ustekinumab prevents IL-12 and IL-23 bioactivity by preventing their interaction with their cell surface IL-12Rβ1 receptor protein. Through this mechanism of action, ustekinumab effectively neutralizes IL-12 (Th1)- and IL-23 (Th17)-mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases, including inflammatory bowel disease (IBD). Therefore, binding and inhibiting the IL-12/23p40 subunit may provide effective therapy in IBD, including Crohn's disease and ulcerative colitis (UC).

Ustekinumab has received marketing approval globally, including countries in North America, Europe, South America, and the Asia-Pacific region, for the treatment of adult patients with chronic moderate to severe plaque psoriasis or active psoriatic arthritis. Ustekinumab is currently being evaluated in a Phase 3 development program for Crohn's disease.

Data from completed Phase 2 studies of ustekinumab in Crohn's disease, along with the shared biology and the similar response to current treatments between Crohn's disease and UC, provide a substantial scientific and clinical rationale to justify a direct-to-Phase-3 approach to the study of ustekinumab in UC. Relative to approved therapies for UC (ie, tumor necrosis factor antagonists and the anti-α4β7 integrin antagonist, vedolizumab), ustekinumab offers the potential for a more convenient treatment regimen, with subcutaneous (SC) administration every 8 to 12 weeks during maintenance, as well as a novel mechanism of action in the treatment of UC, and a documented long-term safety profile.

The Phase 3 development program for ustekinumab in the treatment of UC will be conducted under a single protocol but will be designed and analyzed as 2 separate studies, an induction study and a maintenance study.

OBJECTIVES AND HYPOTHESES

INDUCTION STUDY

Primary Objectives

- To evaluate the efficacy of intravenous (IV) ustekinumab in inducing clinical remission in subjects with moderately to severely active UC.
- To evaluate the safety of IV ustekinumab in subjects with moderately to severely active UC.

Secondary Objectives

- To evaluate the efficacy of IV ustekinumab in inducing endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) in subjects with moderately to severely active UC.
- To evaluate the efficacy of IV ustekinumab in inducing clinical response in subjects with moderately to severely active UC.
- To evaluate the impact of IV ustekinumab on disease-specific health-related quality of life.

- To evaluate the efficacy of ustekinumab treatment on mucosal healing (ie, endoscopic healing and histologic healing).
- To evaluate the efficacy of induction therapy with IV ustekinumab by biologic failure status.
- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of ustekinumab induction therapy in subjects with moderately to severely active UC, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other PD biomarkers.

MAINTENANCE STUDY

Primary Objectives

- To evaluate clinical remission for SC maintenance regimens of ustekinumab in subjects with moderately to severely active UC induced into clinical response with ustekinumab.
- To evaluate the safety of SC maintenance regimens of ustekinumab in subjects with moderately to severely active UC induced into clinical response with ustekinumab.

Secondary Objectives

- To evaluate the efficacy of ustekinumab in maintaining clinical response in subjects induced into clinical response with ustekinumab.
- To evaluate endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) in subjects induced into clinical response with ustekinumab.
- To evaluate the efficacy of ustekinumab in achieving corticosteroid-free clinical remission in subjects induced into clinical response with ustekinumab.
- To evaluate the efficacy of ustekinumab in maintaining clinical remission in subjects induced into clinical remission with ustekinumab.
- To evaluate the efficacy of ustekinumab treatment on mucosal healing (ie, endoscopic healing and histologic healing).
- To evaluate the impact of SC ustekinumab on disease-specific health-related quality of life.
- To evaluate the efficacy of maintenance therapy with SC ustekinumab by biologic failure status.
- To evaluate the PK, immunogenicity, and PD of ustekinumab maintenance therapy, including changes in CRP, fecal calprotectin, fecal lactoferrin, and other PD biomarkers in subjects induced into clinical response with ustekinumab.

Exploratory Objectives

- To evaluate response using the Mayo score without the physician's global assessment (PGA) subscore in both induction and maintenance.
- To evaluate the performance of the Bristol Stool Form Scale score in the induction study.

Hypotheses

Induction Study: Ustekinumab is superior to placebo in inducing clinical remission at Week 8 in subjects with moderately to severely active UC.

Maintenance Study: Ustekinumab maintenance therapy is superior to placebo in achieving clinical remission at Week 44 of maintenance in subjects with moderately to severely active UC who were induced into clinical response with ustekinumab.

OVERVIEW OF STUDY DESIGN

The Phase 3 development program for ustekinumab in the treatment of UC will be conducted under a single protocol but will be designed and analyzed as 2 separate studies, an induction study and a maintenance study. Both will be Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies of ustekinumab in subjects with moderately to severely active UC. The induction study will target subjects with moderately to severely active UC who demonstrate an inadequate response or failure to tolerate conventional or biologic therapy. The maintenance study will be a randomized withdrawal study targeting subjects with moderately to severely active UC who demonstrate a clinical response to induction treatment with IV ustekinumab.

Overall, the program will evaluate ustekinumab treatment in subjects with moderately to severely active UC through at least 1 year of induction and maintenance therapy. After completion of the maintenance study through Week 44, a long-term extension (LTE) will follow eligible subjects for an additional 3 years.

Throughout the induction and maintenance studies, efficacy, PK, biomarkers, and safety will be assessed at timepoints indicated in the appropriate Time and Events Schedules.

Blood samples for pharmacogenomic analyses will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

An interim analysis to assess for futility is planned when the first 30% of subjects randomized in the induction study either complete the induction Week 8 visit or terminate study participation before Week 8.

An independent Data Monitoring Committee will be commissioned for this study.

The end of the CNTO1275UCO3001 study is defined as the date on which the last subject completes the last visit in the LTE.

SUBJECT POPULATION

The target population is men or women 18 years of age or older with moderately to severely active UC, as defined by a Mayo score of 6 to 12, inclusive, at Week 0 of the induction study, including an endoscopy subscore ≥2 as assigned by the central reader. Subjects must not be at imminent risk of colectomy. The broad subject population to be evaluated will include subjects who have had an inadequate response to or are intolerant of either conventional or biologic therapy.

DOSAGE AND ADMINISTRATION

Induction: A target of 951 subjects will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups and will receive their assigned IV dose of study agent at Week 0:

- Placebo IV
- Ustekinumab 130 mg IV
- Weight-range-based ustekinumab doses approximating ustekinumab 6 mg/kg IV (ie, ustekinumab ~6 mg/kg IV):
  - Ustekinumab 260 mg (weight ≤55 kg)
  - Ustekinumab 390 mg (weight >55 kg but ≤85 kg)
  - Ustekinumab 520 mg (weight >85 kg)

At Week 8, all subjects will be evaluated for the primary endpoint of clinical remission, and for clinical response. Further study agent administration will be determined by clinical response status (using the Mayo endoscopy subscore assigned by the local endoscopist) at Week 8, as follows:

- Subjects who are in clinical response at Week 8 are eligible to enter the maintenance study.
- Subjects who are not in clinical response at Week 8 will receive ustekinumab as follows:
  - Subjects who were randomized to placebo at Week 0 will receive 1 dose of ustekinumab ~6 mg/kg IV plus placebo SC (to maintain the blind) at Week 8.
  - Subjects who were randomized to ustekinumab at Week 0 will receive 1 dose of ustekinumab 90 mg SC plus placebo IV (to maintain the blind) at Week 8.

At Week 16, the subjects who were not in clinical response at Week 8 will be re-evaluated for clinical response (clinical response status will be based on the Mayo endoscopy subscore assigned by the local endoscopist):

  - Subjects who achieve clinical response at Week 16 are eligible to enter the maintenance study.
  - Subjects who do not achieve clinical response at Week 16 will not enter the maintenance study and will have a safety follow-up visit approximately 20 weeks after their last (ie, Week 8) administration of study agent.

Maintenance: A target of 327 subjects who are in clinical response to IV ustekinumab induction will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups and will receive their assigned SC dose of study agent at maintenance Week 0:

- Placebo SC
- Ustekinumab 90 mg SC every 12 weeks (q12w)
- Ustekinumab 90 mg SC every 8 weeks (q8w)

Subjects who were in clinical response to IV ustekinumab during induction will comprise the primary population in the maintenance study:

- Subjects who were randomized to receive ustekinumab at Week 0 of the induction study and were in clinical response at induction Week 8.
- Subjects who were randomized to receive placebo at Week 0 of the induction study and were not in clinical response at induction Week 8, but were in clinical response at induction Week 16 after receiving a dose of IV ustekinumab at induction Week 8.

Additional subjects entering the maintenance study will include the following; these subjects will not be part of the primary population:

- Subjects who are in clinical response to placebo IV induction will receive placebo SC.
- Subjects who were delayed responders to ustekinumab induction (ie, were not in clinical response at induction Week 8 but were in clinical response at induction Week 16) will receive ustekinumab 90 mg SC q8w.

All subjects will receive their assigned dose of SC study agent at maintenance Week 0. Thereafter, to maintain the blind, all subjects will receive study agent at all scheduled study agent administration visits specified in the Time and Events Schedule for maintenance. Subjects will be assessed for clinical flare at every visit.

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy evaluations will include the following:

- Mayo score and partial Mayo score
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS)
- C-reactive protein
- Fecal lactoferrin and fecal calprotectin
- Bristol Stool Form Scale
- Inflammatory Bowel Disease Questionnaire (IBDQ)
- 36-item Short Form Health Survey (SF-36)
- EuroQoL-5D Health Questionnaire (EQ-5D)

Induction Endpoints

The **primary endpoint** of the induction study is clinical remission at Week 8.

The following are the **major secondary endpoint**s in the induction study, presented in the order in which they will be tested: endoscopic healing at Week 8; clinical response at Week 8; the change from induction baseline in the total score of the IBDQ at Week 8.

Maintenance Endpoints

The **primary endpoint** of the maintenance study is clinical remission at Week 44.

The following are the **major secondary endpoints** in the maintenance study, presented in the order in which they will be tested: maintenance of clinical response through Week 44; endoscopic healing at Week 44; clinical remission and not receiving concomitant corticosteroids at Week 44; and maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Blood samples will be used to evaluate the PK and immunogenicity of ustekinumab (antibodies to ustekinumab) and will be collected from each subject at the timepoints indicated in the Time and Events Schedules.

BIOMARKER EVALUATIONS

Biomarker assessments will be performed to identify protein, RNA (mRNA or microRNA) expression patterns, and microbial activities that are relevant to ustekinumab treatment and/or UC, to conduct histologic and immunohistochemical assessment of disease and healing, and to evaluate if biomarkers can be used to predict clinical response. Biomarker assessments will include the evaluation of relevant markers in serum and feces for all subjects as specified in the Time and Events Schedules.

PHARMACOGENOMIC (DNA) EVALUATIONS

Whole blood samples of approximately 10 mL will be collected (where local regulations permit) for genetic and epigenetic analyses as specified in the Time and Events Schedules. Only subjects who sign the consent form to participate in the genetic assessment will have whole blood DNA samples collected. Subject participation in the pharmacogenomic research is optional.

SAFETY EVALUATIONS

Safety evaluations will include adverse events; clinical laboratory tests (chemistry and hematology); vital signs and physical examinations; a screening electrocardiogram; allergic reactions, infusion reactions and injection site reactions; and early detection of active tuberculosis.

STATISTICAL METHODS

Clinical remission is the primary endpoint in both the induction and maintenance studies, and is also used to define some of the major secondary endpoints in the maintenance study. Two separate definitions for clinical remission will be used to accommodate the global and US-preferred definitions of clinical remission.

- The following **global definition** of clinical remission will be used for countries outside the United States: a Mayo score ≤2 points, with no individual subscore >1.
- The following **US-specific definition** of clinical remission will be used for the United States: an absolute stool number ≤3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.

Each definition of clinical remission will be applied to all subjects in the analysis population.

Sample Size

Induction: The sample size in the induction study is based on statistical power considerations (for both the global and US-specific definitions of clinical remission) and the objective of providing the primary population for the maintenance study (ie, subjects in clinical response to IV ustekinumab in induction). To control the overall Type I error at the 0.05 significance level, a step-up Hochberg testing procedure will be employed for countries outside of the United States (globally) and the Bonferroni method will be used for the United States. Assuming a 7% clinical remission (global definition) rate in the placebo group and 19% in each ustekinumab group, 135 subjects per treatment group (405 subjects in total) will provide an overall power of 90% using a step-up Hochberg testing procedure at the α=0.05 (2-sided) level. Assuming a 12% clinical remission (US-specific definition) rate in the placebo group and 25% in each ustekinumab group, 220 subjects per treatment group (660 subjects in total) will provide statistical power of 90% for comparison of each ustekinumab induction treatment group versus placebo at a significance level of 0.025 (2-sided). To provide a sufficient number of subjects for the primary population in the maintenance study, however, it is estimated that a target of 951 subjects (317 subjects per treatment group) should be enrolled in the induction study.

Maintenance: Assuming a 20% clinical remission rate (for both the global and US definitions) in the placebo group and 40% in the SC ustekinumab 90 mg q8w group, 109 subjects in each randomized treatment group (327 subjects in total) will provide statistical power of 90% at a significance level of 0.05 (2-sided) based on the fixed-sequence testing procedure, starting with the high dose group (q8w).

Primary Efficacy Analysis

Induction: The primary analysis is based on all randomized subjects. The primary endpoint is clinical remission at Week 8. The definition of clinical remission (as well as the testing procedure) will be different for countries outside the United States and for the United States. For the global definition of clinical remission, a step-up Hochberg testing procedure will be employed to control the Type 1 error. For the US-specific definition, the Bonferroni method will be used to control the overall Type I error rate at the 0.05 level (2-sided) for comparisons of the 2 ustekinumab induction treatment groups with placebo, with each comparison being tested at the 0.025 level (2-sided). For both definitions of clinical remission, the comparisons between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided Cochran-Mantel-Haenszel (CMH) chi-square test stratified by biologic failure status and region.

Maintenance: The primary analysis is based on the primary population (ie, subjects who are in clinical response to IV ustekinumab induction). The primary endpoint is clinical remission at Week 44. The definition of clinical remission is different for countries outside of the United States and for the United States. For both definitions of clinical remission, the comparisons between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the interactive web response system [IWRS]) and induction treatment. For countries outside the United States, a fixed-sequence testing procedure (ustekinumab 90 mg SC q8w will first be tested; if positive, then ustekinumab 90 mg SC q12w will be tested) will be used to control the overall Type I error rate at the 0.05 level for the primary endpoint. For the United States, a fixed-sequence testing procedure will be employed to strongly control the overall Type 1 error rate at the 0.05 level across the primary and all 4 major secondary endpoints and across the 2 ustekinumab doses, starting with the high maintenance dose group of the primary endpoint.

Major Secondary Efficacy Analyses

Induction: For the major secondary endpoints of endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) at Week 8 and clinical response at Week 8, the treatment groups will be compared using a 2-sided CMH chi-square test stratified by biologic failure status and region. For the major secondary endpoint of change from induction baseline in the IBDQ score at Week 8, the treatment groups will be compared using analysis of covariance (ANCOVA) on the van der Waerden normal scores with induction baseline IBDQ score, biologic failure status, region, and treatment group as covariates.

Maintenance: Except for the fourth major secondary endpoint of maintenance of clinical remission, analyses of major secondary endpoints will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the IWRS) and induction treatment. For the fourth major secondary endpoint, a 2-sided CMH chi-square test stratified by induction treatment will be used.

Other Planned Analyses

The consistency of efficacy for clinical remission at Week 8 (induction study) and at Week 44 (maintenance study), for both the global and US-specific definitions, will be examined in subgroups for each study defined by baseline demographics, baseline clinical disease characteristics, baseline concomitant UC medications, UC medication history, and stratification variables. Other planned analyses include analysis of the secondary endpoints for each study, such as alternative definitions of remission, mucosal healing, the partial Mayo score, IBDQ score, CRP, fecal calprotectin and lactoferrin.

Pharmacokinetic Analyses

Serum ustekinumab concentrations will be summarized for each treatment group over time using descriptive statistics. A population PK analysis using a nonlinear mixed-effects model will be used to characterize the PK of ustekinumab. The influence of important covariates on the population PK parameter estimates may be evaluated. Details will be provided in a population PK analysis plan, and results of the population PK analysis will be presented in a separate technical report.

Immunogenicity Analyses

The incidence and titers of antibodies to ustekinumab will be summarized for all subjects who receive a dose of ustekinumab and have appropriate samples for detection of antibodies to ustekinumab (ie, subjects with at least 1 sample obtained after their first dose of ustekinumab).

Biomarker Analyses

Changes in the concentration of individual serum markers from baseline to the selected posttreatment time points will be summarized. RNA analyses and additional analyses such as histology assessment and microbiome analysis will be performed. Biomarker analyses are considered exploratory and will be summarized in a separate technical report.

Genetic and Epigenetic (DNA) Analyses

Genetic and epigenetic (DNA) analyses will be conducted only in subjects who sign the consent form to participate in the genetics and epigenetic assessments. These analyses are considered exploratory and will be summarized in a separate technical report.

Health Economics and Medical Resource Utilization Analyses

The potential pharmacoeconomic benefits of ustekinumab treatment will be examined by comparing the difference in direct medical resource utilization and drivers of indirect costs among treatment groups. Health economics and medical resource utilization data will be descriptively summarized by treatment group.

Safety Analyses

Safety analyses will include summaries of AEs and laboratory parameters. These summaries will be provided separately for the induction and maintenance studies and will be based on subjects who received at least 1 dose of study agent in each respective study.

TIME AND EVENTS SCHEDULE: INDUCTION STUDY

Table 1: Schedule of events: Induction study

Phase	Screening	Treatment					Safety
Study Procedures [a,b,c,d] **Week**	**Within 8 weeks**	**I-0**	**I-2**	**I-4**	**I-8**	**I-16** [e,f]	**Follow-up** [g]
Screening/Administrative							
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Medical history and demographics	X						
Prestudy therapy	X						
Preplanned surgery/procedure(s)	X						
QuantiFERON-TB Gold test [h]	X						
HBV and HCV testing	X						
HIV test	X						
Chest radiograph [i]	X						
Serum pregnancy test [j]	X						
Stool for enteric pathogens [k]	X						
Training on Mayo diary card completion	X						
Study Agent Administration							
Randomization		X					
Administer study agent		X			X [l]		
Safety Assessments							
Physical examination	X				X	X	X
12-lead ECG	X						
TB evaluation [m]/ other infection assessment	X	X	X	X	X	X	X
Vital signs [n]	X	X	X	X	X	X	X
Weight	X	X			X	X	X
Height	X						
Urine pregnancy test [j]		X	X	X	X	X	X
AE review	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X
UC-related surgeries/hospitalizations		X	X	X	X	X	X
Injection-site evaluation (only for subjects who receive study agent at I-8 visit)					X	X	
Efficacy Assessments							
Endoscopy [o]	X [p]				X	X	
Mayo score		X			X	X	
Partial Mayo score	X		X	X			
Bristol Stool Form Scale		X	X	X	X	X	
Collect and review diary cards		X	X	X	X	X	
IBDQ		X			X	X	
SF-36		X			X	X	
EQ-5D		X			X	X	
Health Economics							
Productivity VAS		X			X	X	
WPAI-GH		X			X	X	
Clinical Laboratory Assessments							
Hematology, chemistry	X	X	X	X	X	X	
CRP		X	X	X	X	X	
Stool sample (fecal calprotectin, fecal lactoferrin)		X	X	X	X	X	
Pharmacokinetics							
Serum ustekinumab concentration		X [q]	X	X	X [q]	X	X
Antibodies to ustekinumab		X		X	X	X	X
Biomarkers							
Biopsy (RNA, histology)	X [r]				X	X	
Serum biomarkers	X			X	X	X	
Fecal biomarkers		X		X	X	X	
Genetic and Epigenetic (DNA)							

Table 1: Schedule of events: Induction study

Evaluations							
Whole blood (DNA)[s]	X			X	X	X	

AE=adverse event; CRP=C-reactive protein; ECG=electrocardiogram; EQ-5D=EuroQoL-5D Health Questionnaire; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; I=induction; IBDQ=Inflammatory Bowel Disease Questionnaire; IV=intravenous; PK=pharmacokinetic; PRO=patient-reported outcome; SC=subcutaneous; SF-36=36-item Short Form Health Survey; TB=tuberculosis; UC=ulcerative colitis; VAS=visual analog scale; WPAI-GH=Work Productivity and Activity Impairment Questionnaire-General Health.

a. Screening should occur within 8 weeks before the I-0 visit. Visit dates are based on the subject's original randomization date; visit windows are as follows:
   - I-2 and I-4 visits: day of the scheduled visit **±4 days (ie, plus or minus 4 days).**
   - I-8 and I-16 visits: day of the scheduled visit **+3 days (ie, plus 3 days)**.
b. Subjects who discontinue study agent (but have not terminated study participation) before or at the I-8 visit should complete the I-8 assessments at the time of discontinuation and a safety follow-up visit approximately 20 weeks after their last study agent administration. After Week 8, subjects who do not wish to continue into the maintenance study, but are willing to complete their participation in the induction study, should complete the I-16 assessments at the time of discontinuation and a safety follow-up visit approximately 20 weeks after their last study agent administration.
c. Subjects who terminate their study participation before or at the I-8 visit should complete the I-8 assessments at the time of termination. Subjects who terminate their study participation after the I-8 visit but before or at I-16 visit should complete the I-16 assessments at the time of termination.
d. All assessments are to be completed before study agent administration, unless otherwise specified. It is recommended that PRO assessments be completed first.
e. Only subjects who were not in clinical response to study agent at Week 8 will have an I-16 visit.
f. Subjects who are in clinical response at Week 16 will enter the maintenance study; subjects who are not in clinical response at Week 16 will not enter the maintenance study and will have a safety follow-up visit approximately 20 weeks after their last dose of study agent.
g. Subjects who do not enter the maintenance study (or who have not terminated study participation) should have a safety follow-up visit approximately 20 weeks after their last dose of study agent.
h. All subjects will undergo QuantiFERON-TB Gold testing. In countries where the QuantiFERON-TB Gold test is not registered/approved, TB skin testing will also be required (recommended but not required for study centers in Ukraine if tuberculin is not available).
i. Chest radiograph (posterior-anterior view) must be obtained within 3 months before the I-0 visit.
j. Must be performed before any study agent administration for female subjects of childbearing potential.
k. Stool studies for enteric pathogens may be performed at either the central or local laboratory and must include a stool culture and *Clostridium difficile* toxin assay. These must be performed during screening or have been performed during the current episode of disease exacerbation (as long as the stool studies were performed within 4 months before the first administration of study agent). Additional testing (eg, ova and parasites or *Escherichia coli* O157:H7 assessments) may be performed at the investigator's clinical discretion.
l. Subjects who are not in clinical response at Week 8 as assessed by Mayo score will receive ustekinumab (and placebo to maintain the blind; see Figure 2).
m. If TB is suspected at any time, a chest radiograph and QuantiFERON-TB Gold test should be performed. In countries where the QuantiFERON-TB Gold test is not registered/approved, TB skin testing should also be performed (recommended but not required for study centers in Ukraine if tuberculin is not available).
n. Temperature, pulse/heart rate, respiratory rate, and blood pressure. At a study agent administration visit, vital signs will be obtained before, approximately every 30 minutes during, and twice (at approximately 30-minute intervals) after completion of the IV infusion(s), or before and approximately 30 minutes after the SC injection.
o. Endoscopy findings will be assessed by the investigator (ie, local endoscopist) during the procedure and a video of the endoscopy must be submitted to the central reader.
p. The screening endoscopy must be performed within 2 weeks before the I-0 visit. The interval from the endoscopy procedure to the availability of the Mayo endoscopy subscore as assessed by the central reader is approximately 4 days; therefore, the screening endoscopy must be performed at least 4 days before the baseline (I-0) visit. The Mayo endoscopy subscore assessed by the central reader will be used to determine eligibility (ie, Mayo endoscopy subscore ≥2) and to calculate the baseline Mayo score. A full colonoscopy will replace a sigmoidoscopy if screening for polyps or dysplasia is required. At least 48 hours must elapse between a colonoscopy with polypectomy and the I-0 visit.
q. At study agent administration visits (ie, at I-0 for all subjects and I-8 for nonresponders at Week 8), blood samples for PK analysis should be collected before the start of and approximately 60 minutes after completion of the infusion.
r. The screening biopsy samples for histology and RNA analyses will be collected during the screening endoscopy performed within 2 weeks before the first study agent administration. Additional colonic mucosal biopsies will be performed at the I-8 visit; subjects who are nonresponders at the I-8 visit will undergo an additional colonic mucosal biopsy at the I-16 visit.
s. Whole blood for genetic and epigenetic analyses will be collected only from subjects who sign a separate informed consent form to participate in the DNA substudy.

TIME AND EVENTS SCHEDULE: MAINTENANCE STUDY

Table 2: Schedule of events: Maintenance study

Study Procedures [a,b] Week	M-0	M-4	M-8	M-12	M-16	M-20	M-24	M-28	M-32	M-36	M-40	M-44	Early Term [c]	Safety F/U [d]
Administrative														
Inclusion/exclusion criteria [e]	X													
Study Agent Administration														
Randomization [f]	X													
Study agent administration [g]	X		X	X	X		X		X	X	X			
Safety Assessments														
Physical examination												X	X	X
Weight	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [j]	X		X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation [k]/other infection assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study agent injection-site evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UC-related hospitalizations and surgeries	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments														
Endoscopy [l]	X [h]											X	X	
Mayo score	X [h]											X	X	
Partial Mayo score		X	X	X	X	X	X	X	X	X	X			
IBDQ	X [h]					X						X	X	
SF-36	X [h]					X						X	X	
EQ-5D	X [h]					X						X	X	
Health Economics														
Productivity VAS	X [h]					X						X	X	
WPAI-GH	X [h]					X						X	X	
Clinical Laboratory Assessments														
Hematology and chemistry	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	
CRP	X [h]		X				X					X	X	
Stool sample (fecal lactoferrin and calprotectin)	X [h]		X				X					X	X	
Pharmacokinetics/Immunogenicity														
Serum ustekinumab concentration [m]	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Antibodies to ustekinumab	X [h]	X		X			X			X		X	X	X
Biomarkers														
Biopsy (RNA, histology)												X		
Serum biomarkers	X [h]						X					X		

Table 2: Schedule of events: Maintenance study

Study Procedures [a,b] Week	M-0	M-4	M-8	M-12	M-16	M-20	M-24	M-28	M-32	M-36	M-40	M-44	Early Term [c]	Safety F/U [d]
Fecal biomarkers	X [h]						X					X		
Genetic and Epigenetic (DNA) Evaluations														
Whole blood (DNA) [n]	X [h]						X					X		

AE=adverse event; CRP=C-reactive protein; Early Term=early study termination visit; EQ-5D=EuroQoL-5D Health Questionnaire; F/U=follow-up; I=induction; IBDQ=Inflammatory Bowel Disease Questionnaire; LTE=long-term extension; M=maintenance; PRO=patient-reported outcome; SC=subcutaneous; SF-36=36-item Short Form Health Survey; TB=tuberculosis; VAS=visual analog scale; WPAI-GH=Work Productivity and Activity Impairment Questionnaire-General Health; UC=ulcerative colitis.

a. Except for the M-0 visit, the visit window for each visit is ±10 days. The M-0 visit (ie, Week 0 visit for the maintenance study) should occur within 4 days after the I-8 visit (or the I-16 visit for subjects who were not in clinical response at Week 8 but were in clinical response at Week 16).
b. Subjects in clinical flare who have not previously met the criteria for loss of clinical response (ie, are in clinical flare for the first time or have flared previously and not met the criteria for loss of response) should complete all visit assessments indicated for the M-44 visit (including an endoscopy, which need only be a sigmoidoscopy) during their scheduled visit or at any unscheduled visit. Subjects with subsequent clinical flares after loss of clinical response should complete all assessments indicated for the visit at which the clinical flare occurred.
c. Subjects who discontinue study treatment or terminate study participation should undergo procedures described for an Early Term visit.
d. Subjects who discontinue study agent administration (but have not terminated study participation) or who do not enter the LTE will have a final follow-up safety visit approximately 20 weeks after the last administration of study agent.
e. All subjects enrolled in the maintenance study will be responders to study agent administered in the induction study. Subjects must be able to complete the M-0 visit within 4 days after the I-8 or I-16 visit. At the investigator's discretion, the window may be extended to 8 days to allow appropriate treatment of and/or recovery from nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection). Subjects who initiated or increased the dose of a UC-specific medication (or any restricted/prohibited medication) during the induction study are prohibited from entering the maintenance study.
f. Subjects who were in clinical response to IV ustekinumab induction dosing at the I-8 or I-16 visit.
g. All assessments are to be completed before study agent administration, unless otherwise specified. It is recommended that PRO assessments be completed first.
h. No new data will be collected for this procedure at this visit; data from the study procedure performed at the I-8 visit (for subjects in clinical response at Week 8) or I-16 visit (for subjects who were not in clinical response at Week 8 but were in clinical response at Week 16) will be used for the M-0 visit.
i. Temperature, pulse/heart rate, respiratory rate, and blood pressure. At a study agent administration visit, vital sign measurements should be obtained before and approximately 30 minutes after the SC injection.
j. Must be performed before any study agent administration for female subjects of childbearing potential.
k. If TB is suspected at any time during the study, a chest radiograph and QuantiFERON-TB Gold test should be performed. In countries where the QuantiFERON-TB Gold test is not registered/approved, TB skin testing should also be performed (recommended but not required for study centers in Ukraine if tuberculin is not available).
l. A subject who meets the criteria for clinical flare but has not previously met the criteria of loss of clinical response (ie, is in clinical flare for the first time or flared previously and not met the criteria for loss of response) should undergo an additional endoscopy (which need only be a sigmoidoscopy) to determine loss of response based on the Mayo score. An endoscopy is not required if the subject has a subsequent clinical flare after loss of response criteria were met for the previous clinical flare.
m. Samples should be collected before any study agent administration.
n. Whole blood for genetic and epigenetic analyses will be collected only from subjects who sign a separate informed consent form to participate in the DNA substudy.

TIME AND EVENTS SCHEDULE: LONG-TERM EXTENSION

Table 3: Schedule of events: Long-term extension study

Study Procedures [a,b]	Every 4 weeks [c]	Every 3 months [d,e]	Every 6 months [f,g]	Final Efficacy Visit [h]	Final Safety Visit [i]
Study Agent Administration					
Administer study agent	X			X [j]	
Safety Assessments					
Physical examination				X	X
Weight		X		X	X
Vital signs [k]	X			X	X
Urine pregnancy test [l]	X			X	X
TB evaluation [m]/other infection assessment	X			X	X
Study agent injection-site evaluation	X			X	
AE review	X			X	X
Concomitant medication review	X			X	X
UC-related hospitalizations and surgeries	X			X	X
Efficacy Assessments					
Endoscopy				X	
Mayo score				X	
Partial Mayo score		X			
IBDQ			X	X	
SF-36			X	X	
EQ-5D				X	
Health Economics					
WPAI-GH			X	X	
Productivity VAS			X	X	
Clinical Laboratory Assessments					
Hematology and chemistry		X		X	
CRP		X		X	
Stool sample (fecal lactoferrin and calprotectin)		X		X	
Pharmacokinetics/Immunogenicity					
Serum ustekinumab concentration [n]			X	X	X
Antibodies to ustekinumab			X	X	X

AE=adverse event; CRP=C-reactive protein; EQ-5D=EuroQoL-5D Health Questionnaire; IBDQ=Inflammatory Bowel Disease Questionnaire; M=maintenance; PRO=patient-reported outcome; SC=subcutaneous; SF-36=36-item Short Form Health Survey; TB=tuberculosis; VAS=visual analog scale; WPAI-GH=Work Productivity and Activity Impairment Questionnaire-General Health; UC=ulcerative colitis.

a. Visit window is ±10 days for each visit.
b. All assessments are to be completed before study agent administration unless otherwise specified. It is recommended that PRO assessments be completed first.
c. The first study agent administration in the LTE will occur at Week 48; no study agent will be administered at Week 52. After the study is unblinded to the investigative sites, subjects receiving placebo will be terminated from study participation and subjects receiving ustekinumab will continue to receive ustekinumab, but will have study visits scheduled to coincide with their dose regimen (ie, either every 8 or every 12 weeks).
d. Visits every 3 months include scheduled visits at Weeks 56, 68, 80, 92, 104, 116, 128, 140, 152, 164, 176, and 188.
e. The evaluations specified for visits every 4 weeks should also be conducted at the visits every 3 months.
f. Visits every 6 months include scheduled visits at Weeks 68, 92, 116, 140, 164, and 188.
g. The evaluations specified for visits every 3 months should also be conducted at the visits every 6 months.
h. At Week 200, at the time of study agent discontinuation, or at the time of study participation termination.
i. At Week 220 or approximately 20 weeks after a subject's last administration of study agent (for subjects who have not terminated study participation).
j. Only at Week 200.
k. Temperature, pulse/heart rate, respiratory rate, and blood pressure. At a study agent administration visit, vital signs should be obtained before and approximately 30 minutes after the SC injection.
l. Must be performed before each study agent administration in female subjects of childbearing potential.
m. If TB is suspected at any time, a chest radiograph and QuantiFERON-TB Gold test should be performed. In countries where the QuantiFERON-TB Gold test is not registered/approved, TB skin testing should also be performed (recommended but not required for study centers in Ukraine if tuberculin is not available).
n. At a study agent administration visit, blood samples should be collected before study agent injection.

ABBREVIATIONS

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
6-TG	6-thioguanine
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
anti-HBc	HBV core antibody
anti-HBs	HBV surface antibody
AST	aspartate aminotransferase
AZA	azathioprine
BCG	Bacille Calmette-Guerin
CMH	Cochran-Mantel-Haenszel
CRF	case report form (paper or electronic as appropriate for this study)
CRP	C-reactive protein
DBL	database lock
DMC	Data Monitoring Committee
ECG	electrocardiogram
eDC	electronic data capture
EQ-5D	EuroQoL-5D Health Questionnaire
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FVP	final vialed product
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
I-0, I-8, etc	induction Week 0, induction Week 8 (visit), etc
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
JAK	Janus kinase
LTE	long-term extension
M-0, M-8, etc.	maintenance Week 0, maintenance Week 8 (visit), etc.
mAb	monoclonal antibody
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MTX	methotrexate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCS	physical component summary
PD	pharmacodynamic(s)
PFS	prefilled syringe
PGA	physician’s global assessment
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)

q8w	every 8 weeks
q12w	every 12 weeks
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SF-36	36-item Short Form Health Survey
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TNFα	tumor necrosis factor (alpha)
TPN	total parenteral nutrition
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
VAS	visual analog scale
WPAI-GH	Work Productivity and Activity Impairment Questionnaire–General Health

1. INTRODUCTION

Ustekinumab (STELARA®) is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody (mAb) to human interleukin (IL)-12/23p40 that binds with high affinity to human IL-12 and IL-23. Ustekinumab prevents IL-12 and IL-23 bioactivity by preventing their interaction with their cell surface IL-12Rβ1 receptor protein. Through this mechanism of action, ustekinumab effectively neutralizes IL-12 (Th1)- and IL-23 (Th17)-mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases, including inflammatory bowel disease (IBD). Therefore, binding and inhibiting the IL-12/23p40 subunit may provide effective therapy in IBD, including Crohn's disease and ulcerative colitis (UC).

For comprehensive nonclinical and clinical information regarding the efficacy and safety of ustekinumab, refer to the latest version of the Investigator's Brochure (IB).

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Ustekinumab has received marketing approval globally, including countries in North America, Europe, South America, and the Asia-Pacific region, for the treatment of adult patients with chronic moderate to severe plaque psoriasis or active psoriatic arthritis.

The safety of ustekinumab reflects exposure in 7 controlled Phase 2 and Phase 3 studies in 4,135 adult subjects with psoriasis and/or psoriatic arthritis, including 3,256 exposed for at least 6 months, 1,482 exposed for at least 4 years, and 838 for at least 5 years. These data represent a significant database establishing a favorable benefit/risk for ustekinumab, with a safety profile that is well-established and has been stable for 5 years of maintenance treatment with ustekinumab doses of up to 90 mg given every 8 weeks (q8w).

Considerable data available from other completed or ongoing clinical studies of ustekinumab in additional indications (including Crohn’s disease, multiple sclerosis, primary biliary cirrhosis, sarcoidosis, and rheumatoid arthritis), together with extensive postmarketing data based on an estimated 551,966 person-years of exposure through 31 December 2015, also support the safety profile of ustekinumab.

Ustekinumab has not been previously evaluated in UC. However, the efficacy and safety of ustekinumab in Crohn’s disease has been evaluated in 2 completed Phase 2 clinical studies (C0379T07 and C0743T26) and 2 completed Phase 3 induction studies (CNTO1275CRD3001 and CNTO1275CRD3002). A Phase 3 maintenance study (CNTO1275CRD3003) is ongoing.

Additional details on the clinical and postmarketing experience with ustekinumab are provided in the IB.

1.1.1. Ustekinumab in Crohn's Disease

Evidence for the role of IL-12/23p40 in Crohn's disease was supported by the results of 2 Phase 2 studies in Crohn's disease. C0379T07 was a Phase 2a study of ustekinumab induction therapy administered intravenously (IV) or subcutaneously (SC) in subjects who had failed conventional Crohn's disease therapy[25]; this study demonstrated promising efficacy, with a greater treatment effect observed in subjects who received IV induction. C0743T26 (CERTIFI) was a positive Phase 2b study of ustekinumab in subjects with Crohn's disease who had failed to respond to or were intolerant of anti-tumor necrosis factor alpha (TNF-α) agents.[29]

In the induction phase of C0743T26, subjects received IV doses of 1 mg/kg, 3 mg/kg, or 6 mg/kg ustekinumab or placebo at Week 0. In the maintenance phase, subjects who had been randomized to ustekinumab induction therapy at Week 0 were rerandomized (based on their clinical response status at Week 6) to receive SC maintenance doses of 90 mg ustekinumab or placebo at Weeks 8 and 16 in the induction phase. Efficacy results are summarized below:

- Greater proportions of subjects in the 1 mg/kg, 3 mg/kg, and 6 mg/kg ustekinumab groups achieved clinical response at Week 6 (36.6%, 34.1%, and 39.7%, respectively) compared with subjects in the placebo group (23.5%), and the comparison between the ustekinumab 6 mg/kg group and the placebo group was statistically significant (p=0.005).
- The proportions of subjects who achieved clinical remission at Week 6 in the ustekinumab 1 mg/kg, 3 mg/kg, and 6 mg/kg groups were 16.0%, 15.9%, and 12.2%, respectively, compared with 10.6% in the placebo group. Although this endpoint was not significant at Week 6, remission rates continued to increase over time, particularly in subjects in the 6 mg/kg group. This finding led to the use of the clinical remission at Week 8 endpoint in the Phase 3 Crohn's disease induction studies.
- Among subjects rerandomized as responders to ustekinumab induction, the proportion of subjects who achieved clinical remission at Week 22 in the maintenance phase was significantly greater in the ustekinumab 90 mg SC group (41.7%) compared with the placebo SC group (27.4%, p=0.029).
- The proportion of subjects who achieved clinical response at Week 22 in the maintenance phase was also significantly greater in the ustekinumab 90 mg SC group (69.4%) than in the placebo SC group (42.5%, p=0.001).
- Among the limited number of subjects who achieved clinical remission at Week 6, 78.6% remained in clinical remission at Week 22 in the maintenance study in the ustekinumab 90 mg SC group compared with 53.3% in the placebo SC group (p=0.056).

In the Phase 2 studies, both IV and SC ustekinumab were generally well tolerated and the results indicated a safety profile that was consistent with the safety profile of ustekinumab in the approved psoriasis indication.

The Phase 3 development program in subjects with Crohn's disease includes 2 induction studies (CNTO1275CRD3001 and CNTO1275CRD3002) and 1 maintenance study (CNTO1275CRD3003). To protect the integrity of the maintenance study, the results of the completed induction studies were to remain blinded to all but a select group of individuals within Janssen R&D until the database lock for the primary endpoint of the maintenance study.

Refer to the IB for the most current data on the Phase 2 and 3 studies in Crohn's disease.

1.2. Overall Rationale for the Study

Inflammatory bowel diseases, including UC, are chronic relapsing disorders characterized by destructive inflammation and epithelial injury in the gastrointestinal tract.[4,10] The incidence of UC in the United States is estimated to be between 9 and 12 per 100,000 with a prevalence of 205 to 240 per 100,000.[32] The etiology of UC is unknown; however, abnormal immune responses to contents in the gut, including intestinal microbes, are thought to drive disease in genetically predisposed individuals.[14] Disregulated innate and adaptive immune pathways contribute to aberrant intestinal inflammation in IBD, and cytokines, including IL-12, interferon gamma (IFNγ), and IL-23 have been implicated in the pathogenesis of UC.[14,23]

The involvement of the IL-12/23 pathway in the pathogenesis of IBD is well established. Early studies showed that treatment with anti-IFNγ mAb[5,11] or anti-IL-12p40 mAb prevented disease in experimental colitis models, suggesting an important role for Th-1 cells in promoting intestinal inflammation.[24] Subsequently, an important role for IL-23 in intestinal inflammation was elucidated in colitis.[1,19,35,38] In humans, genome-wide association studies have implicated several genetic loci in the IL-12/23 pathway that are associated with increased susceptibility to UC, including IL-23R, IL-12B, Janus kinase (JAK) 2, and STAT3 genes.[2,6] Patients with active UC were shown to have significantly more IL-23, IL-22, IL-22R1 and p-STAT3-positive cells than patients with inactive UC and normal controls.[39] Th1- and Th17-related genes are upregulated comparably in the mucosa of both UC and Crohn's disease patients, suggesting that once established, the inflammatory mechanisms at the mucosal level between the two diseases are largely the same[15]; similar conclusions were reached in a genome-wide association study of IBD patients conducted by Jostins and colleagues.[20]

Ustekinumab, which neutralizes both IL-12 and IL-23 by binding to the common p40 subunit of these cytokines, has already demonstrated efficacy in a Phase 2b study in subjects with moderate to severe Crohn's disease[29] and is currently being studied in a global Phase 3 program for the treatment of Crohn's disease. Of note, biologic therapies currently approved for the treatment of UC are either TNF-α or integrin inhibitors and, when tested, these therapies have also demonstrated efficacy in Crohn's disease.[8,16,28,30]

Biologic therapies for the treatment of patients with moderately to severely active UC include anti-TNF agents such as infliximab (REMICADE), adalimumab (Humira), golimumab (SIMPONI), and the recently approved α4β7 integrin antagonist vedolizumab (Entyvio). These agents are currently approved for the treatment of patients with UC who are no longer responding to corticosteroids or immunomodulators; however, only vedolizumab has demonstrated efficacy in patients who have had an inadequate response to (ie, primary

nonresponse or secondary loss of response) or are intolerant of anti-TNFs. These agents are administered either IV (infliximab and vedolizumab) or SC (golimumab and adalimumab). Anti-TNFs have safety risks associated with immunosuppression and not all patients adequately respond to therapy, while the long-term safety of vedolizumab has yet to be established. Therefore, there is a need for novel therapies with alternative mechanisms of action and potentially more favorable safety profiles.

Ustekinumab is a novel therapy with a favorable long-term safety profile that has the potential to offer an SC treatment option for maintenance, following a single IV induction dose, that could be safe and efficacious for patients with moderately to severely active UC who have had an inadequate response to or are intolerant of either conventional or biologic therapy, thereby addressing a clear unmet medical need in this patient population.

These data, along with the shared biology of, and similar response to current treatments between, Crohn's disease and UC provide a substantial scientific and clinical rationale to justify a direct-to-Phase-3 approach to the study of ustekinumab in UC. Relative to approved therapies for UC (ie, anti-TNFs and vedolizumab), ustekinumab offers the potential for a more convenient treatment regimen, with SC administration every 8 to 12 weeks during maintenance. Finally, ustekinumab provides a novel mechanism of action in the treatment of UC, with a documented long-term safety profile in excess of 5 years of clinical data, which is complemented by postmarketing data representing 551,966 person-years of exposure.

The Phase 3 development program for ustekinumab in the treatment of UC will be conducted under a single protocol but will be designed and analyzed as 2 separate studies, an induction study and a maintenance study. Both will be Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies of ustekinumab in subjects with moderately to severely active UC. A long-term extension study (LTE) will follow subjects for an additional 3 years.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

2.1.1. Induction Study

2.1.1.1. Primary Objectives

- To evaluate the efficacy of IV ustekinumab in inducing clinical remission in subjects with moderately to severely active UC.
- To evaluate the safety of IV ustekinumab in subjects with moderately to severely active UC.

2.1.1.2. Secondary Objectives

- To evaluate the efficacy of IV ustekinumab in inducing endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) in subjects with moderately to severely active UC.

- To evaluate the efficacy of IV ustekinumab in inducing clinical response in subjects with moderately to severely active UC.
- To evaluate the impact of IV ustekinumab on disease-specific health-related quality of life.
- To evaluate the efficacy of ustekinumab treatment on mucosal healing (ie, endoscopic healing and histologic healing).
- To evaluate the efficacy of induction therapy with IV ustekinumab by biologic failure status.
- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of ustekinumab induction therapy in subjects with moderately to severely active UC, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other PD biomarkers.

2.1.2. Maintenance Study

2.1.2.1. Primary Objectives

- To evaluate clinical remission for SC maintenance regimens of ustekinumab in subjects with moderately to severely active UC induced into clinical response with ustekinumab.
- To evaluate the safety of SC maintenance regimens of ustekinumab in subjects with moderately to severely active UC induced into clinical response with ustekinumab.

2.1.2.2. Secondary Objectives

- To evaluate the efficacy of ustekinumab in maintaining clinical response in subjects induced into clinical response with ustekinumab.
- To evaluate endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) in subjects induced into clinical response with ustekinumab.
- To evaluate the efficacy of ustekinumab in achieving corticosteroid-free clinical remission in subjects induced into clinical response with ustekinumab.
- To evaluate the efficacy of ustekinumab in maintaining clinical remission in subjects induced into clinical remission with ustekinumab.
- To evaluate the efficacy of ustekinumab treatment on mucosal healing (ie, endoscopic healing and histologic healing).
- To evaluate the impact of SC ustekinumab on disease-specific health-related quality of life.
- To evaluate the efficacy of maintenance therapy with SC ustekinumab by biologic failure status.
- To evaluate the PK, immunogenicity, and PD of ustekinumab maintenance therapy, including changes in CRP, fecal calprotectin, fecal lactoferrin, and other PD biomarkers in subjects induced into clinical response with ustekinumab.

2.1.3. Exploratory Objectives

- To evaluate response using the Mayo score without the physician's global assessment (PGA) subscore in both induction and maintenance.
- To evaluate the performance of the Bristol Stool Form Scale score in the induction study.

2.2. Hypotheses

2.2.1. Induction Study

Ustekinumab is superior to placebo in inducing clinical remission at Week 8 in subjects with moderately to severely active UC.

2.2.2. Maintenance Study

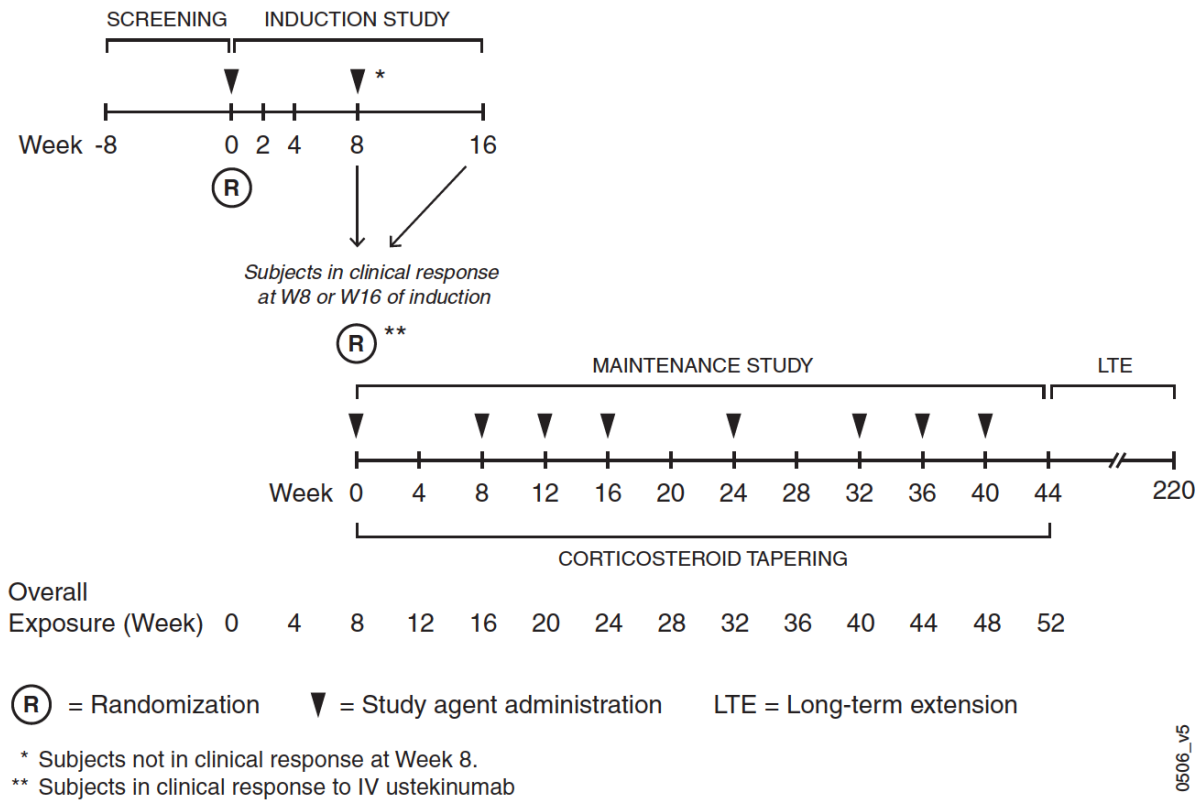
Ustekinumab maintenance therapy is superior to placebo in achieving clinical remission at Week 44 of maintenance in subjects with moderately to severely active UC who were induced into clinical response with ustekinumab.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

The Phase 3 development program for ustekinumab in the treatment of UC will be conducted under a single protocol but will be designed and analyzed as 2 separate studies, an induction study and a maintenance study. Both studies will be Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies of ustekinumab in subjects with moderately to severely active UC. The induction study will target subjects with moderately to severely active UC who have demonstrated an inadequate response or failure to tolerate conventional or biologic therapy. The maintenance study will be a randomized withdrawal study targeting subjects with moderately to severely active UC who have demonstrated a clinical response to induction treatment with IV ustekinumab. Overall, the program will evaluate ustekinumab treatment in subjects with moderately to severely active UC through at least 1 year of induction and maintenance therapy; after completion of the maintenance study through Week 44, an LTE will follow eligible subjects for an additional 3 years.

Figure 1: Overall schema for CNTO1275UCO3001 protocol



The target population is men or women 18 years of age or older with moderately to severely active UC, as defined by a Mayo score of 6 to 12, inclusive, at Week 0 of the induction study, including an endoscopy subscore ≥2 as assessed by the central reader. Subjects must not be at imminent risk of colectomy.

A broad subject population will be evaluated and will include both subjects who have failed biologic therapy and those who have not:

- Subjects may be biologic failures, ie, have received treatment with 1 or more TNF antagonists or vedolizumab at a dose approved for the treatment of UC, and either did not respond initially, responded initially but then lost response, or were intolerant to the medication. A minimum of 40% and a maximum of 50% of the total subject population in the induction study will be biologic failures.
- Subjects may be biologic-naive or may have been exposed to biologic therapy but not demonstrated an inadequate response or intolerance to treatment with a biologic agent (ie, a TNF antagonist or vedolizumab). These subjects must have demonstrated an inadequate response to, or have failed to tolerate, at least 1 of the following conventional UC therapies: oral or IV corticosteroids or the immunomodulators azathioprine (AZA) or 6-mercaptopurine (6-MP). Subjects who have demonstrated corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of UC) are also eligible for entry into the study.

Throughout the induction and maintenance studies, efficacy, PK, biomarkers, and safety will be assessed at timepoints indicated in the appropriate Time and Events Schedules.

Endpoints are defined in Section 9.2.2.4.

Blood samples for pharmacogenomic analyses will be collected from subjects who consent separately to this component of the protocol (where local regulations permit). Subject participation in pharmacogenomic research is optional.

An independent Data Monitoring Committee (DMC) will assess the safety of subjects participating in the induction and maintenance studies, participate in the futility interim analysis (Section 11.11.1), and make recommendations to the sponsor about continuation of the studies. Refer to Section 11.12 for details.

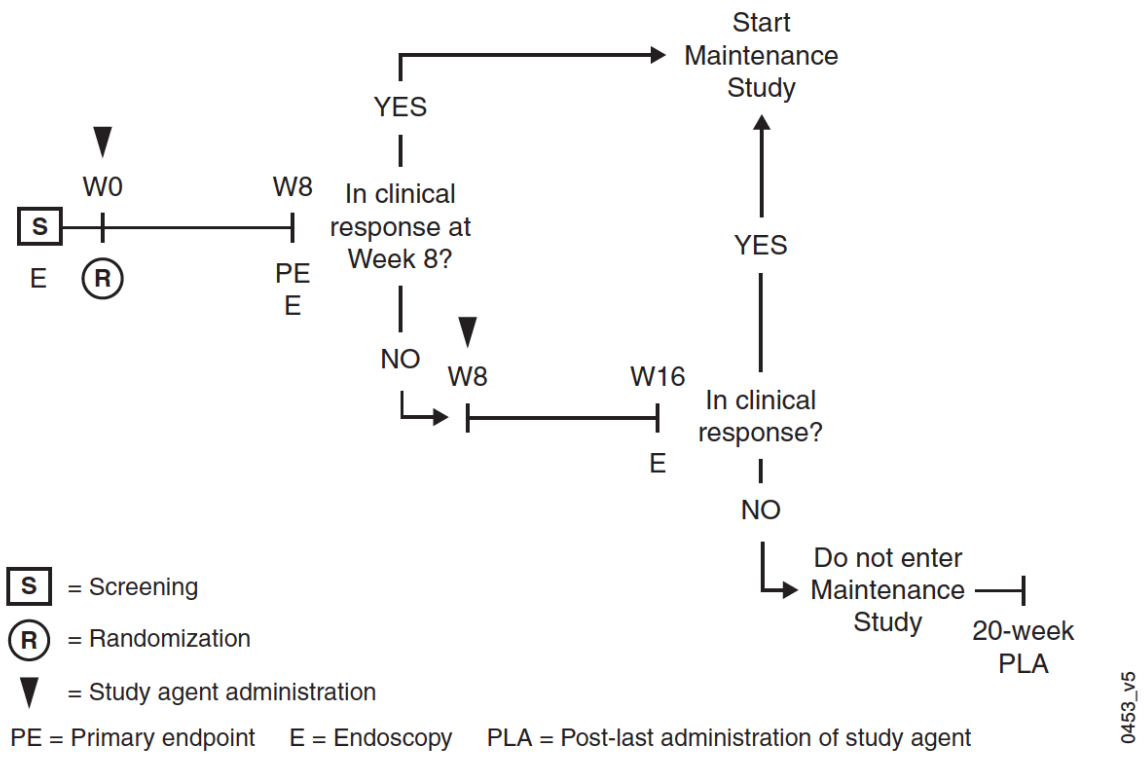
3.1.1. Induction Study

In the placebo-controlled induction study, a target of 951 subjects will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups:

- Placebo IV
- Ustekinumab 130 mg IV
- Weight-range-based ustekinumab doses approximating ustekinumab 6 mg/kg IV (ie, ustekinumab ~6 mg/kg IV):
  - Ustekinumab 260 mg (weight ≤55 kg)
  - Ustekinumab 390 mg (weight >55 kg but ≤85 kg)
  - Ustekinumab 520 mg (weight >85 kg)

The schema for the induction study is shown in Figure 2.

Figure 2: Schema for the CNTO1275UCO3001 induction study



Eligible subjects will be allocated to a treatment group using permuted block randomization with biologic failure status (yes or no) and region (Eastern Europe, Asia, or rest of world) as stratification variables.

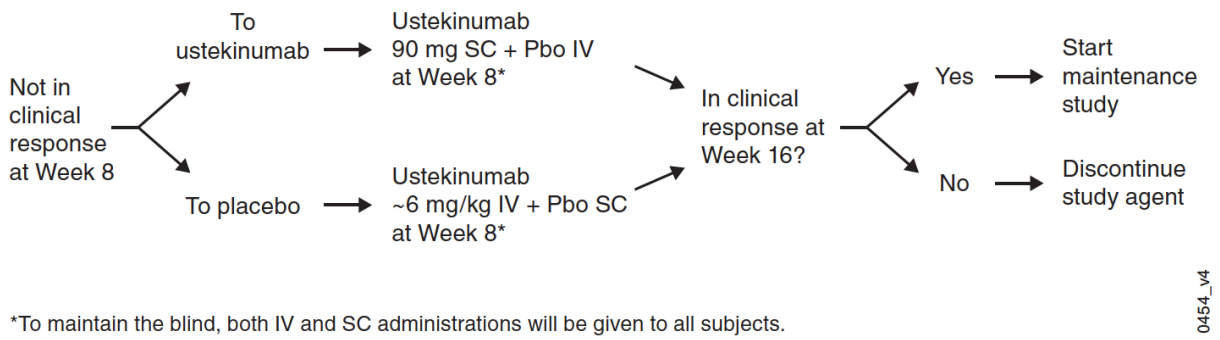
Randomized subjects will receive their assigned IV dose of ustekinumab or placebo at Week 0. At Week 8, all subjects will be evaluated for the primary endpoint of clinical remission. All subjects will also be assessed for clinical response at Week 8. Further study agent administration will be determined by clinical response status (using the Mayo endoscopy subscore assigned by the local endoscopist) at Week 8, as follows:

- Subjects who are in clinical response at Week 8 are eligible to enter the maintenance study (Section 3.1.2).
- Subjects who are not in clinical response at Week 8 will receive ustekinumab as follows (Figure 3):
  - Subjects who were randomized to placebo at Week 0 will receive 1 dose of ustekinumab ~6 mg/kg IV plus placebo SC (to maintain the blind) at Week 8.
  - Subjects who were randomized to ustekinumab at Week 0 will receive 1 dose of ustekinumab 90 mg SC plus placebo IV (to maintain the blind) at Week 8.

At Week 16, the subjects who were not in clinical response at Week 8 will be re-evaluated for clinical response (clinical response status will be based on the Mayo endoscopy subscore assigned by the local endoscopist):

- Subjects who achieve clinical response at Week 16 are eligible to enter the maintenance study (Section 3.1.2).
- Subjects who do not achieve clinical response at Week 16 will not enter the maintenance study and will have a safety follow-up visit approximately 20 weeks after their last (ie, Week 8) administration of study agent.

Figure 3: Treatment of subjects who are not in clinical response to induction in CNTO1275UCO3001



*To maintain the blind, both IV and SC administrations will be given to all subjects.

All UC-specific medical therapies (ie, oral corticosteroids, oral 5-aminosalicylate (5-ASA) compounds, or the immunomodulators 6-MP, AZA, or methotrexate [MTX]) must be maintained at a stable dose through to the end of the induction study and can only be discontinued or reduced in dose if investigator judgment requires it because of toxicity or medical necessity (Section 8.1.1). The initiation or increase in dose of UC-specific therapies (or any restricted/prohibited medication or therapy) during the induction study will prohibit a subject from entering the maintenance study (Section 8.1.1.1).

The primary endpoint of the induction study is clinical remission at Week 8; the major secondary endpoints are endoscopic healing at Week 8, clinical response at Week 8, and the change from induction baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 8.

Efficacy, PK parameters, biomarkers, and safety will be assessed according to the Time and Events Schedule (Table 1).

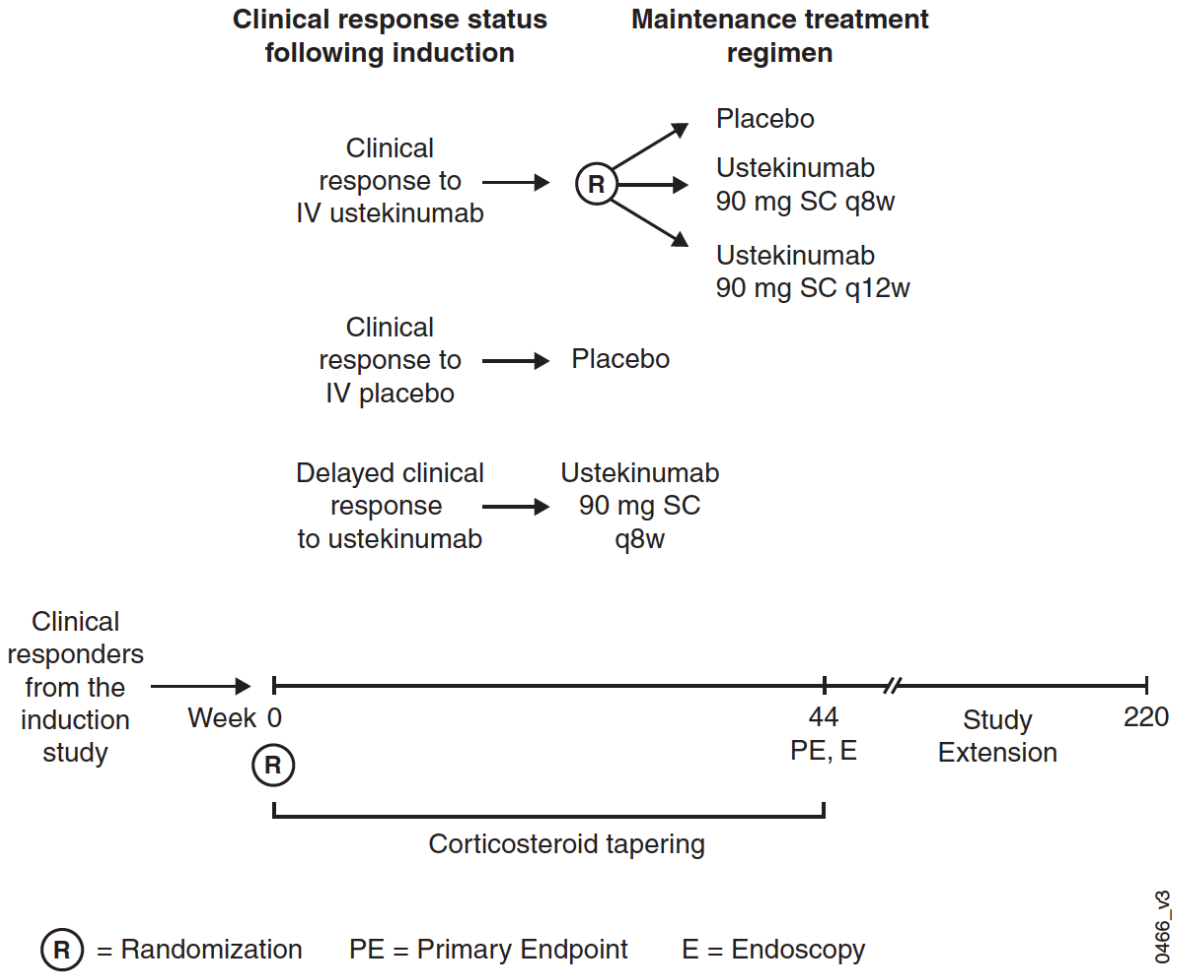
An interim analysis to assess for futility is planned when the first 30% of subjects either complete the induction Week 8 (I-8) visit or terminate study participation before Week 8. This analysis will be based on clinical remission at Week 8. The whole study may be stopped for futility when the conditional power (ie, the probability of success at the end of the study, given the data at the interim analysis) on **both** ustekinumab doses is less than a prespecified cutoff. Refer to Section 11.11 for details.

Three database locks (DBLs) are planned for the induction study. The first is for the futility analysis and will occur when the first 30% of randomized subjects in the induction study have either completed the I-8 visit or have terminated study participation before Week 8. The second DBL will occur when **all** randomized subjects in the induction study have either completed the I-8 visit or have terminated study participation before Week 8. The third DBL will occur when all randomized subjects in the induction study have either entered the maintenance study, or have completed their final safety visit (20 weeks after the last administration of study agent) for those not participating in the maintenance study, or have terminated their study participation.

3.1.2. Maintenance Study

In the randomized-withdrawal maintenance study, all subjects enrolled will be responders to study agent administered in the induction study. The schema for the maintenance study is shown in Figure 4.

Figure 4: Schema for the CNTO1275UCO3001 maintenance study



Subjects who were in clinical response to IV ustekinumab during induction will comprise the primary population in the maintenance study; this population will include the following:

- Subjects who were randomized to receive ustekinumab at Week 0 of the induction study and were in clinical response at induction Week 8.
- Subjects who were randomized to receive placebo at Week 0 of the induction study and were not in clinical response at induction Week 8, but were in clinical response at induction Week 16 after receiving an induction dose of IV ustekinumab (~6 mg/kg) at induction Week 8.

A target of 327 subjects who are in clinical response to IV ustekinumab induction will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups at the maintenance Week 0/baseline (M-0) visit of the maintenance study:

- Placebo SC
- Ustekinumab 90 mg SC every 12 weeks (q12w)
- Ustekinumab 90 mg SC q8w

Eligible subjects will be allocated to a treatment group using a permuted block randomization with clinical remission status at maintenance baseline (yes/no), oral corticosteroid use at maintenance baseline (yes/no), and induction treatment (placebo IV [I-0]→ ustekinumab ~6 mg/kg IV [I-8], ustekinumab 130 mg IV [I-0], or ustekinumab ~6 mg/kg IV [I-0]) as stratification variables.

Additional subjects entering the maintenance study will include the following; these subjects will not be part of the primary population:

- Subjects who are in clinical response to placebo IV induction will receive placebo SC.
- Subjects who were delayed responders to ustekinumab induction (ie, were not in clinical response to ustekinumab at induction Week 8 but were in clinical response at induction Week 16) will receive ustekinumab 90 mg SC q8w.

All subjects will receive their assigned dose of SC study agent at the M-0 visit. Thereafter, to maintain the blind, all subjects will receive study agent at all scheduled study agent administration visits specified in Table 2. Subjects will be assessed for clinical flare at every visit and, if loss of response is confirmed (based on the Mayo score that includes the endoscopy subscore assigned by the local endoscopist), may be eligible for rescue medication, as described in Section 3.1.2.1.

Concomitant medical therapy for UC must have been stable from the I-0 visit through the M-0 visit unless, in the judgment of the investigator, the therapy had to be discontinued or reduced in dose because of toxicity or medical necessity (Section 8.1.1). Subjects who initiated or increased the dose of a UC-specific medication (or any restricted/prohibited medication) during the induction study are prohibited from entering the maintenance study (Section 8.1.1.1).

With the exception of corticosteroids, which should be tapered, UC-specific medical therapies (ie, oral 5-ASA compounds, or the immunomodulators 6-MP, AZA, or MTX) must be maintained at stable doses through Week 44 unless investigator judgment requires that the therapy be discontinued or the dose reduced because of toxicity or medical necessity, or unless there is a documented loss of response that makes the subject eligible for rescue medication. Corticosteroids will be tapered beginning at the M-0 visit for all subjects who enter the maintenance study. Refer to Section 8.1.2 for details.

The primary endpoint of the maintenance study is clinical remission at Week 44 among subjects who were responders to IV ustekinumab induction. The major secondary endpoints of the maintenance study are maintenance of clinical response through Week 44; endoscopic healing at Week 44; clinical remission and not receiving concomitant corticosteroids at Week 44; and maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline.

Efficacy, PK parameters, biomarkers, and safety will be assessed according to the Time and Events Schedule (Table 2). Blood samples for pharmacogenomics analyses will be collected from subjects who consent separately to this component of the study (where local regulations permit).

The primary DBL will occur when all subjects in the maintenance study have either completed the M-44 visit or have terminated study participation before Week 44. The final DBL will occur when all subjects have either completed the Week 220 visit or have terminated study participation before Week 220. One or more additional DBLs may occur between Week 44 and Week 220 for publication purposes or for regulatory requirements.

No interim analysis is planned during the maintenance study.

3.1.2.1. Management of Clinical Flare and Loss of Response

During the maintenance study, subjects who meet the following criteria will be considered to be in clinical flare: an increase from maintenance baseline in the partial Mayo score (ie, the Mayo score without the endoscopy subscore) of at least 2 points **and** an absolute partial Mayo score ≥4; **OR** an absolute partial Mayo score ≥7 points (Section 9.1.4.1).

Subjects in clinical flare who have not previously met the criteria for loss of clinical response in the maintenance study (ie, are in clinical flare for the first time or have flared previously and not met the criteria for loss of response) should undergo endoscopy, which need only be a sigmoidoscopy, and be evaluated for loss of clinical response (based on the Mayo score that includes the endoscopy subscore assigned by the local endoscopist). These subjects should maintain stable doses of their UC medications after meeting clinical flare criteria and while waiting for their endoscopy score to establish loss of clinical response.

Subjects who have lost response will be eligible to receive rescue medication (ie, corticosteroids, 6-MP, AZA, MTX, and/or 5-ASAs; Section 8.1.2.1) while continuing to receive study agent administration as scheduled.

Subjects who have lost response will be assessed 16 weeks after the visit at which the loss of clinical response criteria was met. During this interval, clinical flare criteria will not be applied. Subjects who have not achieved a partial Mayo response (ie, a decrease from induction baseline of ≥2 in the partial Mayo score) at 16 weeks after loss of response will be discontinued from study agent administration, and should return for a final safety visit approximately 20 weeks after their last study agent administration. Subjects who are assessed as being in partial Mayo response will continue in the study.

After the 16 weeks following loss of clinical response, subjects who remain in the study will continue to be assessed for clinical flare using the criteria based on the partial Mayo score. Subjects who subsequently meet the criteria for clinical flare again will not be required to undergo an endoscopy. These subjects will be eligible to receive rescue medication at the time of clinical flare and be assessed for partial Mayo response 16 weeks after the visit at which clinical flare was met and managed as described above.

Subjects will be strongly encouraged to undergo endoscopy at the time of first clinical flare to establish if loss of clinical response criteria were met. A subject who declines to undergo an endoscopy on initial clinical flare will be assessed for partial Mayo response 16 weeks after the initial flare.

A subject who meets the criteria of clinical flare on more than 2 occasions during the maintenance study will be discontinued from study agent administration.

3.1.3. Long-Term Extension

Subjects who complete the safety and efficacy evaluations at Week 44 and who may benefit from continued treatment, in the opinion of the investigator, will have the opportunity to participate in the LTE. The LTE begins **after** the assessments listed for the M-44 visit (ie, the last assessments in the maintenance study) have been completed and will continue through Week 220 or until the sponsor decides not to pursue an indication in UC, whichever occurs first.

Subjects will continue to receive the same treatment regimen during the LTE that they were receiving at the end of the maintenance study (either placebo or ustekinumab 90 mg SC q8w or q12w), with the first dose in the LTE being administered at Week 48.

During the LTE, all subjects will be assessed for worsening of disease activity based on the clinical judgment of the investigator. Subjects in the primary analysis population whose UC disease activity worsens will be eligible for a dose adjustment as follows:

- Placebo SC → ustekinumab 90 mg SC q8w
- Ustekinumab 90 mg SC q12w → ustekinumab 90 mg SC q8w
- Ustekinumab 90 mg SC q8w → continue on ustekinumab 90 mg SC q8w

The first visit at which a subject can be considered for a dose adjustment is at Week 56. Subjects will be allowed 1 dose adjustment during the LTE.

The interactive web response system (IWRS) will ensure that SC ustekinumab is not administered more frequently than q8w. For example, subjects randomized to the ustekinumab 90 mg SC q12w group who meet dose adjustment criteria will receive ustekinumab 90 mg SC at the current visit only if the last dose of ustekinumab was administered at least 8 weeks before this visit. If the last administration of ustekinumab 90 mg SC was less than 8 weeks before, the next administration of ustekinumab 90 mg SC will be initiated at the next scheduled visit that occurs at least 8 weeks after the previous administration of ustekinumab.

Subjects who are not in the primary analysis population (ie, induction placebo responders, delayed ustekinumab responders) will not be eligible for a dose adjustment during the LTE.

Any subject who has not shown improvement in his or her UC disease activity by 16 weeks after worsening of their UC disease activity (as assessed by the investigator) will be discontinued from further study agent administration.

During the LTE, all concomitant medications, including UC-specific medications (with the exception of the prohibited medications listed in Section 8.1.1.1.2), may be administered at the discretion of the investigator.

Efficacy evaluations during the LTE will generally be based on the partial Mayo score, markers of inflammation, and corticosteroid use. The full Mayo score (including an endoscopy) will be assessed at the final efficacy visit. Selected patient-reported outcomes (PRO) and health economics data will also be collected. Safety evaluations will include an assessment of adverse events (AEs) and routine laboratory analyses. All study evaluations to be performed during the LTE are listed in the Time and Events Schedule (Table 3).

The study blind will be maintained during the LTE until the last subject in the maintenance study has completed the M-44 visit evaluations and the Week 44 analyses have been completed. Therefore, subjects will continue to receive study agent at all monthly visits until that time. After the study is unblinded to the investigative sites, subjects receiving placebo will be terminated from study participation, and subjects receiving ustekinumab will continue to receive ustekinumab, but will have their study visits scheduled to coincide with their dose regimen (either q8w or q12w, as appropriate for their dose regimen).

3.2. Study Design Rationale

3.2.1. Study Population

Ustekinumab is a novel therapy with a favorable long-term safety profile in psoriasis that has the potential to offer an SC treatment option for maintenance, following a single IV induction dose, which could be safe and efficacious for patients with moderately to severely active UC who have had an inadequate response to or are intolerant of either conventional or biologic therapy. There is a clear unmet medical need in this broad patient population (Section 1.2), which will be the target population for the induction study.

3.2.1.1. Induction

Subjects with moderately to severely active UC (defined as a Mayo score of 6 to 12 inclusive, including a Mayo endoscopy score ≥2) who have had an inadequate response or have failed to tolerate conventional or biologic therapy will be eligible for the induction study. At Week 8, all subjects will be evaluated for clinical response; those in clinical response (either to ustekinumab or placebo) will be eligible to enter the maintenance study as described in Section 3.1.2.

Subjects who were randomized to placebo and are not in clinical response at Week 8 will receive a single IV infusion of ustekinumab at the highest dose studied (ie, ~6 mg/kg) in a blinded manner. This will ensure that those subjects who did not achieve clinical response with placebo have the option to receive and potentially respond to active drug.

Subjects who were randomized to ustekinumab and are not in clinical response at Week 8 will receive a single SC injection of 90 mg ustekinumab in a blinded manner. This will allow the study to identify if a delayed response can be achieved for some subjects.

All subjects who were not in clinical response at Week 8 and who received additional induction treatment at Week 8 will be evaluated for clinical response at Week 16. Those who do not achieve clinical response at Week 16 will not be eligible to enter the maintenance study, to limit exposure to a therapy from which they are not deriving benefit. Subjects who are in clinical response at Week 16 will be eligible to enter the maintenance study as described in Section 3.1.2.

Among the subjects in clinical response at Week 16 will be those who are delayed responders to ustekinumab (ie, did not respond to IV ustekinumab administered at induction Week 0 but responded after an additional SC administration of ustekinumab at Week 8). Enrollment of these subjects in the maintenance study will allow an evaluation of the benefit-risk of continued therapy with ustekinumab following a delayed induction response to ustekinumab. However, these subjects will not be included in the primary population for maintenance.

An additional group of subjects in clinical response at Week 16 will be those who were initially randomized to IV placebo at induction Week 0 and were not in clinical response at Week 8, but responded at Week 16 after a single IV administration of ustekinumab at induction Week 8. Like the subjects initially randomized to a single IV administration of ustekinumab at induction Week 0, these subjects will be considered part of the primary population for maintenance (ie, subjects in clinical response 8 weeks after a single IV administration of ustekinumab) to assess the evaluation of the benefit-risk of continued therapy with ustekinumab following an initial response.

To limit the exposure of subjects with UC should ustekinumab treatment prove to be ineffective, a futility analysis based on the primary endpoint of clinical remission at Week 8 will be conducted when the first 30% of randomized subjects in the induction study reach Week 8 (Section 11.11.1).

3.2.1.2. Maintenance

Subjects with moderately to severely active UC who were in clinical response to IV ustekinumab during induction will comprise the primary population in the maintenance study (Section 3.1.2) and will be randomized to receive ustekinumab (90 mg q8w or 90 mg q12w) or placebo to evaluate the efficacy and safety of ustekinumab maintenance therapy.

Additional subjects, including placebo induction responders and delayed responders (ie, those who were not in clinical response to ustekinumab IV at induction Week 8 but were in clinical response at induction Week 16) will be enrolled in the maintenance study to maintain the blind but will not be randomized.

All subjects will be evaluated for clinical flare and potential loss of clinical response throughout the 44 weeks of the maintenance study. Subjects who lose response will continue to receive study agent and be eligible to receive rescue medications to manage the increase in their UC disease activity (Section 8.1.2.1).

To limit exposure to a potentially ineffective therapy, subjects will be evaluated for response 16 weeks after loss of clinical response (Section 3.1.2.1). If a prespecified measure of response is not achieved (ie, partial Mayo response), the administration of further study agent will be discontinued.

3.2.2. Endpoints

3.2.2.1. Induction

The primary endpoint of the induction study is clinical remission at Week 8. Clinical remission is generally considered to reflect the absence of ongoing symptoms. The choice of Week 8 is based on Phase 2b data with ustekinumab induction in Crohn's disease.[29]

3.2.2.2. Maintenance

The primary endpoint of the maintenance study is clinical remission at Week 44 among IV ustekinumab induction responders. At this timepoint, subjects will have had at least 52 weeks of exposure to ustekinumab and will have received either 4 or 6 maintenance doses (depending on their dose frequency of either q12w or q8w, respectively), which is deemed sufficient to assess the efficacy and safety of the maintenance regimens. This will be followed by an LTE of up to 3 additional years to assess longer-term safety and efficacy.

3.2.3. Efficacy Assessments

The efficacy evaluations selected for the induction and maintenance studies (eg, Mayo score, partial Mayo score; Section 9.2.1) are accepted disease activity measures in UC studies.

3.2.4. Pharmacokinetic Assessments

Pharmacokinetic assessments will be used to further understand the disposition of ustekinumab in subjects with UC.

3.2.5. DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the PK, PD, or efficacy of ustekinumab and to identify genetic factors associated with UC.

Biomarker samples will be collected to evaluate the mechanism of action of ustekinumab, help explain interindividual variability in clinical outcomes, or help to identify population subgroups that respond differently to a drug. The goal of the biomarker analyses is to evaluate the PD of ustekinumab and aid in evaluating the drug-clinical response outcome relationship.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of more effective and ultimately individualized therapies.

3.2.6. Patient-Reported Outcomes on Health-Related Quality of Life

Patient-reported outcomes evaluations (eg, IBDQ, 36-item Short Form Health Survey [SF-36], EuroQoL-5D Health Questionnaire [EQ-5D]); Section 9.2.1) will be used to assess general as well as disease-specific health-related quality of life.

3.2.7. Health Economics and Medical Resource Utilization

Medical resource utilization evaluations such as UC-related hospitalizations and UC-related surgeries will be collected for evaluation of the health economics of ustekinumab treatment. Additionally, the impact of ustekinumab treatment on work productivity will be assessed using the Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH) and work productivity visual analog scale (VAS).

3.2.8. Control, Randomization, and Blinding in the Induction and Maintenance Studies

In the induction study and for the primary population of the maintenance study, a placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. The choice of a placebo comparator accommodates the enrollment of patients with the highest unmet need, namely patients who have failed or are intolerant of the anti-TNFs, which are the current gold standard for biologic therapy in moderately to severely active UC. Furthermore, the overall objective of the maintenance study is to assess the benefit-risk of continuing treatment with ustekinumab following induction response and is therefore designed as a randomized withdrawal study targeting subjects who are in clinical response to ustekinumab, who are randomized to continue treatment with ustekinumab compared with subjects who are withdrawn from therapy and receive placebo.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

3.2.9. Dose Rationale

Ustekinumab has not been studied in UC. However, considering the similarities in the genetics and biology of UC and Crohn's disease, it is reasonable to assume that ustekinumab will also be effective in UC. The doses selected for this Phase 3 protocol for ustekinumab in subjects with UC parallel those being studied in the Phase 3 program for ustekinumab in subjects with Crohn's disease.

3.2.9.1. Induction

Intravenous administration was chosen for the induction studies in the ustekinumab Crohn's disease program because the evaluation of biomarker changes in response to ustekinumab treatment in the Phase 2a ustekinumab study (C0379T07) suggested a very rapid onset of action after IV administration that was not observed after SC administration.

The specific IV doses selected for the Phase 3 induction studies in the ustekinumab Crohn's disease program were based on the results of the Phase 2b ustekinumab study (C0743T26). Greater proportions of subjects in the ustekinumab 1 mg/kg, 3 mg/kg, and 6 mg/kg treatment groups were in clinical response at Week 6 (36.6%, 34.1%, and 39.7%, respectively) and at Week 8 (32.1%, 31.8%, and 43.5%, respectively) compared with placebo (23.5% and 17.4% at Weeks 6 and 8, respectively). However, in the 1 mg/kg group, serum ustekinumab concentrations through Week 8 appeared lower in nonresponders compared with responders at Week 6; this difference between responders and nonresponders was not apparent in the 3 mg/kg or the 6 mg/kg treatment groups. Furthermore, subjects in the 1 mg/kg treatment group appeared to lose response earlier than those in the 3 mg/kg or 6 mg/kg treatment groups, suggesting that some subjects in the 1 mg/kg group may not have had sufficient drug exposure to achieve or maintain clinical response through 8 weeks.

Accordingly, it was determined that a single 6 mg/kg IV dose (which was well tolerated and was the most effective induction dose in C0743T26), along with a lower dose (which would be higher than 1 mg/kg), would be evaluated in the Phase 3 Crohn's disease studies. In addition, an approach was adopted that allowed the use of complete vials, resulting in simpler drug administration. Based on these considerations, a ustekinumab 130 mg IV fixed dose (approximately 2 mg/kg on a milligram per kilogram basis) was chosen for the low-dose arm, while weight-range-based doses approximating 6 mg/kg IV (<55 kg: 260 mg ustekinumab; 55-90 kg: 390 mg ustekinumab; >90 kg: 520 mg ustekinumab) were chosen as the high-dose arm in the Phase 3 Crohn's disease studies and will be used in this induction study of ustekinumab in UC.

3.2.9.2. Maintenance

The two SC ustekinumab regimens planned for the UC maintenance study are the same as those being used in the Phase 3 maintenance study in the ustekinumab Crohn's disease program, which were chosen based on data from the Phase 2b study in Crohn's. The ustekinumab 90 mg SC q8w regimen was selected because it was considered safe and effective in achieving remission at Week 22 among subjects randomized as responders to ustekinumab induction. To explore a lower dose regimen, the ustekinumab 90 mg SC every 12 weeks (q12w) regimen was included because it was the next lower dose regimen that had been studied extensively in psoriasis and was thought likely to succeed in maintaining clinical efficacy over time in patients with Crohn's disease. These maintenance doses provided systemic exposures that were likely to meet the safety and efficacy objectives for the development of ustekinumab in Crohn's disease.

Similarly, the dose adjustment planned for the LTE is based on the strategy for dose adjustment in the Phase 3 Crohn's disease maintenance study. Subjects randomized to receive ustekinumab 90 mg SC q12w who subsequently lose clinical response in that study can be dose adjusted to the more frequent q8w dose regimen (shown to be effective in the Phase 2b study).

4. SUBJECT POPULATION

A target of 951 subjects will be randomized in the induction study so that approximately 327 subjects will be randomized in the maintenance study.

Screening for eligible subjects will be performed within 8 weeks before study agent administration in the induction study. Inclusion and exclusion criteria are described in the following subsections. For questions about inclusion or exclusion criteria, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the induction study:

1. Be a man or woman 18 years of age or older.
2. Has a clinical diagnosis of UC at least 3 months before screening.
3. Has moderately to severely active UC, defined as a baseline (Week 0) Mayo score of 6 to 12, inclusive, using the Mayo endoscopy subscore assigned during the central reading of the video endoscopy.
4. Has a screening endoscopy with ≥2 endoscopy subscore of the Mayo score as determined by a central reading of the video endoscopy.
5. Have failed biologic therapy, ie, have received treatment with 1 or more TNF antagonists or vedolizumab at a dose approved for the treatment of UC, **and** have a documented history of failure to respond to or tolerate such treatment; Attachment 1);

   OR

Be naïve to biologic therapy (ie, TNF antagonists or vedolizumab) or not have demonstrated a history of failure to respond to, or tolerate, a biologic therapy (Attachment 1) **and** have a prior or current UC medication history that includes at least 1 of the following:

a. Inadequate response to or failure to tolerate current treatment with oral corticosteroids or immunomodulators (6-MP or AZA) (Attachment 2).

OR

b. History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA) (Attachment 2).

OR

c. History of corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of UC; Attachment 2).

6. Before the first administration of study agent, the following conditions must be met:

a. If receiving conventional immunomodulators (ie, AZA, 6-MP, or MTX), must have been taking them for ≥12 weeks, and on a stable dose for at least 4 weeks.

b. If AZA, 6-MP, or MTX has been recently discontinued, it must have been stopped for at least 4 weeks.

c. If receiving oral 5-ASA compounds, the dose must have been stable for at least 2 weeks.

d. If receiving oral corticosteroids other than budesonide or beclomethasone, the dose must be ≤20 mg/day prednisone or its equivalent and must have been stable for at least 2 weeks.

e. *Criterion modified per Amendment 2.*

e.1 If receiving budesonide or beclomethasone dipropionate, the dose must have been stable for at least 2 weeks.

f. *Criterion modified per Amendment 2.*

f.1 If oral 5-ASA compounds or oral corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks.

7. The following medications/therapies must have been discontinued before first administration of study agent:

a. Vedolizumab for at least 4 months.

b. *Criterion modified per Amendment 2.*

b.1 TNF-antagonist therapy (eg, infliximab, etanercept, certolizumab, adalimumab, golimumab [or approved biosimilars for these therapies]) for at least 8 weeks.

c. Cyclosporine, tacrolimus, or sirolimus, for at least 4 weeks.

d. 6-thioguanine (6-TG) must have been discontinued for at least 4 weeks.

e. *Criterion modified per Amendment 2.*

e.1 Rectal corticosteroids (ie, corticosteroids administered to the rectum or sigmoid colon via foam or enema or suppository) for at least 2 weeks.

f. Rectal 5-ASA compounds (ie, 5-ASAs administered to the rectum or sigmoid colon via foam or enema or suppository) for at least 2 weeks.

g. Parenteral corticosteroids for at least 2 weeks.

h. Total parenteral nutrition (TPN) for at least 2 weeks.

i. Antibiotics for the treatment of UC (eg, ciprofloxacin, metronidazole, or rifaximin) for at least 2 weeks.

8. *Criterion modified per Amendment 2.*

   8.1 A subject ≥45 years of age must either have had a full colonoscopy to assess for the presence of adenomatous polyps within 5 years before the first administration of study agent or a full colonoscopy to assess for the presence of adenomatous polyps at the screening visit. The adenomatous polyps must be removed before the first administration of study agent.

9. *Criterion modified per Amendment 2.*

   9.1 A subject who has had extensive colitis for ≥8 years, or disease limited to the left side of the colon for ≥10 years, must either have had a full colonoscopy to assess for the presence of dysplasia within 1 year before the first administration of study agent or a full colonoscopy to assess for the presence of malignancy at the screening visit.

10. Is considered eligible according to the following tuberculosis (TB) screening criteria:

    a. Has no history of latent or active TB before screening. An exception is made for subjects who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB before the first administration of study agent, or have documentation of having completed appropriate treatment for latent TB within 3 years before the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculous treatment and provide appropriate documentation.

    b. Has no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

    c. Has had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first administration of study agent.

    d. Within 2 months before the first administration of study agent, has a negative QuantiFERON-TB Gold test result (Attachment 3), or has a newly identified positive QuantiFERON-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study agent. Within 2 months before the first administration of study agent, a negative tuberculin skin test (Attachment 4), or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study agent, is additionally required if the QuantiFERON-TB Gold test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities. A tuberculin skin test is recommended but not required for study centers in Ukraine if tuberculin is not available.

A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated (Section 9.1.2). In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject may be enrolled without treatment for latent TB, if active TB is ruled out, his/her chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

The QuantiFERON-TB Gold test and tuberculin skin test are not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; subjects with documentation of having completed adequate treatment as described above **are not** required to initiate additional treatment for latent TB.

e. Has a chest radiograph (posterior-anterior view), taken within 3 months before the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

11. Before randomization, a woman must be either:

a. Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle-stimulating hormone level >40 IU/L); permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy.

OR

b. Of childbearing potential: if heterosexually active, must be practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

Note: If the subject's childbearing potential changes after the start of the study (eg, a woman who is not heterosexually active becomes active, a premenarchal woman experiences menarche), that subject must begin practicing a highly effective method of birth control as described above.

12. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin) pregnancy test result at screening and a negative urine pregnancy test result at Week 0.

13. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 20 weeks after the last study agent administration.

14. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; all men must also agree not to donate sperm during the study and for 20 weeks after receiving the last administration of study agent.
15. Has screening laboratory test results within the following parameters:
    a. Hemoglobin ≥8.0 g/dL (SI: ≥80.0 g/L)
    b. White blood cell count (WBC) $\geq 3 \times 10^3$ cells/μL (SI: $\geq 3.0 \times 10^9$ cells/L)
    c. Neutrophils $\geq 1.5 \times 10^3$ cells/μL (SI: $\geq 1.5 \times 10^9$ cells/L)
    d. Platelets $\geq 100 \times 10^3$ cells/μL (SI: $\geq 100 \times 10^9$ cells/L)
    e. Serum creatinine ≤1.5 mg/dL (SI: ≤133 μmol/L)
    f. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations must be within 2 times the upper limit of the normal range (ULN) for the laboratory conducting the test.
16. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
17. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the subject and his or her legally acceptable representative.
18. Each subject must sign a separate ICF if he or she agrees to provide optional DNA samples for research where local regulations permit. (In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the subject and his or her legally acceptable representative.) Refusal to give consent for the optional DNA samples does not exclude a subject from participation in the study.

4.2. Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participating in the induction study:

1. Has severe extensive colitis as evidenced by:
    a. Current hospitalization for the treatment of UC.

    OR

    b. Investigator judgment that the subject is likely to require a colectomy within 12 weeks of baseline.

    OR

c. Symptom complex at screening or baseline visits that includes at least 4 of the following:

1) Diarrhea with ≥6 bowel movements/day with macroscopic blood in stool

2) Focal severe or rebound abdominal tenderness

3) Persistent fever (≥37.5°C)

4) Tachycardia (>90 beats/minute)

5) Anemia (hemoglobin <8.5 g/dL)

2. Has UC limited to the rectum only or to <20 cm of the colon.

3. Presence of a stoma.

4. Presence or history of a fistula.

5. Require, or required within the 2 months before screening, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage, or other conditions possibly confounding the evaluation of benefit from study agent treatment.

6. Presence of symptomatic colonic or small bowel obstruction, confirmed by objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon or small bowel proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy).

7. History of extensive colonic resection (eg, less than 30 cm of colon remaining) that would prevent adequate evaluation of the effect of study agent on clinical disease activity.

8. History of colonic mucosal dysplasia. Subjects will not be excluded from the study because of a pathology finding of "indefinite dysplasia with reactive atypia."

9. Presence on screening endoscopy of adenomatous colonic polyps, if not removed before study entry, or history of adenomatous colonic polyps that were not removed.

10. Diagnosis of indeterminate colitis, microscopic colitis, ischemic colitis, or Crohn's disease or clinical findings suggestive of Crohn's disease.

11. Has a stool culture or other examination positive for an enteric pathogen, including *Clostridium difficile* toxin, in the previous 4 months, unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.

Concomitant or previous medical therapies received:

12. Has received the following concomitant or previous medical therapies:

a. A biologic therapy targeted at IL-12 and/or IL-23 (eg, ustekinumab, briakinumab, guselkumab).

b. Natalizumab within 12 months of first study agent administration.

c. Agents that deplete B or T cells (eg, rituximab, alemtuzumab) within 12 months of first study agent administration, or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte-depleting agents.

d. Any investigational drug within 4 weeks before first administration of study agent or within 5 half-lives of the investigational agent, whichever is longer.

e. *Criterion modified per Amendment 2*.

e.1 Apheresis (eg, Adacolumn or Cellsorba apheresis) within 2 weeks before the first administration of study agent.

Infections or predisposition to infections:

13. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criterion 10 for information regarding eligibility with a history of latent TB.

14. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis, recurrent cystitis), an open, draining, or infected skin wound, or an ulcer.

15. Has a chest radiograph within 3 months before the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB.

16. Have a history of being human immunodeficiency virus (HIV) antibody-positive, or tests positive for HIV at screening.

17. *Criterion modified per Amendment 2*.

17.1 Are seropositive for antibodies to hepatitis C virus (HCV) without a history of successful treatment, defined as being negative for HCV RNA at least 24 weeks after completing antiviral treatment.

18. Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), and HBV core antibody (anti-HBc) total:

a. Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) **are eligible** for this study.

b. Subjects who test positive for surface antigen (HBsAg+) **are not eligible** for this study, regardless of the results of other hepatitis B tests.

c. Subjects who test negative for surface antigen (HBsAg-) and test positive for core antibody (anti-HBc+) and surface antibody (anti-HBs+) **are eligible** for this study.

d. Subjects who test positive only for surface antibody (anti-HBs+) **are eligible** for this study.

e. Subjects who test positive only for core antibody (anti-HBc+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is positive, the subject **is not eligible** for this study. If the HBV DNA test is negative, the subject **is eligibl**e for this study. In the event the HBV DNA test cannot be performed, the subject **is not eligible** for this study.

Note: For subjects who **are not eligible** for this study due to HIV, HCV, and HBV test results, consultation with a physician with expertise in the treatment of those infections is recommended.

19. Has had a Bacille Calmette-Guerin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks before baseline.
20. Has or has ever had a nontuberculous mycobacterial infection or serious opportunistic infection (eg, cytomegalovirus colitis, *Pneumocystis carinii*, aspergillosis).
21. Has had a serious infection (eg, hepatitis, pneumonia, or pyelonephritis), has been hospitalized for an infection, or has been treated with parenteral antibiotics for an infection within 2 months before first administration of study agent. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.
22. Has evidence of a herpes zoster infection ≤8 weeks before baseline.

Malignancy or increased potential for malignancy:

23. Has any known malignancy or has a history of malignancy (with the exception of basal cell carcinoma; squamous cell carcinoma in situ of the skin; or cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years before screening).
24. Presence or history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic areas), or clinically significant hepatomegaly or splenomegaly, or monoclonal gammopathy of undetermined significance.

Coexisting medical conditions or past medical history:

25. Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients (refer to the ustekinumab IB).
26. Has severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease, or signs or symptoms thereof.
27. Has a transplanted organ (with the exception of a corneal transplant performed >12 weeks before screening).
28. Has previously undergone allergy immunotherapy for prevention of anaphylactic reactions.
29. *Criterion modified per Amendment 2*.

    29.1 Has a history of drug or alcohol abuse according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-V), within 1 year before screening.

30. Has poor tolerability of venipuncture or lacks adequate venous access for required blood sample collections during the study period.
31. Is a woman who is pregnant, or breast-feeding, or planning to become pregnant, or is a man who plans to father a child while enrolled in this study or within 20 weeks after the last dose of study agent.
32. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

General:

33. Is currently participating or intends to participate in any other study using an investigational agent or procedure during participation in this study.
34. Employees of the investigator or study site with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study agent is given, such that the subject no longer meets all eligibility criteria, that subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Must agree not to receive a live virus or live bacterial vaccination, including a BCG vaccination, during the study and for 12 months after receiving study agent for BCG vaccination or 20 weeks after receiving the last administration of study agent for other live vaccines.
2. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (as described in Inclusion Criterion 11b) during the study and for 20 weeks after receiving the last administration of study agent.
3. A woman must agree not to donate eggs (ie, ova, oocytes) for the purposes of assisted reproduction during the study and for 20 weeks after receiving the last administration of study agent.
4. A man who is sexually active with a woman of childbearing potential and who is not surgically sterile must agree to use a barrier method of birth control (as described in Inclusion Criterion 14) during the study and for 20 weeks after receiving the last administration of study agent.
5. All male subjects must also agree not to donate sperm during the study and for 20 weeks after receiving the last administration of study agent.
6. Subjects who require treatment for latent TB must complete the appropriate course of TB therapy.

A complete list of prohibited therapies is provided in Section 8.

5. TREATMENT ALLOCATION AND BLINDING

Central randomization for treatment allocation will be implemented in the induction and maintenance studies. A computer-generated randomization schedule will be prepared for each study under the supervision of the sponsor.

In the induction study, subjects will be randomized at Week 0 to 1 of 3 treatment groups (placebo IV, ustekinumab 130 mg IV, or ustekinumab ~6 mg/kg IV) using permuted block randomization with biologic failure status (yes/no) and region (Eastern Europe, Asia, or rest of world) as stratification variables. At Week 8, subjects who are not in clinical response will be assigned to treatment and matching placebo, as described in Section 3.1.1. To maintain the blind, both IV and SC administrations will be given to these subjects.

In the maintenance study, subjects in the primary population will be randomized to 1 of 3 treatment groups (placebo SC, ustekinumab 90 mg SC q8w, or ustekinumab 90 mg SC q12w) using a permuted block randomization with clinical remission status at maintenance baseline (yes/no), oral corticosteroid use at maintenance baseline (yes/no), and induction treatment (placebo IV → ustekinumab ~6 mg/kg IV, ustekinumab 130 mg IV, or ustekinumab ~6 mg/kg IV) as stratification variables. Other subject populations will not be randomized, but will be assigned to treatment as described in Section 3.1.2. All subjects will receive their assigned dose of SC study agent at the M-0 visit. Thereafter, to maintain the blind, all subjects will receive study agent at all scheduled study agent administration visits specified in Table 2.

At each call to the IWRS for a treatment assignment, the IWRS will assign a treatment code that will dictate the treatment assignment and matching study agent kit for each subject. The requestor must use his or her own personal identification number when contacting the IWRS.

Blinding

To maintain the study blind, the study agent container will have a label containing the study name, medication number, and reference number. A tear-off label is designed to be torn off, separated from the study agent container, and attached to the subject's source documents. The label will not identify the study agent in the container. The medication number will be entered in the case report form (CRF) when the drug is dispensed. The study agents will be identical in appearance and packaging.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, study agent serum concentrations, antibodies to study agent) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the study unblinding.

The postbaseline results of CRP, fecal lactoferrin, and fecal calprotectin tests performed by the central laboratory will be blinded to the investigative sites. If an investigative site requests these data, it will be provided to them after the Week 44 analyses for the maintenance study have been completed.

Treatment assignment blinding will be maintained for investigative sites, site monitors, and subjects participating in this protocol until the Week 44 analyses for the maintenance study have been completed.

In the induction study, at the first DBL for the futility analysis, the induction treatment assignment information will be unblinded for the first 30% of randomized subjects in the study and released for analysis to an external statistical support group (the sponsor will remain blinded). The induction treatment assignment for the remaining subjects and the maintenance treatment assignment information for all subjects will remain blinded at that time. Further details about unblinding for the futility analysis will be provided in the Interim Analysis Plan (IAP). At the second DBL when all randomized subjects in the induction study have either completed the I-8 visit or have terminated study participation before Week 8, the induction treatment assignment information will be unblinded for all subjects and released to selected sponsor personnel for analysis. The maintenance treatment assignment information for all subjects will remain blinded at that time. At the third DBL when all randomized subjects in the induction study have entered the maintenance study, or have completed their final safety visit (20 weeks after the last administration of study agent) for those not participating in the maintenance study, or have terminated their study participation, data will be released to selected sponsor personnel for analysis. The maintenance treatment assignment information for all subjects will continue to remain blinded at that time. Identification of sponsor personnel who will have access to the unblinded subject-level data at the time of each DBL will be documented before unblinding.

The sponsor will be blinded to maintenance treatment assignment until after the Week 44 database lock has occurred.

Under normal circumstances, the blind should not be broken until the Week 44 analyses of the maintenance study have been completed and the databases for the induction and maintenance studies are finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event that the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the CRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Additionally, a given subject’s treatment assignment may be unblinded to the sponsor, the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and site personnel to fulfill regulatory reporting requirements for serious unexpected associated adverse reactions (SUAs). If a subject is unblinded by the site, the information must be entered in the appropriate section of the CRF and in the subject's source documents.

Subjects who have had their treatment assignment unblinded by the investigator will not be eligible to receive further study agent, but should complete evaluations specified in the appropriate Time and Events Schedule for subjects who discontinue study agent (Section 10.2).

A separate code-break procedure will be available for use by J&J Global Medical Safety group to allow for unblinding of individual subjects to comply with specific requests from regulatory or health authorities.

6. DOSAGE AND ADMINISTRATION

6.1. Induction Study

Subjects in the induction study will receive a single IV administration of study agent (placebo or ustekinumab) at Week 0. Intravenous study agent will be administered to each subject over a period of not less than 1 hour. The infusion should be completed within 4 hours of preparation of the study agent. Detailed instructions about study agent administration are provided in the investigational product manual.

As described in Section 3.1.1, subjects who are not in clinical response at Week 8 will receive an additional dose of study agent at Week 8. This additional administration will include both IV and SC study agent to maintain the blind; SC study agent is described in Section 14.1.

6.2. Maintenance Study

Subjects in the maintenance study will receive SC study agent (placebo or ustekinumab) at Week 0 and q8w or q12w thereafter, according to their assigned treatment (eg, randomization).

7. TREATMENT COMPLIANCE

In the induction study, study agent will be administered as an IV infusion or SC injection (Week 8 only) by qualified staff. The details of each administration will be recorded in the CRF, including date, start and stop times of the IV infusion and volume infused, or date and time of SC injection.

In the maintenance study, study agent will be administered as an SC injection by qualified staff. The details of each administration will be recorded in the CRF, including date and time of injection.

8. PRESTUDY AND CONCOMITANT THERAPY

For all randomized subjects in the induction study, prestudy therapies administered up to 30 days before the first dose of study agent must be recorded in the CRF.

Concomitant therapies must be recorded throughout the study, beginning with the start of the first administration of study agent to the last study visit.

All therapies (eg, prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study agent must be recorded in the CRF.

Recorded information will include a description of the type of therapy, treatment period, dosage, route of administration, and its indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

8.1.1. Induction Study

The following medical therapies for UC **may not be initiated or have the dose increased** during the induction study:

- Oral 5-ASA compounds (eg, sulfasalazine, mesalamine, olsalazine, balsalazide).
- Oral corticosteroids.
- 6-MP, AZA, or MTX.

Subjects who are receiving any of these therapies for UC at the time of the first administration of study agent **must keep their prescribed dosage stable** throughout the induction study **and** the therapy can only be discontinued or reduced in dose if investigator judgment requires it because of toxicity or other medical necessity; even if the toxicity resolves, the therapy should not be restarted.

Subjects who initiate or increase the dose of these UC medications will not be eligible for entry into the maintenance study.

Laxatives may be used only in preparation for endoscopy or other procedures.

8.1.1.1. Restricted or Prohibited Medications/Therapies

Medications/therapies that may confound the assessment of efficacy or safety are not permitted during the induction study. Subjects who initiate these medications after randomization in the induction study will be precluded from entering the maintenance study.

8.1.1.1.1. Restricted Medications/Therapies

Subjects who initiate the following treatments will complete all protocol-specified visits.

- Rectal corticosteroids (ie, corticosteroids administered to the rectum or sigmoid colon via foam, enema, or suppository).
- Rectal 5-ASA compounds (ie, 5-ASA compounds administered to the rectum or sigmoid colon via foam, enema, or suppository).
- Parenteral corticosteroids.
- TPN.
- Antibiotics used to treat UC (including, but not limited to, ciprofloxacin, metronidazole, or rifaximin).
- Apheresis.

8.1.1.1.2. Prohibited Medications/Therapies

Subjects who initiate the following treatments will be discontinued from further study agent administration and should have a final safety follow-up visit approximately 20 weeks after their last study agent administration.

- Immunomodulatory agents other than 6-MP, AZA, or MTX (including, but not limited to, 6-TG, cyclosporine, mycophenolate mofetil [MMF], tacrolimus, sirolimus, tofacitinib, and other JAK inhibitors).
- Immunomodulatory biologic agents (including, but not limited to, TNF antagonists, natalizumab, abatacept, vedolizumab).
- A biologic therapy targeted at IL-12 and/or IL-23 (eg, commercial ustekinumab, briakinumab, guselkumab).
- Investigational drugs.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1.2. Maintenance Study

Concomitant medical therapy for UC must have been stable from Week 0 of the induction study through Week 0 of the maintenance study unless, in the judgment of the investigator, the therapy had to be discontinued or reduced in dose because of toxicity or medical necessity; even if the toxicity resolves, the therapy should not have been restarted.

Laxatives may be used only in preparation for endoscopy or other procedures.

8.1.2.1. Rescue Medication on Loss of Response

Any initiation of, or increase in the dose of, a medical therapy for UC (ie, corticosteroids, 6-MP, AZA, MTX, and/or 5-ASAs) that is required to treat a loss of response is considered a rescue medication. Prohibited medications (Section 8.1.1.1.2) cannot be used as rescue medication.

8.1.2.2. Oral 5-ASA Compounds and Immunomodulators

The following UC-specific medical therapies **should not be initiated or have the dose increased** during the maintenance study, unless these therapies are used as rescue medication for loss of response (Section 3.1.2.1):

- Oral 5-ASA compounds (eg, sulfasalazine, mesalamine, olsalazine, balsalazide)
- 6-MP, AZA, or MTX

Subjects who were receiving any of these medical therapies for UC at the time of entry into the maintenance study and do not lose response **must keep their prescribed dosage stable** through completion of the Week 44 assessments in the maintenance study unless investigator judgment requires discontinuation or dose reduction because of toxicity or other medical necessity; even if the toxicity resolves, the therapy should not be restarted.

8.1.2.3. Corticosteroids

Oral corticosteroids for UC **should not be initiated or have the dose increased** during the maintenance study, unless corticosteroids are used as rescue medication for loss of response (Section 3.1.2.1).

For subjects who are receiving oral corticosteroids on entry into the maintenance study, the investigator should begin tapering the daily dose of corticosteroids beginning at Week 0 of the maintenance study.

An increase in corticosteroid dose above the dose received at maintenance baseline for subjects who underwent or are undergoing corticosteroid tapering and lost clinical response will be considered a rescue medication. Tapering of corticosteroids used as rescue medications must begin 2 weeks after the change in corticosteroid therapy.

Recommended tapering schedule for oral prednisone-equivalent corticosteroids:

- Subjects receiving >20 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until 0 mg/day.
- Subjects receiving ≤20 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

Tapering of budesonide or beclomethasone dipropionate should follow local clinical practice.

Subjects may transiently (ie, for ≤4 weeks) use increased doses of corticosteroids **for reasons other than** loss of response (eg, stress doses of corticosteroids for surgery, asthma flare, adrenocortical insufficiency).

8.1.2.4. Restricted or Prohibited Medications/Therapies

Restricted medications or therapies that are not permitted during the induction study (listed in Section 8.1.1.1) are also not permitted during the first 44 weeks of the maintenance study, unless the following therapies are used as rescue medication on loss of response (Section 3.1.2.1): parenteral or rectal corticosteroids and/or rectal 5-ASAs.

Subjects who initiate prohibited medications or therapies (Section 8.1.1.1.2) during the maintenance study or the LTE are required to discontinue study agent during the maintenance study or the LTE. Prohibited therapies cannot be used as rescue medications.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

Informed consent must be obtained before any study-related procedures are performed in the induction study. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by both the subject and his or her legally acceptable representative.

The Time and Events Schedules summarize the frequency and timing of efficacy, PK, immunogenicity, biomarker, DNA, PRO, medical resource utilization, health economics, and safety measurements applicable to this study.

All assessments are to be completed before study agent administration, unless otherwise specified. It is recommended that PRO assessments be completed first.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the CNTO1275UCO3001 study.

In the induction study, the total blood volume to be collected from each subject is approximately 134.5 mL, including the safety follow-up visit, but not including DNA samples (approximately 48 mL), which are optional.

In the maintenance study, the total blood volume to be collected from each subject is approximately 156.5 mL. This does not include DNA samples (approximately 24 mL), which are optional, or an early termination visit, the total blood volume for which would be approximately 12.0 mL (2.5 mL chemistry, 2.0 mL hematology, 7.5 mL PK and immunogenicity samples).

In the LTE, the total blood volume to be collected from each subject is approximately 118.5 mL, including the final efficacy and safety visits.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

After written informed consent has been obtained and within 8 weeks before randomization, all screening evaluations (eg, laboratory test results, clinical data, and concomitant medication data) that establish subject eligibility will be performed by the principal investigator or designee to confirm that the subject satisfies all inclusion criteria and does not violate any exclusion criteria. Subjects who meet all of the inclusion and none of the exclusion criteria can be enrolled in the induction study. Every effort should be made to adhere to the Time and Events Schedules for each subject. The collection of AEs will start at the time informed consent is obtained.

Mayo diaries will be provided to each subject to record concomitant medications, stool production, and episodes of rectal bleeding. A Mayo diary will be completed from recall at screening and will be used to calculate a partial Mayo score (Section 9.2.1) to assess the subject's eligibility for further screening and to train the subject on the use of the diary card. Subjects with a partial Mayo score ≥3 can proceed with endoscopy.

Bristol Stool Form Scale diaries will also be provided to subjects to classify the form (or consistency) of their stools during the induction study (Section 9.2.1).

Subjects will be instructed to complete Mayo diary cards and Bristol Stool Form Scale diaries 7 days immediately before each visit and bring them to every visit for data collection and review by the investigator/study coordinator. Bristol Stool Form Scale diaries are required only during the induction study.

The screening endoscopy must be performed within 2 weeks (and at least 4 days) before the induction Week 0/baseline (I-0) visit. Subjects who are identified as being at increased risk for colon cancer (Inclusion Criterion 9) or for adenomatous polyps (Inclusion Criterion 8) will undergo a full colonoscopy instead of a sigmoidoscopy to allow screening for dysplasia or to assess for the presence of adenomatous polyps, respectively. Any screening colonoscopy for malignancy should include surveillance biopsies consistent with local practice. At least 48 hours must elapse between a colonoscopy with polypectomy and the I-0 visit.

Women of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at the I-0 visit. Sexually active subjects must consent to use a highly effective method of birth control, as specified in Inclusion Criterion 11, and continue to use contraception for the duration of the study and for 20 weeks after the last study agent administration. The method(s) of contraception used by each subject must be documented.

Subjects must undergo testing for TB (Attachment 3 and Attachment 4) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON-TB Gold test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with prerandomization procedures. A tuberculin skin test is recommended but not required for study centers in Ukraine if tuberculin is not available. Subjects with a newly identified positive QuantiFERON-TB Gold (or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed, or the subject will be excluded from the study.

A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject may be enrolled without treatment for latent TB, if active TB is ruled out, his/her chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

A subject with clinical laboratory test results outside the normal reference ranges may be enrolled only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator. ·

Note: Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening phase.

If a subject needs to be rescreened, this should be discussed with the sponsor and/or designee. If a subject is a screen failure but at some point in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on 1 occasion only after consultation with the sponsor. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then start a new screening phase.

Completion of screening and randomization procedures within the specified 8-week window is required. If the subject is approaching the completion of that period, the medical monitor can be contacted to discuss eligibility.

If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph, stool analysis), the subject will be considered a screen failure because he/she will not meet eligibility criteria, and the expired assessments (along with the non-time-specific laboratory tests) will have to be repeated on rescreening.

9.1.3. Induction Study

Subjects will be randomized in a 1:1:1 ratio and receive their assigned IV dose of ustekinumab or placebo at the I-0 visit. Procedures to be performed at each visit during the induction study are outlined in the Time and Events Schedule (Table 1). All procedures are to be conducted before administration of study agent, unless otherwise specified. It is recommended that PRO assessments be completed first.

Visit dates are based on the subject's original randomization date. The visit window for the I-2 and I-4 visits is the day of the scheduled visit **±4 days (ie, plus or minus 4 days)**; for the I-8 and I-16 visits, the visit window is the day of the scheduled visit **+3 days (ie, plus 3 days)**.

At Week 8, all subjects will be evaluated for the primary endpoint of clinical remission (Section 9.2.2.4) and for clinical response (Section 9.2.2.4). Further study agent administration will be determined by clinical response status (using the Mayo endoscopy subscore assigned by the local endoscopist) at Week 8.

Subjects who are in clinical response at Week 8 are eligible to enter the maintenance study as discussed in Section 3.1.1 and shown in Figure 3. Subjects who are not in clinical response at Week 8 will receive an administration of ustekinumab and be re-evaluated for clinical response status at Week 16. Those who achieve clinical response at Week 16 (using the Mayo endoscopy subscore assigned by the local endoscopist) are eligible to enter the maintenance study; those who do not achieve clinical response at Week 16 will not be eligible to enter the maintenance study and will receive no further study agent administration. These subjects will have a safety follow-up visit approximately 20 weeks after their last study agent administration.

Subjects who discontinue study agent before or at the I-8 visit should complete the I-8 assessments at the time of discontinuation and a safety follow-up visit approximately 20 weeks after their last study agent administration, as specified in the Time and Events Schedule (Table 1). After Week 8, subjects who do not wish to continue into the maintenance study, but are willing to complete their participation in the induction study, should complete the I-16 assessments at the time of discontinuation, and a safety follow-up visit approximately 20 weeks after their last study agent administration.

Subjects who terminate study participation before or at the I-8 visit should complete the I-8 assessments at the time of study termination (as specified in the Time and Events Schedule [Table 1]). Subjects who terminate study participation after the I-8 visit but before or at the I-16 visit should complete the I-16 assessments at the time of study termination (as specified in the Time and Events Schedule [Table 1]).

Study agent should not be administered at Week 0 (or Week 8) to any subject with a clinically important, active infection.

9.1.4. Maintenance Study

All subjects enrolled in the maintenance study will be responders to study agent administered in the induction study (ie, have received study agent at Week 0 in the induction study and been in clinical response at Week 8, or at Week 16 in subjects who were not responders at Week 8). **Subjects who initiated or increased their dose of UC medications (ie, oral 5-ASAs, oral corticosteroids, or the immunomodulators AZA, 6-MP, or MTX) or initiated a restricted or prohibited medication during the induction study are not eligible to enter maintenance.**

Subjects who were in clinical response to IV ustekinumab induction will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups for the maintenance study, as discussed in Section 3.1.2 and shown in Figure 4; these subjects will comprise the primary population for analysis. Additional subjects entering the maintenance study will include those who were in clinical response to IV placebo induction and those who were delayed responders to ustekinumab induction.

All subjects will receive study agent at the M-0 visit. Thereafter to maintain the blind, all subjects will receive study agent at all scheduled study agent administration visits specified in Table 2.

Assessments will be performed as indicated in the Time and Events Schedule (Table 2). All assessments are to be completed before any study agent administration, unless otherwise specified. It is recommended that PRO assessments be completed first.

To enroll in the maintenance study, a subject must be able to complete the M-0 visit within 4 days after the I-8 or I-16 visit. At the discretion of the investigator, the window may be extended to 8 days to allow for appropriate treatment of and/or recovery from nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection). The window for other visits during the maintenance study is ±10 days.

Subjects will be evaluated for efficacy and safety through Week 44. Subjects should return for efficacy and/or safety evaluations at each timepoint, including evaluations at Week 44. Following any final visit in which a blood sample is collected, subjects may be contacted by study site personnel within 3 days to record any AEs that occurred within 24 hours of that blood sample collection and were related to it.

Subjects who discontinue study agent administration before the M-44 visit should undergo the procedures for an early termination visit as specified in the Time and Events Schedule (Table 2), as well as a safety follow-up visit approximately 20 weeks after their last study agent administration. Subjects who terminate their study participation should undergo the procedures for an early termination visit as specified in the Time and Events Schedule (Table 2).

Study agent should not be administered at any visit during the maintenance study to a subject with a clinically important, active infection.

9.1.4.1. Management of Clinical Flare and Loss of Response

Subjects who meet the following criteria will be considered to have a clinical flare:

- an increase from maintenance baseline in the partial Mayo score of at least 2 points with an absolute partial Mayo score ≥4;

  OR

- an absolute partial Mayo score ≥7 points.

Subjects who meet the criteria for clinical flare and who have not previously met the criteria for loss of clinical response in the maintenance study (ie, are in clinical flare for the first time or have flared previously and not met the criteria for loss of response) should undergo an endoscopy to assess the Mayo endoscopy subscore, as well as the safety and efficacy evaluations specified for the M-44 visit (Table 2) during their scheduled visit or at any unscheduled visit. The endoscopy at the time of clinical flare need only be a sigmoidoscopy. The Mayo score should be calculated from the partial Mayo obtained at the assessment for clinical flare and the subsequent Mayo endoscopy subscore as assigned by the local endoscopist.

Subjects should maintain stable doses of their UC medications after meeting clinical flare criteria and while waiting for their endoscopy score. However, rescue medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise subject safety while waiting for their endoscopy score.

Subjects with a clinical flare are eligible for rescue medication only if they meet the criteria for loss of response (ie, are no longer in clinical response relative to their induction baseline Mayo score).

Subjects who have a loss of response will be assessed 16 weeks after the visit at which the loss of clinical response criteria was met. During this interval, clinical flare criteria will not be applied. Subjects who have not achieved a partial Mayo response (ie, a decrease from induction baseline of ≥2 in the partial Mayo score) at 16 weeks after loss of response will be discontinued from study agent administration, and should return for a final safety visit approximately 20 weeks after their last study agent administration. Subjects who are assessed as being in partial Mayo response will continue in the study.

After the 16 weeks following loss of clinical response, subjects who remain in the study will continue to be assessed for clinical flare using the criteria based on the partial Mayo score. Subjects who subsequently meet the criteria for clinical flare again will not be required to undergo an endoscopy. These subjects will be eligible to receive rescue medication at the time of clinical flare and be assessed for partial Mayo response 16 weeks after the visit at which clinical flare was assessed and managed as noted above.

Subjects will be strongly encouraged to undergo endoscopy at the time of first clinical flare to establish if loss of clinical response criteria were met. A subject who declines to undergo an endoscopy on initial clinical flare will be assessed for partial Mayo response 16 weeks after the initial flare.

A subject who meets the criteria of clinical flare on more than 2 occasions during the maintenance study will be discontinued from study agent administration.

9.1.5. Long-Term Extension

Subjects who enter the LTE will continue with study agent injections every 8 or 12 weeks according to their dose regimen. To maintain the blind, study agent injections will be administered every 4 weeks, with the first dose administered at Week 48. After the study is unblinded to the investigative sites, subjects receiving placebo will be terminated from study participation and subjects receiving ustekinumab will continue to receive ustekinumab, but will have their study visits scheduled to coincide with their dose regimen (q8w or q12w, as appropriate, through Week 200).

Procedures will be performed monthly, every 3 months, or every 6 months, as indicated in the Time and Events Schedule (Table 3). Study visits after Week 44 (ie, in the LTE) may occur at the week indicated ±10 days.

The partial Mayo score will be assessed every 3 months during the LTE. The Mayo score (including an endoscopy) will be assessed at the final efficacy visit.

The final efficacy assessments will be performed at Week 200 and the final safety assessments will be performed at Week 220 (or approximately 20 weeks after a subject's last administration of study agent). Assessments will be performed as indicated in the Time and Events Schedule (Table 3).

Subjects who discontinue study agent administration during the LTE should undergo the procedures for a final efficacy visit as specified in the Time and Events Schedule (Table 3), as well as a safety follow-up visit approximately 20 weeks after their last study agent administration. Subjects who terminate their study participation during the LTE should undergo the procedures for a final efficacy visit as specified in the Time and Events Schedule (Table 3).

9.1.5.1. Dose Adjustment During the LTE

During the LTE, if a subject's UC disease activity worsens (in the investigator's judgment), the subject may be eligible for a dose adjustment, as described in Section 3.1.3. These subjects will be allowed 1 dose adjustment during the LTE. The IWRS will ensure that a subject is eligible for a dose adjustment and, if he or she is eligible, that SC ustekinumab is not administered more frequently than q8w. The first opportunity for dose adjustment in the LTE is at the Week 56 visit.

If, by 16 weeks after the worsening of a subject's UC disease activity, the subject has not shown an improvement in his or her UC disease activity (as assessed by the investigator), the subject should be discontinued from further study agent administration and complete the final efficacy and safety assessments indicated in the Time and Events Schedule (Table 3).

9.2. Efficacy

The Mayo score will be the primary tool for assessing disease activity response to ustekinumab. The degree of inflammation will be assessed by measuring serum CRP concentrations and fecal markers of inflammation (ie, lactoferrin and calprotectin). Subject well-being will be measured using the IBDQ, the SF-36, and the EQ-5D.

9.2.1. Evaluations

Efficacy evaluations will include the following:

- Mayo score and partial Mayo score.
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS)
- CRP
- Fecal lactoferrin and fecal calprotectin
- Bristol Stool Form Scale
- Inflammatory Bowel Disease Questionnaire (IBDQ)

- 36-item Short Form Health Survey (SF-36)
- EuroQoL-5D Health Questionnaire (EQ-5D)

The **Mayo score** (Attachment 5) was developed from the criteria of Truelove and Witts[34] for mild, moderate, and severe UC and from the criteria of Baron et al[3] for grading endoscopic appearance. The Mayo score is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, PGA, and endoscopy findings) and ranges from 0 to 12 points. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severe disease. The endoscopic findings will be assessed by the investigator (ie, local endoscopist) during the endoscopy procedure and by the central reader reviewing a video of the endoscopy. Subject eligibility at baseline will be based on the final reported endoscopic subscore as determined by the following process:

- If the local endoscopist and the central reader agree on the endoscopic subscore, the agreed score will be the final reported endoscopic subscore.
- If there is a discrepancy between the local endoscopist and the central reader subscores, the video endoscopy will be submitted to a second central reader (designated for adjudication). The median score of the 3 completed reads (ie, local read, central read 1, and central read 2 designated for adjudication) will be the final reported endoscopic subscore.

Specific details will be provided in the imaging charter. A subject's clinical response status at Week 8 (or Week 16) of the induction study, or loss of response status in the maintenance study, to determine subsequent treatment, will be based on the endoscopy subscore assigned by the local endoscopist.

Mayo scores are calculated using the following:

1. The stool frequency and rectal bleeding data from the most recent consecutive 3-day period within the 1 week before the visit. The average of the 3-day period will be used to calculate the stool frequency and rectal bleeding subscores for the visit. Days on which the following conditions are met should be excluded from the calculation:
   a. The day on which medications for constipation, diarrhea, or irregularity were taken. (For subjects maintained on a stable dose of bulking or stool-softening agents throughout the study, the days on which these agents are taken should not be excluded from consideration in calculating the Mayo score.)
   b. The day(s) of a procedure or preparation for a procedure (eg, enemas, other laxatives, a clear liquid diet) that would affect bowel frequency and/or blood content of the stool.
   c. The 48 hours after the use of antimotility agents (ie, diphenoxylate hydrochloride with atropine sulfate, loperamide, or other opioids).
   d. The 48 hours immediately following a colonoscopy.
2. The physician's global assessment.
3. The results of a sigmoidoscopy or colonoscopy.

The **partial Mayo score** is the Mayo score without the endoscopy subscore and ranges from 0 to 9 points.

If 1 or more of the 4 Mayo subscores is missing at a specific visit, but not all 4 subscores are missing, the last available value for each missing subscore will be carried forward to compute a full Mayo score and a partial Mayo score at that visit. If all 4 subscores are missing at a specific visit, the Mayo score and partial Mayo score will be considered missing at that visit.

The **UCEIS** is an index that provides an overall assessment of endoscopic severity of UC, based on mucosal vascular pattern, bleeding, and ulceration.[33] The score ranges from 3 to 11. The UCEIS score will be assessed only by the central video readers for all endoscopies.

C-reactive protein has been demonstrated to be useful as a marker of inflammation in patients with IBD. In UC, elevated CRP has been associated with severe clinical activity, an elevated sedimentation rate, and active disease as detected by colonoscopy. CRP will be assayed using a validated, high-sensitivity CRP assay.

Fecal lactoferrin and **fecal calprotectin** have been demonstrated to be sensitive and specific markers in identifying intestinal inflammation and response to treatment in patients with IBD.[7,9,21] Stool samples for fecal lactoferrin and calprotectin concentrations will be collected from all subjects at visits indicated in the Time and Events Schedules. Assays for fecal lactoferrin and calprotectin concentrations will be performed using a validated method. Additional tests may also be performed on the stool samples for additional markers related to intestinal inflammation and treatment response.

The **Bristol Stool Form Scale** is a medical aid to classify the form (or consistency) of human feces into 7 categories.[22] It has been used as a research tool to evaluate the effectiveness of treatments for various diseases of the bowel (eg, irritable bowel syndrome [IBS]).[12] The daily average of the same 3-day period used to calculate the stool frequency and rectal bleeding subscores of the Mayo score will be used to calculate the average Bristol Stool Form Scale score for the visit.

The **IBDQ**[18] is a 32-item questionnaire for subjects with IBD that will be used to evaluate the disease-specific health-related quality of life across 4 dimensional scores: bowel (loose stools, abdominal pain), systemic (fatigue, altered sleep pattern), social (work attendance, need to cancel social events), and emotional (anger, depression, irritability).

The **SF-36** was developed as part of the Rand Health Insurance Experiment and consists of 8 multi-item scales: limitations in physical functioning due to health problems; limitations in usual role activities due to physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities due to personal or emotional problems; limitations in social functioning due to physical or mental health problems; vitality (energy and fatigue); and general health perception. Scales are scored from 0 to 100, with higher scores indicating better health. Another algorithm yields 2 summary scores, the physical component summary (PCS) and the mental component summary (MCS), which are also scaled

with higher scores indicating better health, but are scored using a norm-based system where linear transformations are performed to transform scores to a mean of 50 and standard deviations of 10, based upon general US population norms.[36] The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.[37]

The **EQ-5D** is a self-administered, non-disease-specific measure of health status that provides a simple descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care and in population health surveys. Specifically, the EQ-5D assesses health outcomes from a wide variety of interventions on a common scale for purposes of evaluation, allocation, and monitoring.

9.2.2. Endpoints

Unless otherwise stated, the analysis time points mentioned for each study refer to Week 0 of that study; for example, Week 44 in the maintenance study refers to 44 weeks after Week 0 of the maintenance study, *not* 44 weeks after Week 0 of the induction study.

For the primary and major secondary endpoints involving the endoscopy subscore of the Mayo score (eg, clinical remission, clinical response, endoscopic healing), the final reported endoscopic subscore will be used, as described in Section 9.2.1.

Clinical remission is the primary endpoint in both the induction and maintenance studies. Additionally, clinical remission is used to define some major secondary endpoints in the maintenance study. In this protocol, two separate definitions for clinical remission will be applied to the primary and major secondary endpoints of remission for both the induction and maintenance studies, as applicable, to accommodate the global and US-preferred definitions of clinical remission. These definitions of clinical remission will use Mayo score data from all subjects and are described below. (A complete list of definitions for efficacy endpoints is provided in Section 9.2.2.4).

- The following **global definition** of clinical remission will be used for countries outside the United States: a Mayo score ≤2 points, with no individual subscore >1. This definition will also be used to stratify subjects by clinical remission status at maintenance baseline for the maintenance study.
- The following **US-specific definition** of clinical remission will be used for the United States: an absolute stool number ≤3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.

9.2.2.1. Induction

9.2.2.1.1. Primary Endpoint

The primary endpoint of the induction study is clinical remission at Week 8.

9.2.2.1.2. Major Secondary Endpoints

The following are the major secondary endpoints in the induction study, which are presented in the order in which they will be tested:

- Endoscopic healing at Week 8.
- Clinical response at Week 8.
- The change from induction baseline in the total score of the IBDQ at Week 8.

9.2.2.1.3. Other Secondary Endpoints

- The change from induction baseline in the Mayo score at Week 8
- The change from induction baseline in the partial Mayo score through Week 8.
- Individual Mayo subscores through Week 8.
- Remission at Week 8 based on a stool frequency subscore of **0 or 1**, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
- Remission at Week 8 based on a stool frequency subscore of **0**, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
- Symptomatic remission at Week 8.
- Normal or inactive mucosal disease at Week 8.
- Clinical remission at Week 8 by biologic failure status.
- Endoscopic healing at Week 8 by biologic failure status.
- Clinical response at Week 8 by biologic failure status.
- The change from induction baseline in each of the 4 dimensions of the IBDQ at Week 8.
- A >20-point improvement from induction baseline in the IBDQ score at Week 8.
- The change from induction baseline for each of the 8 individual subscales of the SF-36 and the PCS and MCS scores at Week 8.
- The changes from induction baseline in the EQ-5D dimensions, EQ-5D index, and health state VAS scores at Week 8.
- Mucosal healing at Week 8.
- The change from induction baseline in CRP through Week 8.
- The change from induction baseline in fecal lactoferrin concentration through Week 8.
- The change from induction baseline in fecal calprotectin concentration through Week 8.
- Normalization of CRP concentration through Week 8 among subjects with abnormal CRP concentration at induction baseline.

- Normalization of fecal lactoferrin concentration through Week 8 among subjects with abnormal fecal lactoferrin concentration at induction baseline.
- Normalization of fecal calprotectin concentration through Week 8 among subjects with abnormal fecal calprotectin concentration at induction baseline.

9.2.2.2. Maintenance

9.2.2.2.1. Primary Endpoint

The primary endpoint of the maintenance study is clinical remission at Week 44.

9.2.2.2.2. Major Secondary Endpoints

The following are the major secondary endpoints, which are presented in the order in which they will be tested:

- Maintenance of clinical response through Week 44.
- Endoscopic healing at Week 44.
- Clinical remission and not receiving concomitant corticosteroids at Week 44.
- Maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline.

9.2.2.2.3. Other Secondary Endpoints

- The change from maintenance baseline in the Mayo score at Week 44.
- The change from induction baseline in the Mayo score through Week 44.
- Individual Mayo subscores through Week 44.
- The change from maintenance baseline in the partial Mayo score over time through Week 44.
- The change from induction baseline in the partial Mayo score over time through Week 44.
- Remission at Week 44 based on a stool frequency subscore of **0 or 1**, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
- Remission at Week 44 based on a stool frequency subscore of **0**, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
- Symptomatic remission at Week 44.
- Clinical remission at Week 44 by biologic failure status.
- Maintenance of clinical response through Week 44 by biologic failure status.
- Endoscopic healing at Week 44 by biologic failure status.
- The proportion of subjects who demonstrate endoscopic healing at Week 44 among the subjects who had achieved endoscopic healing at maintenance baseline.
- Normal or inactive mucosal disease at Week 44.

- Clinical remission and not receiving concomitant corticosteroids at Week 44 among the subjects receiving concomitant corticosteroids at maintenance baseline.
- The change from maintenance baseline in corticosteroid use over time through Week 44 among the subjects receiving concomitant corticosteroids at maintenance baseline.
- Subjects who are not receiving concomitant corticosteroids at Week 44 among the subjects who were receiving concomitant corticosteroids at maintenance baseline.
- Subjects who maintained improvement in IBDQ at Week 44 from induction baseline among subjects who had a >20-point improvement in the total IBDQ score at maintenance baseline from induction baseline.
- The change from maintenance baseline in the total IBDQ score and each of the 4 IBDQ dimensions through Week 44.
- The change from maintenance baseline in the SF-36 physical and mental component summary scores and the individual scale scores through Week 44.
- The changes from maintenance baseline in the EQ-5D dimensions, EQ-5D index, and health state VAS scores through Week 44.
- Mucosal healing at Week 44.
- The change from maintenance baseline in CRP concentration over time through Week 44.
- The change from maintenance baseline in fecal lactoferrin concentration over time through Week 44.
- The change from maintenance baseline in fecal calprotectin concentration over time through Week 44.
- The time to loss of clinical response through Week 44.
- The time to loss of clinical remission through Week 44 among subjects in clinical remission at maintenance baseline.

9.2.2.3. Exploratory Endpoints

- Response using the Mayo score without the PGA subscore in both induction and maintenance.
- Average Bristol Stool Form Scale score over time in induction.

9.2.2.4. Efficacy Endpoint Definitions

Definitions for efficacy endpoints are as follows:

- **Induction baseline**: Week 0 of the induction study (I-0 visit).
- **Maintenance baseline**: Week 0 of the maintenance study (M-0 visit).
- **Clinical remission (global definition):** Mayo score ≤2 points, with no individual subscore >1.
- **Clinical remission (US-specific definition):** Absolute stool number ≤3, rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1.

- **Clinical response**: A decrease from induction baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore = 0 or 1.
- **Endoscopic healing** (ie, improvement in the endoscopic appearance of the mucosa): Endoscopy subscore of the Mayo score = 0 or 1.
- **Normal or inactive mucosal disease**: Endoscopy subscore = 0.
- **Mucosal healing**: endoscopic healing and histologic healing.
- **Normalization of CRP concentration**: CRP concentration <8 mg/L.
- **Normalization of fecal lactoferrin concentration**: fecal lactoferrin concentration <10 µg/mL.
- **Normalization of fecal calprotectin concentration**: fecal calprotectin concentration <250 mg/kg.
- **Symptomatic remission:** Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Blood samples will be used to evaluate the PK and immunogenicity of ustekinumab (antibodies to ustekinumab). Samples collected for analyses of serum ustekinumab concentration and antibodies to ustekinumab may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

Blood samples will be collected from each subject at timepoints indicated in the Time and Events Schedules. At visits at which serum concentration and antibodies to ustekinumab will be evaluated, 1 blood sample of sufficient volume can be used. Venous blood samples will be collected and each serum sample will be divided into 3 aliquots (1 each for PK, antibodies to study agent, and a back-up).

9.3.1.1. Endpoints

Serum ustekinumab concentrations and antibodies to ustekinumab will be analyzed to assess the PK and immunogenicity of ustekinumab in subjects with UC treated with ustekinumab.

9.3.2. Analytical Procedures

9.3.2.1. Pharmacokinetics

Serum samples will be analyzed to determine concentrations of ustekinumab using a validated, specific, and sensitive method by or under the supervision of the sponsor.

9.3.2.2. Immunogenicity

The detection and characterization of antibodies to ustekinumab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to ustekinumab will also be evaluated for ustekinumab serum concentration to enable interpretation of the antibody data.

9.3.3. Pharmacokinetic Parameters

Serum samples will be used to evaluate various PK parameters using population PK modeling.

9.3.4. Immunogenicity Assessments (Antibodies to Ustekinumab)

Antibodies to ustekinumab will be evaluated in serum samples collected from all subjects according to the Time and Events Schedules. Additionally, serum samples should also be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to ustekinumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to ustekinumab and/or further characterize the immunogenicity of ustekinumab.

9.4. Biomarkers

Biomarker assessments will be performed to identify protein, RNA (mRNA or microRNA) expression patterns, and microbial activities that are relevant to ustekinumab treatment and/or UC, to conduct histologic and immunohistochemical assessment of disease and healing, and to evaluate if biomarkers can be used to predict clinical response. Biomarker assessments (described in further detail below) will include the evaluation of relevant markers in serum and feces for all subjects as specified in the Time and Events Schedules. In addition, colonic mucosal biopsies will be obtained at the screening, I-8, and M-44 visits. Subjects who are nonresponders at the I-8 visit will undergo an additional colonic mucosal biopsy at the I-16 visit; other biomarker samples (serum and feces) will also be collected from these subjects at the I-16 visit.

Instructions for the collection and shipment of biomarker samples will be found in the Laboratory Reference Manual.

9.4.1. Serum

Serum samples for biomarker analyses will be obtained from all subjects as specified in the Time and Events Schedules. Analysis of serum samples for biomarkers may include proteins associated with proinflammatory and anti-inflammatory effects, the recruitment and proliferation of cells associated with inflammation and repair, and markers associated with tissue injury or repair.

9.4.2. Fecal Biomarkers

Fecal samples will be collected from all subjects as specified in the Time and Events Schedules. Microbiome and associated products analysis will be conducted to evaluate the association

between microbial activities and ustekinumab and/or UC. The relationships between microbiome, metabolites, and biomarkers in other tissue samples will also be assessed.

9.4.3. Mucosal Biopsy RNA and Histology

Mucosal biopsy samples will be collected during endoscopy as specified in the Time and Events Schedules. Total RNA will be isolated and used for differential gene expression analyses to identify mRNA or microRNA expression patterns that are relevant to ustekinumab treatment and/or UC, and to evaluate markers that can predict clinical response. The biopsy samples collected will also be used for the histologic and immunohistochemical assessment of disease and healing.

9.5. Genetic and Epigenetic (DNA) Evaluations

Genetic (encoded DNA sequence) and epigenetic (non-encoded DNA variation by promoter methylation, histone acetylation, and other modifications) variation may be important contributory factors to interindividual differences in drug disposition, response, and clinical outcomes. Genetic (DNA) and epigenetic factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to a drug.

DNA samples will be analyzed for identification of genetic and epigenetic factors to better understand the molecular effects of ustekinumab and/or UC, and to evaluate markers that can predict clinical response. Genetic (DNA) research may consist of the analysis of 1 or more candidate genes or analysis of the entire genome (as appropriate) in relation to ustekinumab and/or UC. The goal of the epigenetic component of this study is to identify epigenetic factors related to UC or to the PK, PD, efficacy, or tolerability of ustekinumab.

Whole blood samples of approximately 10 mL will be collected for genetic and epigenetic analyses as specified in the Time and Events Schedules. Only subjects who sign the consent form to participate in the genetic assessment will have whole blood DNA samples collected.

9.6. Health Economics and Medical Resource Utilization

Medical resource utilization, including UC-related hospitalizations and UC-related surgeries, will be collected during the induction and maintenance studies. Additionally, the potential impact of ustekinumab on subjects' work limitations and daily productivity will be assessed through the Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH) and the productivity visual analog scale (VAS), respectively.

The **WPAI-GH** is a validated instrument created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to general health. The WPAI-GH consists of 6 questions to determine employment status, hours missed from work due to UC, hours missed from work for other reasons, hours actually worked, the degree to which general health affected work productivity while at work, and the degree to which general health affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work

impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Higher scores indicate greater impairment.

The **productivity VAS** will measure the impact of disease on subjects' daily productivity using a VAS (0=no impact at all to 10=impact productivity very much).

9.7. Safety Evaluations

Details about the independent Data Monitoring Committee are provided in Section 11.12.

Any clinically relevant changes occurring during the induction and maintenance studies and the LTE must be recorded in the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study or at early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached or follow-up is no longer possible (eg, the subject withdraws consent, the subject is lost to follow-up).

The studies will include the following evaluations of safety and tolerability at the time points specified in the Time and Events Schedules.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the studies. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. At each visit, subjects (or, when appropriate, a caregiver, surrogate, or the subject's legally acceptable representative) will be questioned about any AEs (eg, “side effects”) occurring since the previous visit and the outcomes for any AEs reported at previous visits.

Clinical Laboratory Tests

Blood samples will be collected for routine hematology and blood chemistry laboratory analyses at timepoints specified in the Time and Events Schedules.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the studies in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory.

- **Hematology panel**
  - Hemoglobin
  - Hematocrit
  - WBC with differential
  - Platelet count

- **Serum chemistry panel**
  - sodium
  - potassium
  - chloride
  - blood urea nitrogen (BUN)
  - creatinine
  - AST
  - ALT
  - total and direct bilirubin
  - alkaline phosphatase
  - calcium
  - phosphate
  - albumin
  - total protein
- **Pregnancy testing:** Female subjects of childbearing potential will undergo a serum β-HCG pregnancy test at screening, and a urine pregnancy test before all study agent administration visits.
- Serology for HIV antibody at screening.
- Serology for HCV antibody at screening.
- Serology for HBV antibody, HBsAg, anti-HBs, and anti-HBc total at screening.

For some tests related to screening criteria, existing local or central laboratory results are acceptable to satisfy study requirements (eg, QuantiFERON-TB Gold test, stool pathogens) provided that they are obtained within the specified window; results should be retained with the source documents. Use of local laboratories is allowed in cases where initiation of treatment or safety follow-up is time sensitive and the central laboratory results are not expected to be available before the need to begin administration of study agent or if actions need to be taken for safety reasons. These laboratory results will not be entered into the CRF, but should be retained with the source documents.

Electrocardiogram (ECG)

A 12-lead ECG will be performed at screening. During an ECG, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving arms or legs. If blood sample collection or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood sample collection.

Vital Signs

Vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained before, approximately every 30 minutes during, and twice (at approximately 30-minute intervals) after completion of the IV infusion(s) during the induction study. Vital signs should be obtained before and approximately 30 minutes after every SC study agent injection.

Physical Examination

Physical examinations will be performed as specified in the Time and Events Schedules. Height and weight will be recorded at screening; weight will also be recorded at timepoints specified in the Time and Events Schedules.

Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

Infusion Reactions

An infusion reaction is defined as an AE that occurs during or within 1 hour after the infusion of study agent, with the exception of laboratory abnormalities. Minor infusion reactions may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study agent is stopped because of an infusion reaction and the reaction, in the opinion of the investigator, is not severe or does not result in a serious adverse event (SAE; Section 12.1.1), the infusion may be restarted with caution.

Injection Site Reaction

A study agent injection-site reaction is any adverse reaction at an SC study agent injection site. The injection sites will be evaluated for reactions and any injection site reactions will be recorded as an AE.

Allergic Reactions

Before any SC injection or IV infusion, appropriately trained personnel and medications must be available to treat allergic reactions, including anaphylaxis. Appropriate medical personnel must be in attendance at the time of the injection or infusion and for at least 30 minutes after the SC injection or for at least 1 hour after the start of the IV infusion.

Appropriate medical personnel must remain in close proximity to the infusion center for the remaining duration of the infusion, and for 1 hour after the end of the infusion in the event that emergency resuscitation is required. All subjects must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives).

If a mild or moderate allergic reaction is observed, acetaminophen, NSAIDs, and/or diphenhydramine may be administered. In the case of a severe allergic reaction (eg, anaphylaxis), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available at the study site where the injections or infusions are being given.

Subjects who experience serious adverse reactions related to an injection or infusion should be discontinued from further study agent administrations (Section 10.2).

For severe reactions related to an injection or infusion, the subject may be permanently discontinued from further study injections at the discretion of the investigator (Section 10.2).

Subjects who experience reactions after an injection or infusion that result in bronchospasm with wheezing and/or dyspnea that requires ventilatory support OR that result in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg will not be permitted to receive additional study agent.

Infections

Study agent should not be administered to a subject with a clinically important, active infection. Investigators are required to evaluate subjects for any signs or symptoms of infection at scheduled visits as specified in the Time and Events Schedules. If a subject develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study agent administration must be considered. For an active varicella-zoster infection or a significant exposure to varicella-zoster infection in a subject without a history of chickenpox, study agent administration should be interrupted until the symptoms have resolved and no active infection is present.

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (refer to Time and Events Schedules) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON-TB Gold test, a repeat tuberculin skin test (Attachment 4) in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. A tuberculin skin test is recommended but not required for study centers in Ukraine if tuberculin is not available. If the QuantiFERON-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2. Subjects should be encouraged to return for all subsequent study visits as specified in the Time and Events Schedules.

Refer to Attachment 3 and Attachment 4 for details regarding QuantiFERON-TB Gold In-Tube and tuberculin skin testing and to Section 9.1.2 for additional details regarding TB testing during the study.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedules for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

10.1.1. Induction Study

A subject will be considered to have completed the induction study if he or she enters the maintenance study, or has completed the safety follow-up visit approximately 20 weeks after last study agent administration if he/she does not enter the maintenance study.

10.1.2. Maintenance Study

A subject will be considered to have completed the double-blind phase of the maintenance study if he or she enters the LTE, or has completed the safety follow-up visit approximately 20 weeks after his or her last study agent administration if he/she does not enter the LTE.

10.1.3. Long-Term Extension

A subject will be considered to have completed the LTE if he or she has completed the final safety visit after the final dosing visit **or** the sponsor decides not to further pursue an indication in UC.

10.2. Discontinuation of Study Agent

If a subject's study agent must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study agent should be discontinued if:

- The investigator believes that for safety reasons (eg, AE), it is in the best interest of the subject to discontinue study agent.
- The subject becomes pregnant or plans a pregnancy within the study period.
- The subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
  - A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result (and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities [recommended but not required for study centers in Ukraine if tuberculin is not available]), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated before the next administration of study agent and continued to completion. Indeterminate QuantiFERON-TB Gold test results should be handled as described in Section 9.1.2. Subjects with persistently indeterminate QuantiFERON-TB Gold test results may continue without treatment for latent TB, if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.
  - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- A serious adverse reaction occurs that is related to an injection or an infusion, including an injection site or infusion reaction, resulting in bronchospasm with wheezing and/or dyspnea that requires ventilatory support **OR** that results in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg.
- Malignancy, including squamous cell skin cancer. Consideration may be given to allowing subjects who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study agent.
- The initiation of any protocol-prohibited medications/therapies, as specified in Section 8.
- A systemic opportunistic infection.

- The subject (or the subject's representative) withdraws consent for administration of study agent.
- The subject has a colectomy.

During the maintenance study, a subject who meets the criteria of clinical flare on more than 2 occasions should be discontinued from study agent administration.

Discontinuation of study agent administration must be considered for subjects who develop a severe injection site or infusion reaction or who develop a serious infection. Any subject who experiences a severe reaction after an injection or infusion that result in bronchospasm with wheezing and/or dyspnea that requires ventilatory support OR that result in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg will not be permitted to receive additional study agent.

During the induction study, subjects who discontinue study agent (but have not terminated study participation) before or at the I-8 visit should complete the I-8 assessments specified in the Time and Events Schedule (Table 1) at the time of discontinuation and a final safety visit approximately 20 weeks after their last study agent administration. After Week 8, subjects who do not wish to continue into the maintenance study, but are willing to complete their participation in the induction study, should complete the I-16 assessments at the time of discontinuation, and a safety follow-up visit approximately 20 weeks after their last study agent administration.

During the maintenance study, subjects who discontinue study agent (but have not terminated study participation) should complete the assessments specified in the Time and Events Schedule (Table 2) for an early termination visit, as well as a final follow-up safety visit approximately 20 weeks after their last administration of study agent.

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Sponsor decision (eg, significant noncompliance)

Before a subject is considered lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study agent assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

During the induction study, subjects who terminate their study participation before or at the I-8 visit should complete the assessments indicated on the Time and Events Schedule for the I-8 visit (Table 1) at the time of termination. Subjects who terminate their study participation after the I-8 visit but before or at the I-16 visit should complete the I-16 assessments at the time of termination.

During the maintenance study, subjects who terminate study participation should complete the assessments specified for an early termination visit on the Time and Events Schedule (Table 2).

A subject who withdraws from the study will have the following options regarding the optional research sample(s):

- The collected sample(s) will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional research sample(s), in which case the sample(s) will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample(s) have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research sample(s) will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

Descriptive statistics (eg, mean, median, standard deviation, interquartile range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphic data displays (eg, line plots) may also be used to summarize data.

Analyses suitable for categorical data (eg, chi-square tests, Cochran-Mantel-Haenszel chi-square tests, or logistic regression, as appropriate) will be used to compare the proportions of subjects

achieving selected endpoints (eg, clinical response). In cases of rare events, the Fisher exact test will be used for treatment comparisons. Continuous response parameters will be compared using an analysis of variance (ANOVA) or covariance (ANCOVA), unless otherwise specified. If the normality assumption is in question, an ANOVA or ANCOVA on the van der Waerden normal scores will be used.

When the endpoint is time-to-event, a log-rank or stratified log-rank test will be used.

In this protocol, the induction and maintenance studies are considered to be 2 separate studies. All statistical testing will be performed at the α=0.05 (2-sided) level with appropriate multiplicity adjustment employed for the primary and major secondary endpoints of each respective study. Nominal p-values will be displayed for all treatment comparisons.

11.1. Subject Information

Demographic and baseline disease characteristic data, including UC-specific concomitant medications, will be summarized for all randomized subjects in the induction study and all enrolled subjects in the maintenance study.

11.2. Sample Size Determination

11.2.1. Induction Study

The sample size in the induction study is based on statistical power considerations and the objective of providing the primary population for the maintenance study.

Sample size/power calculations were based on the chi-square test to detect a significant difference for the primary endpoint of clinical remission (for both the global and US-specific definitions) at Week 8 between the induction ustekinumab treatment groups and placebo.

It is assumed that the clinical remission rate based on the global definition is 19% for each induction ustekinumab treatment group and 7% for the placebo group. These remission rates are similar to other recently approved therapies in active UC.[13,26,31] The clinical remission rates based on the US definition are assumed to be 25% for each induction ustekinumab treatment group and 12% for the placebo group based on data from the golimumab UC induction study (C0524T17).

The treatment effect has been assumed to be the same for the 2 induction ustekinumab treatment groups because the data from the Phase 2b study of ustekinumab in Crohn's disease showed similar levels of response across the range of doses studied.[29]

A step-up multiple testing procedure[17] will be employed globally to control the Type 1 error. For the United States, the Bonferroni method will be used to control the overall Type I error rate at the 0.05 level (2-sided) for comparisons of the 2 induction ustekinumab treatment groups with placebo, with each comparison being tested at the 0.025 level (2-sided).

Assuming a 7% clinical remission (global definition) rate in the placebo group and 19% in each ustekinumab group, 135 subjects per treatment group (405 subjects in total) will provide an overall power of 90% using a step-up testing procedure at the α=0.05 (2-sided) level.

Assuming a 12% clinical remission (US-specific definition) rate in the placebo group and 25% in each ustekinumab group, 220 subjects per treatment group (660 subjects in total) will provide statistical power of 90% for comparison of each ustekinumab induction treatment group versus placebo at a significance level of 0.025 (2-sided).

To provide a sufficient number of subjects for the primary population in the maintenance study, however, it is estimated that a target of 951 subjects (317 subjects per treatment group) should be enrolled in the induction study (Section 11.2.2). Therefore, enrollment in the induction study will continue until at least 951 subjects have been enrolled. Table 4 and Table 5 show the power for detecting a treatment difference between the ustekinumab induction treatment groups and the placebo group based on different proportions of subjects in clinical remission at Week 8 for the global and US-specific definitions with a fixed sample size of 951.

Table 4: Power for detecting a treatment effect based on different proportions of subjects in clinical remission at Week 8 (global definition) with a fixed sample size of 951 subjects (317 per treatment group)

Proportion of Subjects in Clinical Remission at Week 8 (%)			
Placebo	**One Ustekinumab Treatment Group**	**Other Ustekinumab Treatment Group**	**Power[a] (%)**
7	19	19	99
	15	19	99
	13	15	90
	14	14	89
	7	16	92
	7	15	85
	7	14	75

a: Based on the Hochberg testing procedure.

Table 5: Power for detecting a treatment effect based on different proportions of subjects in clinical remission at Week 8 (US-specific definition) with a fixed sample size of 951 subjects (317 per treatment group)

Proportion of Subjects in Clinical Remission at Week 8 (%)		
Placebo	**Ustekinumab**	**Power[a] (%)**
12	25	97
	23	92
	22	86
	21	79

a: Based on α=0.025 (2-sided).

Additionally, to ensure that there will be enough subjects from the induction study to meet the required number of subjects for the primary population of the maintenance study, at a designated timepoint near the completion of planned enrollment of the induction study, the IWRS system will project, based on the available data and a predefined algorithm, whether or not the target number of subjects for the primary population of the maintenance study will be reached, and, if not, how many more subjects from the induction study will need to be enrolled to reach the target. If the information provided by the IWRS vendor indicates that more subjects will be needed in the induction study, the sponsor may increase the number of subjects in the induction study. Of note, the only data from the induction study that will be used for this projection are the proportion of subjects in the induction study who have been randomized into the maintenance study. These data will be available only to the IWRS vendor; no sponsor personnel will have access. Importantly, no comparisons (blinded or unblinded) of the data from the induction study will be performed for this projection. Therefore, no adjustments will be made to the overall Type 1 error rate (α=0.05, 2-sided) for the primary and major secondary endpoint analyses.

A sample size of 951 subjects (317 per treatment group) also provides sufficient power for the major secondary endpoints of endoscopic healing at Week 8 and clinical response at Week 8. The given sample size will provide 99% power to detect a 15% difference (40% vs 25% for a ustekinumab dose group vs placebo) in endoscopic healing at Week 8 and to detect a 20% difference (50% vs 30% for each ustekinumab dose group vs placebo) in clinical response at Week 8 based on the Hochberg testing procedure at the α=0.05 (2-sided) level; the given sample size will have 96% and 99% power for the respective comparisons at the α=0.025 (2-sided) level for each ustekinumab dose group versus placebo according to the Bonferroni method. The assumptions noted above are based on the relevant clinical difference observed for other biologics in this indication.[13,26,31]

11.2.2. Maintenance Study

The major efficacy analyses in the maintenance study will be based on the primary population, ie, subjects who were in clinical response to IV ustekinumab induction. Unless otherwise stated, the sample size/power calculations in this section refer to this population.

A fixed-sequence testing procedure, starting with the high dose group (q8w), will be used to control the overall Type I error rate at the 0.05 level (2-sided). As such, sample size/power calculations were based on the chi-square test to detect a significant difference between subjects receiving SC ustekinumab 90 mg q8w and those receiving placebo.

The treatment effect for the primary endpoint in the maintenance study, clinical remission at Week 44, was based on maintenance data from similarly designed studies of the anti-TNFα golimumab and of vedolizumab. In the golimumab UC maintenance study,[27] the proportions of subjects in clinical remission (global definition) at Week 54 (among subjects in clinical response to golimumab induction) were 34% and 22% in the 100 mg group and the placebo group, respectively. In the vedolizumab UC study,[13] the proportions of subjects in clinical remission (global definition) at Week 52 (among subjects in clinical response at Week 6) were 42% and 16% in the vedolizumab q8w group and the placebo group, respectively. For the

CNTO1275UCO3001 maintenance study, it was assumed that clinical remission rates (global definition) at Week 44 were 40% and 20%, respectively, for the ustekinumab 90 mg SC q8w and placebo groups. The clinical remission rates at Week 44 based on the US definition are also assumed to be 40% and 20%, respectively, for the ustekinumab 90 mg SC q8w and placebo groups based on data from the golimumab UC maintenance study (C0524T18).

Assuming a 20% clinical remission rate (for both the global and US definitions) in the placebo group and 40% in the SC ustekinumab 90 mg q8w group, 109 subjects in each treatment group (327 subjects in total) will provide statistical power of 90% at a significance level of 0.05 (2-sided). Table 6 shows the power for detecting a treatment difference between the SC ustekinumab 90 mg q8w and the placebo group based on different proportions of subjects in clinical remission (for both the global and US definitions) at Week 44 with a fixed sample size of 327.

Table 6: Power for detecting a treatment effect based on different proportions of subjects in clinical remission (both global and US definitions) at Week 44 with a fixed sample size of 327 subjects (109 in each treatment group)

Proportion of Subjects in Clinical Remission at Week 44 (%)		
Placebo	**Ustekinumab**	**Power[a] (%)**
20	45	98
	42	94
	40	90
	37	80
	35	70

a: Based on testing the ustekinumab 90 mg SC q8w group versus placebo at α=0.05 (2-sided).

Table 7 shows the power for detecting a treatment difference between the ustekinumab 90 mg SC q8w and the placebo group for each of the major secondary endpoints with 327 subjects in the primary population. The assumptions about the proportion of subjects achieving each major secondary endpoint have been based on data from the golimumab[27] and vedolizumab[13] maintenance studies in subjects with moderately to severely active UC.

Table 7: Power for detecting a treatment effect for each of the major secondary endpoints with 327 subjects in the primary population (109 in each treatment group)

Major secondary endpoints	Proportion of subjects achieving the endpoint		Power[a] (%)
	Placebo	Ustekinumab	
Maintenance of clinical response through Week 44	25	50	97
Endoscopic healing at Week 44	25	45	88
Clinical remission and not receiving concomitant corticosteroids at Week 44	15	30	76
Maintenance of clinical remission through Week 44 *among the subjects who had achieved clinical remission at maintenance baseline (both global and US definitions)* [b]	25	50	65

a: Based on testing the SC ustekinumab 90 mg q8w group versus placebo at α=0.05 (2-sided).
b: It is estimated that about 37% of subjects in the primary population (40 subjects per treatment group) will be in clinical remission at Week 0 of maintenance.

The number of subjects in the primary analysis population of the maintenance study will depend on the number of subjects from the following 2 groups of the induction study: 1) subjects in clinical response to IV ustekinumab induction at Week 8 of the induction study (**Group A**), and 2) subjects who were not in clinical response to IV placebo induction at Week 8 of the induction study but were in clinical response at induction Week 16 after receiving an induction dose of IV ustekinumab at Week 8 (**Group B**). If the average clinical response rate to IV ustekinumab induction is 45%, 317 subjects in each induction treatment group (for a total of 951subjects) will result in about 328 subjects in the primary population of the maintenance study, assuming 15% attrition from the induction study to the maintenance study. However, the average clinical response rate to IV ustekinumab induction could range from 40% to 50% and attrition from the induction study to the maintenance study could range from 10% to 15%. With 317 subjects in each induction treatment group, the number of subjects in the primary population of the maintenance study could range from 290 to 385 (Table 8).

Table 8: Projected number of subjects in the primary population of the maintenance study with a sample size of 951 subjects (317 per treatment group) in the induction study

Attrition From Induction Study to Maintenance Study	Clinical Response Rate to IV Ustekinumab Induction	Subjects in Group A Entering Maintenance	Subjects in Group B Entering Maintenance[a]	Number of Subjects in Primary Population of Maintenance
15%	40%	216	75	291
	45%	243	85	328
	50%	269	94	363
10%	40%	228	80	308
	45%	257	90	347
	50%	285	100	385

Group A=Subjects in clinical response to IV ustekinumab induction at induction Week 8; Group B=Subjects not in clinical response to IV placebo induction at induction Week 8 but in clinical response at induction Week 16 after receiving an induction dose of IV ustekinumab at Week 8.
a: The proportion of subjects not in clinical response to intravenous placebo induction at Week 8 of the induction study is assumed to be 70%.

Additionally, as discussed in Section 11.2.1, the IWRS system will be used to project whether or not the target number of subjects for the primary population of the maintenance study will be reached based on enrollment in the induction study. If the information provided by the IWRS vendor indicates that more subjects will be needed in the induction study, the sponsor may increase the number of subjects in the induction study to make sure that enough subjects will be enrolled to supply the required number of subjects for the primary population of the maintenance study. Of note, the only data from the maintenance study that will be used for this projection are the number of subjects who have already entered the primary population. These data will be available only to the IWRS vendor; no sponsor personnel will have access. Importantly, no comparisons (blinded or unblinded) of the maintenance data will be performed before the Week 44 database lock. Therefore, no adjustments will be made to the overall Type 1 error rate (α=0.05, 2-sided) for the primary and major secondary endpoint analyses.

11.3. Efficacy Analyses

In this protocol, the induction and maintenance studies are considered to be 2 separate studies. As such, the Type I error rate for each study is considered separately at the 0.05 level of significance.

11.3.1. Induction Study

11.3.1.1. Population for Efficacy Analyses

Unless otherwise noted, efficacy analyses will be based on all randomized subjects in the induction study. Subjects will be analyzed according to the treatment group to which they were randomized regardless of the treatment they actually received.

11.3.1.2. Primary Analysis

The primary endpoint is clinical remission at Week 8. The definition of clinical remission (as well as the testing procedure) will be different for countries outside the United States and for the United States, as described below. Each definition of clinical remission will be based on all randomized subjects.

In countries outside the United States (global): Clinical remission is defined as a Mayo score ≤2 points, with no individual subscore >1. Subjects who have a colectomy or ostomy or have protocol-prohibited medication changes before the I-8 visit will be considered not to be in clinical remission, regardless of the actual Mayo score. Subjects with a missing Mayo score (ie, all 4 Mayo subscores are missing) at Week 8 will be considered not to be in clinical remission.

The comparison between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided Cochran-Mantel-Haenszel (CMH) chi-square test stratified by biologic failure status (yes or no) and region (Eastern Europe, Asia, or rest of world).

A step-up multiple testing procedure[17] will be employed to control the Type 1 error. For this procedure, if p-values for both ustekinumab treatment groups are ≤0.05, then it will be concluded that both ustekinumab treatment groups are effective compared with placebo. Otherwise, the

smaller of the 2 p-values will be compared with α=0.025; if the smaller p-value is ≤0.025, then it will be concluded that the ustekinumab treatment group associated with the smaller of the 2 p-values is effective compared with placebo. A positive study is defined as a statistically significant test for at least 1 ustekinumab treatment group.

For the United States: Clinical remission is defined as an absolute stool number ≤3, a rectal bleeding subscore of 0, and an Mayo endoscopy subscore of 0 or 1. The absolute stool number at a visit is calculated as the average number of stools per day over a 3-day period before the visit. Subjects who have a colectomy or ostomy or have protocol-prohibited medication changes before the I-8 visit will be considered not to be in clinical remission. Subjects who are missing the absolute stool number, rectal bleeding subscore, and Mayo endoscopy subscore at Week 8 will also be considered not to be in clinical remission.

The Bonferroni method will be used to control the overall Type I error rate at the 0.05 level (2-sided) for comparisons of the 2 ustekinumab induction treatment groups with placebo, with each comparison being tested at the 0.025 level (2-sided). The comparison between each ustekinumab treatment group and the placebo group will be based on a 2-sided CMH chi-square test stratified by biologic failure status and region at the 0.025 level of significance.

11.3.1.3. Major Secondary Endpoint Analyses

The major secondary endpoint analyses in the induction study will be based on all randomized subjects. The major secondary endpoints of endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) at Week 8 and clinical response at Week 8 will be compared between each ustekinumab treatment group and the placebo group using a 2-sided CMH chi-square test stratified by biologic failure status and region. For the major secondary endpoint of change from induction baseline in the IBDQ score at Week 8, the treatment groups will be compared using ANCOVA on the van der Waerden normal scores with induction baseline IBDQ score, biologic failure status, region, and treatment group as covariates.

Subjects who have a colectomy or ostomy, or have protocol-prohibited medication changes before the I-8 visit will be considered not to have endoscopic healing and not to be in clinical response, and for the IBDQ score, their induction baseline value will be carried forward to Week 8. Subjects who have a missing Mayo endoscopy subscore at Week 8 will be considered not to have endoscopic healing; subjects who have all 4 Mayo subscores missing at Week 8 will be considered not to be in clinical response; and subjects who have a missing IBDQ score at Week 8 will have the last available value carried forward to Week 8.

The major secondary endpoints for a dose will be tested only if the primary endpoint for that dose is significant.

Type I error control in countries outside the United States: A fixed-sequence testing procedure will be employed to control the overall Type 1 error rate over the 3 major secondary efficacy analyses at the 2-sided 0.05 significance level **within** a dose group. The major secondary endpoints for a dose will be tested only if the primary endpoint of clinical remission (global definition) is significant for that dose at the 2-sided 0.05 significance level, and the major

secondary endpoints will be tested in a hierarchical manner for that dose in the order listed in Section 9.2.2.1.2. A major secondary endpoint for a dose group will be tested only if that dose tests positive at the 2-sided 0.05 level of significance for the previous endpoint.

Type I error control in the United States: To control the overall Type I error rate at the 0.05 (2-sided) significance level over 2 doses, the major secondary endpoints will be tested in a hierarchical manner within each ustekinumab induction dose group at the 0.025 level of significance. More specifically, for a given ustekinumab dose group, the first major secondary endpoint (endoscopic healing) will be tested if the primary hypothesis (US definition of clinical remission) has been tested positive at the 0.025 level of significance for that dose group. Only if the first test for endoscopic healing is positive for the given dose group at the 0.025 level of significance will the second endpoint (clinical response) be tested. The third endpoint (change from induction baseline in the IBDQ at Week 8) will be tested only if the second test for clinical response is positive at the 0.025 level of significance for the given dose group.

11.3.1.4. Other Planned Analyses

The consistency of efficacy for clinical remission at Week 8 (for both the global and US-specific definitions) will be examined in subgroups defined by baseline demographics, baseline clinical disease characteristics, baseline concomitant UC medications, UC medication history, and stratification variables (biologic failure status, region).

The following endpoints will be summarized and compared between each of the ustekinumab treatment groups and the placebo treatment group:

- The change from induction baseline in the Mayo score at Week 8
- The change from induction baseline in the partial Mayo score through Week 8.
- Remission at Week 8 based on a stool frequency subscore of **0 or 1**, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
- Remission at Week 8 based on a stool frequency subscore of **0**, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
- Symptomatic remission at Week 8.
- Normal or inactive mucosal disease at Week 8.
- Endoscopic healing at Week 8 by biologic failure status.
- Clinical response at Week 8 by biologic failure status.
- The change from induction baseline in each of the 4 dimensions of the IBDQ at Week 8.
- A >20-point improvement from induction baseline in the IBDQ score at Week 8.
- The change from induction baseline for each of the 8 individual subscales of the SF-36 and the PCS and MCS scores at Week 8.
- The change from induction baseline in the EQ-5D dimensions, EQ-5D index, and health state VAS scores at Week 8.

- Mucosal healing at Week 8.
- The change from induction baseline in CRP through Week 8.
- The change from induction baseline in fecal lactoferrin concentration through Week 8.
- The change from induction baseline in fecal calprotectin concentration through Week 8.
- Normalization of CRP concentration through Week 8 among subjects with abnormal CRP concentration at baseline.
- Normalization of fecal lactoferrin concentration through Week 8 among subjects with abnormal fecal lactoferrin concentration at baseline.
- Normalization of fecal calprotectin concentration through Week 8 among subjects with abnormal fecal calprotectin concentration at baseline.

Mayo subscores through Week 8 will also be summarized.

11.3.2. Maintenance Study

11.3.2.1. Population for Efficacy Analyses

The primary population will be all randomized subjects in the maintenance study, which consists of subjects in clinical response to IV ustekinumab induction as determined by the IWRS (ie, subjects who were in clinical response to IV ustekinumab induction at Week 8 of the induction study, and subjects who were not in clinical response to IV placebo induction at Week 8 of the induction study but were in clinical response at induction Week 16 after receiving an induction dose of IV ustekinumab at Week 8). The Mayo endoscopy subscore assigned by the local endoscopist will be used by the IWRS to calculate clinical response status.

All efficacy analyses are based on the primary population, with the exception of selected efficacy summaries in nonrandomized subjects (ie, subjects in clinical response to IV placebo induction at Week 8 of the induction study or delayed ustekinumab responders).

For all efficacy analyses, unless otherwise specified, data will be analyzed according to the treatment group to which subjects were randomized, regardless of the treatment they actually received.

For the primary and major secondary endpoints involving clinical remission, the global definition of clinical remission will be used for countries outside of the United States and the US-specific definition will be used for the United States.

11.3.2.2. Primary Analysis

The primary endpoint is clinical remission at Week 44. The definition of clinical remission is different for countries outside the United States and for the United States, as described below. Each definition of clinical remission will be based on the primary population.

In the countries outside the United States (global definition): Clinical remission is defined as a Mayo score ≤2 points, with no individual subscore >1. Subjects who have a colectomy or ostomy, discontinue study agent due to lack of therapeutic effect or due to an AE of worsening of UC, use a rescue medication, or have protocol-prohibited medication changes before the M-44 visit will be considered not to be in clinical remission, regardless of the actual Mayo score. Subjects with a missing Mayo score (ie, all 4 Mayo subscores are missing) at Week 44 will be considered not to be in clinical remission.

The comparisons between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (yes/no as determined by the IWRS) and induction treatment (placebo IV [I-0] → ustekinumab ~6 mg/kg IV [I-8], ustekinumab 130 mg IV [I-0], or ustekinumab ~6 mg/kg IV [I-0]).]).

A fixed-sequence testing procedure will be used to control the overall Type I error rate at the 0.05 level for the primary endpoint. Specifically, the high maintenance dose group (ustekinumab 90 mg SC q8w) will first be compared with the placebo maintenance dose group at the 2-sided 0.05 level of significance. Only if this test is positive will the low maintenance dose group (ustekinumab 90 mg SC q12w) be compared with the placebo maintenance dose group at the 2-sided 0.05 level of significance.

The study will be considered positive if the test involving the high maintenance dose group (ustekinumab 90 mg SC q8w) is positive, regardless of the result of the test for the low maintenance dose group (ustekinumab 90 mg SC q12w).

For the United States: Clinical remission is defined as an absolute stool number ≤3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. The absolute stool number at a visit is calculated as the average number of stools per day over a 3-day period before the visit. Subjects who have a colectomy or ostomy, discontinue study agent due to lack of therapeutic effect or due to an AE of worsening of UC, use a rescue medication, or have protocol-prohibited medication changes before the M-44 visit will be considered not to be in clinical remission. Subjects who are missing absolute stool number, rectal bleeding subscore, and Mayo endoscopy subscore at Week 44 will be considered not to be in clinical remission.

The comparison between each ustekinumab treatment group and the placebo group will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status (as determined by the IWRS) at maintenance baseline and induction treatment.

A fixed-sequence testing procedure will be employed for the United States to strongly control the overall Type 1 error rate at the 0.05 level across the primary and all 4 major secondary endpoints and across the 2 ustekinumab doses, starting with the high maintenance dose group (ustekinumab 90 mg SC q8w) of the primary endpoint. The exact testing procedure will be detailed in the SAP before the Week 44 DBL in the maintenance study. The study will be considered positive if the test involving the high maintenance dose group is positive.

11.3.2.3. Major Secondary Endpoint Analyses

The major secondary endpoint analyses will be based on the primary population.

Except for the fourth major secondary endpoint of maintenance of clinical remission, analyses of major secondary endpoints will be conducted using a 2-sided CMH chi-square test stratified by clinical remission status at maintenance baseline (as determined by the IWRS) and induction treatment. For the fourth major secondary endpoint, a 2-sided CMH chi-square test stratified by induction treatment will be used. Note that, for the United States, for the fourth major secondary endpoint of maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline, the US-specific definition of clinical remission should also be used to determine whether or not a subject had achieved clinical remission at maintenance baseline.

Subjects who have a colectomy or ostomy, discontinue study agent due to lack of therapeutic effect or due to an AE of worsening of UC, use a rescue medication, or have protocol-prohibited medication changes before the M-44 visit will be considered not to have achieved the respective endpoints. At Week 44, subjects who have a missing Mayo endoscopy subscore will be considered not to have endoscopic healing; subjects who have all 4 Mayo subscores missing will be considered not to be in clinical response or clinical remission (for the global definition of remission). For the US-specific definition of clinical remission, subjects who are missing the absolute stool number, rectal bleeding subscore, and Mayo endoscopy subscore at Week 44 will be considered not to be in clinical remission. Subjects who lose clinical response at any time before Week 44 will be considered not to be in clinical response **through** Week 44.

Type I error control in countries outside the United States: A fixed-sequence testing procedure will be employed to control the overall Type 1 error rate over the 4 major secondary efficacy analyses at the (2-sided) 0.05 significance level **within** a dose group. The major secondary endpoints for a dose will be tested only if the primary endpoint is significant for that dose, and the major secondary endpoints will be tested in a hierarchical manner for that dose in the order listed in Section 9.2.2.2.2. A major secondary endpoint for a dose group will be tested only if that dose tests positive at the 2-sided 0.05 level of significance for the previous endpoint.

Type I error control in the United States: A US-specific testing procedure will be employed to strongly control the overall Type 1 error rate at the 0.05 level across all of the primary and major secondary endpoints over 2 ustekinumab doses. The exact testing procedure will be determined after the results of the Phase 3 maintenance study of ustekinumab in Crohn's disease are available, and will be described in the SAP before the Week 44 DBL in the maintenance study.

11.3.2.4. Other Planned Analyses

The consistency of efficacy for clinical remission at Week 44 (for both the global and US-specific definitions) will be examined in subgroups defined by baseline demographics, baseline clinical disease characteristics, baseline concomitant UC medications, UC medication history, stratification variables, biologic failure status, and region.

The following endpoints will be summarized and compared between each of the ustekinumab treatment groups and the placebo treatment group.

- The change from maintenance baseline in the Mayo score at Week 44.
- The change from maintenance baseline in the partial Mayo score over time through Week 44.
- Remission at Week 44 based on a stool frequency subscore of **0 or 1**, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
- Remission at Week 44 based on a stool frequency subscore of **0**, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
- Symptomatic remission at Week 44.
- Maintenance of symptomatic remission through Week 44 among the subjects who had achieved symptomatic remission at maintenance baseline.
- Endoscopic healing at Week 44 by biologic failure status.
- Maintenance of clinical response through Week 44 by biologic failure status.
- The proportion of subjects who demonstrate endoscopic healing at Week 44 among the subjects who had achieved endoscopic healing at maintenance baseline.
- Normal or inactive mucosal disease at Week 44.
- Clinical remission and not receiving concomitant corticosteroids at Week 44 among the subjects receiving concomitant corticosteroids at maintenance baseline.
- The change from maintenance baseline in corticosteroid use over time through Week 44 among the subjects receiving concomitant corticosteroids at maintenance baseline.
- Subjects who are not receiving concomitant corticosteroids at Week 44 among the subjects who were receiving concomitant corticosteroids at maintenance baseline.
- Subjects who maintained improvement in IBDQ at Week 44 from induction baseline among subjects with a >20-point improvement in the total IBDQ score at maintenance baseline.
- The change from maintenance baseline in the total IBDQ score and each of the 4 IBDQ dimensions through Week 44.
- The change from maintenance baseline in the SF-36 physical and mental component summary scores and the individual scale scores through Week 44.
- The changes from maintenance baseline in the EQ-5D dimensions, EQ-5D index, and health state VAS scores through Week 44.
- Mucosal healing at Week 44.
- The change from maintenance baseline in CRP concentration over time through Week 44.
- The change from maintenance baseline in fecal lactoferrin concentration over time through Week 44.
- The change from maintenance baseline in fecal calprotectin concentration over time through Week 44.

- The time to loss of clinical response through Week 44.
- The time to loss of clinical remission (global definition) through Week 44 among subjects who had achieved clinical remission (global definition) at maintenance baseline.
- The time to loss of clinical remission (US-specific definition) through Week 44 among subjects who had achieved clinical remission (US-specific definition) at maintenance baseline.

In addition, the following endpoints will be summarized:

- The change from induction baseline in the Mayo score over time through Week 44.
- The change from induction baseline in the partial Mayo score over time through Week 44.
- Mayo subscores through Week 44.

11.3.3. Exploratory Analyses

Exploratory analyses will be conducted in the induction and maintenance studies for the endpoint of response using the Mayo score stool without the PGA subscore.

Analyses of the average Bristol Stool Form Scale score over time in the induction study will be conducted.

11.3.4. Criteria for Endpoints

11.3.4.1. Induction Study

The induction study will be considered positive if at least one of the ustekinumab induction treatment groups shows a statistically significant difference versus placebo for the induction primary endpoint of clinical remission at Week 8 by the global definition. The global definition of clinical remission is based on the Mayo score and is defined as a Mayo score ≤2 points, with no individual subscore >1.

The induction study will be considered positive for the United States if at least one of the ustekinumab induction treatment groups shows a statistically significant difference versus placebo for the induction primary endpoint of clinical remission at Week 8 by the US-specific definition. The US-specific definition of clinical remission comprises the following: an absolute stool number ≤ 3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.

A significant testing (taking the testing procedure into account) in one or more of the major secondary endpoints of endoscopic healing, clinical response, or the change from induction baseline in the IBDQ score (all at Week 8) will be considered confirmative evidence of the efficacy of ustekinumab induction therapy.

The major secondary endpoint of **endoscopic healing** at Week 8 is based on the endoscopy subscore of the Mayo score. Endoscopic healing is defined as an endoscopy subscore of 0 or 1.

The major secondary endpoint of **clinical response** at Week 8 is based on the Mayo score. Clinical response is defined as a decrease from induction baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from induction baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

The major secondary endpoint of the **change from induction baseline in the IBDQ score** at Week 8 is based on a 32-item questionnaire[18] for subjects with IBD. The change is calculated as the IBDQ score at Week 8 minus the induction baseline IBDQ score.

11.3.4.2. Maintenance Study

The maintenance study will be considered positive if the test involving the high maintenance dose group (ustekinumab 90 mg SC q8w) shows a statistically significant difference versus placebo for the maintenance primary endpoint, clinical remission at Week 44 (global definition for the countries outside the United States and US-specific definition for the United States).

A significant testing (taking the testing procedure into account) in one or more of the major secondary endpoints (Section 9.2.2.2.2) will be considered confirmative evidence of the efficacy of ustekinumab maintenance therapy. The definitions of clinical remission, clinical response, and endoscopic healing are provided in Section 11.3.4.1.

11.4. Pharmacokinetic Analyses

Serum ustekinumab concentrations will be summarized for each treatment group over time using descriptive statistics. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics.

Median serum ustekinumab concentration time profiles will be plotted after the first dose of ustekinumab.

A population PK analysis using a nonlinear mixed-effects model will be used to characterize the PK of ustekinumab. The influence of important covariates on the population PK parameter estimates may be evaluated. Details will be provided in a population PK analysis plan, and results of the population PK analysis will be presented in a separate technical report.

Subjects will be excluded from the PK analysis if their data do not allow for accurate PK assessment (eg, incomplete administration of the study agent; missing dosing or sampling time information).

11.5. Immunogenicity Analyses

The incidence and titers of antibodies to ustekinumab will be summarized for all subjects who receive a dose of ustekinumab and have appropriate samples for detection of antibodies to ustekinumab (ie, subjects with at least 1 sample obtained after their first dose of ustekinumab).

11.6. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum ustekinumab concentration and efficacy will be explored. If feasible, an exposure-response model may be developed to describe further characterize such relationships.

11.7. Biomarkers Analysis

Changes in the concentration of individual serum markers from baseline to the selected posttreatment time points will be summarized. RNA analyses and additional analyses such as histology assessment and microbiome analysis will be performed. Biomarker analyses are considered exploratory and will be summarized in a separate technical report.

11.8. Genetic and Epigenetic (DNA) Analysis

Genetic and epigenetic (DNA) analyses will be conducted only in subjects who sign the consent form to participate in the genetics and epigenetic assessments. These analyses are considered exploratory and will be summarized in a separate technical report.

11.9. Health Economics and Medical Resource Utilization Analyses

The potential pharmacoeconomic benefits of ustekinumab treatment will be examined by comparing the difference in direct medical resource utilization and drivers of indirect costs among treatment groups. These comparisons will be based on data through Week 44 such as UC-related hospitalizations and surgeries, medical visits, daily productivity, and time lost from work.

Health economics and medical resource utilization data will be descriptively summarized by treatment group.

11.10. Safety Analyses

Safety analyses will be provided separately for the induction and maintenance studies and will be based on subjects who received at least 1 dose of study agent in each respective study.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase of each study (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline of each study) will be included in the analysis of each respective study. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Analyses of AEs in this study will include:

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of reasonably related AEs.
- Frequency and type of AEs leading to discontinuation of study agent.

- Frequency of infusion reactions (induction study only).
- Frequency of injection-site reactions.
- Frequency and type of infections, including infections requiring oral or parenteral antimicrobial treatment.
- Frequency and type of serious infections.

Listings of subjects with SAEs and AEs leading to discontinuation of study agent will also be provided. Any deaths, malignancies, or major cardiovascular events will either be presented in a listing or described in the clinical study report.

Clinical Laboratory Tests

The following summaries of clinical laboratory tests will be used to assess the safety of subjects in this study:

- Box plots of the observed values and changes from baseline over time for selected clinical laboratory parameters.
- Summary of maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade for postbaseline laboratory values.

Listings of subjects with any abnormal postbaseline laboratory values of CTCAE grade ≥2 will also be provided.

11.11. Interim Analysis

11.11.1. Induction Study

A futility analysis based on the primary endpoint of clinical remission (global definition) at Week 8 will be conducted when 30% of randomized subjects have either completed the I-8 visit or have terminated study participation before Week 8. The whole study may be stopped for futility when the conditional power (ie, the probability of success at the end of the study, given the data at the interim analysis) on **both** ustekinumab doses is less than a prespecified cutoff. The DMC will review the interim analysis results and form a recommendation on whether or not to stop the trial for futility. The sponsor decision committee will then review the DMC's recommendation and make a final decision.

This futility analysis will result in minimal loss in power (≤2% when the treatment effect is in the expected range of 10% to 12%) and will not affect the overall Type I error rate (α=0.05, 2-sided) for the primary endpoint analysis.

For the futility analysis, the induction treatment assignment information will be unblinded for the first 30% of randomized subjects in the trial (the induction treatment assignment for the remaining subjects and the maintenance treatment assignment information for all subjects will remain blinded at this time). To protect the integrity of the study, the unblinding of the treatment assignments for the futility analysis will be handled by an external statistical support group. Details about the futility analysis will be specified in the SAP or IAP before the time at which the futility analysis is performed.

11.11.2. Maintenance Study

No interim analysis is planned for the maintenance study.

11.12. Data Monitoring Committee

A DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this protocol. The committee will meet periodically to review safety data. After the review, the DMC will make recommendations regarding the continuation of the study. The same DMC will also review the interim analysis results from the induction study and form a recommendation to the sponsor on whether or not to stop the trial for futility. Details will be provided in a separate DMC charter.

The DMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

An SAE, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ustekinumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

Adverse Events Associated with the Study Population

Anticipated events are events that are considered common for the study population defined in this protocol and, when determined to be serious, should be reported by the investigator as described in Section 12.3.2. Anticipated events will be recorded and reported as described in Attachment 6.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation; prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study agent that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study agent
- Suspected abuse/misuse of a sponsor study agent
- Inadvertent or accidental exposure to a sponsor study agent
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study agent, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). SAEs, including those spontaneously reported to the investigator within 20 weeks after the last dose of study agent, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Anticipated events will be recorded and reported as described in Attachment 6.

All adverse events, regardless of seriousness, severity, or presumed relationship to study agent, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Subjects (or their designees, if appropriate) must be provided with a "study wallet card" indicating, but not limited to, the following information:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Study site number
- Subject number

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study agent or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as performance of an endoscopy).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study agent, is considered an SAE.

Lack of improvement in the condition/indication under investigation is not an AE unless it meets the criteria for an SAE (eg, hospitalization). Hospitalization due to disease progression or hospitalization due to lack of improvement in the condition/indication under investigation is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, congenital anomaly)

are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study agent on sperm is unknown, pregnancies in partners of male subjects included in the study must be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.4. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study agent(s) in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 12.3.2. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY AGENT INFORMATION

14.1. Physical Description of Study Agent(s)

14.1.1. Induction Study

Ustekinumab 5 mg/mL final vialed product (FVP) (IV) is supplied for this study as a single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume). No preservatives are present. It will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Placebo for FVP (IV) is supplied as a single-use, sterile solution in 30 mL vials with a 26 mL nominal volume. The composition of the placebo is 10 mM histidine, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine, and 20 µg/mL EDTA disodium salt, dihydrate at pH 6.0.

Placebo administrations will have the same appearance as the respective ustekinumab administrations.

14.1.2. Maintenance Study

Ustekinumab is supplied as sterile liquid for SC injection in a single-use prefilled syringe (PFS). Each single-use PFS contains 90 mg (1 mL fill of liquid) ustekinumab in an aqueous medium of L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0. No preservatives are present.

Placebo is supplied as a sterile liquid for SC injection at a fill volume of 1.0 mL in a single-use PFS. Each PFS contains L-histidine, sucrose, and polysorbate 80 at pH 6.0.

Placebo administrations will have the same appearance as the respective ustekinumab administrations.

The needle cover on the PFS contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Details regarding the study agents are provided in the investigational product manual.

14.2. Packaging

The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

The study agent will be packaged in individual subject kits. Each kit will consist of a single vial or PFS packaged inside a protective outer carton.

14.3. Labeling

Study agent labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study agent must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C), not frozen, and protected from light. Vigorous shaking of the product should be avoided. Prior to administration, the product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used.

Study agent in glass vials and PFS will be ready to use. Study agent will be prepared according to the subject's treatment assignment (and weight for weight-range-based doses). The pharmacist (or designated personnel) who is blinded to treatment will prepare the required volume of study agent using the appropriate number of vials.

Aseptic procedures must be used during the preparation and administration of the study material. Exposure to direct sunlight should be avoided during preparation and administration.

Refer to the Site Investigational Product Procedures Manual and/or Investigational Product Preparation Instructions (ie, pharmacy manual) for additional guidance on study agent preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study agent received at the site is inventoried and accounted for throughout the study. The study agent administered to the subject must be documented on the drug accountability form. All study agent will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study agent containers.

Study agent must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study agent must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return of unused study agent or used returned study agent for destruction will be documented on the applicable drug return form. When the study site is an authorized destruction unit and/or is using an offsite authorized destruction company for destruction, verification and documentation must also be noted on the applicable drug return form. Destruction documentation, verifying the destruction, needs to be in place.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study agent should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study agent will be supplied only to subjects participating in the study. Returned study agent must not be dispensed again, even to the same subject. Study agent may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study agent from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB)
- Investigational Product Binder
- Central Laboratory Manual
- eCRF completion instructions
- IWRS Manual
- Patient recruitment materials
- Subject study card
- Informed consent form
- Mayo diaries

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross (1 pint/473 mL of blood for donation).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study agent
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her UC. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF, the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

Subjects must be able to read and write and give informed consent without assistance. A subject who is unable to read or write is not eligible to participate in the study.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Biomarker, DNA, and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ustekinumab, to understand UC, to understand differential drug responders, to identify biomarkers capable of predicting ustekinumab response in UC, and to develop tests/assays related to ustekinumab and UC. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor

representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study agent to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)

- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study agent administration information; and date of study completion and reason for early discontinuation of study agent or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria, and Section 4.2, Exclusion Criteria, that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor or delegate, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database, they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit for the last subject participating in the LTE. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study agent development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding ustekinumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ustekinumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory biomarker analyses, performed after the Clinical Study Report has been issued, will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with the performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally

should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNF Antagonist Therapies (Infliximab, Adalimumab, Golimumab, or Approved Biosimilars for Infliximab or Adalimumab) or Vedolizumab

The criteria for inadequate initial response, response followed by loss of response, or intolerance to infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab are described in items I, II, and III, below.

I. Inadequate initial response to at least 8 weeks of therapy with infliximab, adalimumab, or golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab (primary nonresponse)

Eligible subjects must satisfy criteria A, B, and C.

A. Have received induction doses of:

- REMICADE (infliximab; 3 intravenous [IV] doses ≥5 mg/kg) at Weeks 0, 2, and 6 (or approved biosimilar for infliximab)

  OR

- Humira (adalimumab; subcutaneous [SC] doses of 160 mg at Week 0 and ≥80 mg at Week 2 followed by a dose ≥40 mg every 2 weeks) or approved biosimilar for adalimumab

  OR

- SIMPONI (golimumab; SC doses of 200 mg at Week 0 and 100 mg at Week 2, followed by 50 or 100 mg every 4 weeks)

  OR

- Entyvio (vedolizumab; IV doses of 300 mg at Weeks 0, 2, and 6)

AND

B. Did not initially respond to these induction doses of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab, as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of ulcerative colitis (UC), as assessed by a treating physician:

- Lack of improvement or worsening in stool frequency
- Lack of improvement or worsening in rectal bleeding
- Lack of improvement or worsening in daily abdominal pain
- Lack of improvement or worsening in urgency
- Lack of improvement or worsening in the endoscopic appearance of the colonic mucosa

These signs and symptoms of UC must have occurred ≥2 weeks after receiving the last induction dose of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab and are offered only as a benchmark of the minimally acceptable criteria required to designate a subject as having had an inadequate initial response to infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab.

AND

C. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the dates and doses of the failed infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab induction therapy.
- Documents that the subject had persistence of disease activity following infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab induction therapy.

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

II. Initial response followed by loss of response to current or prior therapy with infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab (secondary nonresponse)

Eligible subjects must satisfy criteria A, B, C, and D.

A. Initially responded to induction therapy

AND

B. Have received at least 2 maintenance doses of:

- Infliximab (at a dose ≥5 mg/kg, or approved biosimilar for infliximab)

  or
- Adalimumab (at a dose ≥40 mg, or approved biosimilar for adalimumab)

  or
- Golimumab (at a dose of 50 of 100 mg)

  or
- Vedolizumab (at a dose ≥300 mg)

AND

C. Have or had at least 1 of the following signs or symptoms related to recurrence of UC, as assessed by a treating physician:

- Worsening in stool frequency
- Worsening in rectal bleeding
- Worsening in daily abdominal pain

- Worsening in urgency.
- Worsening in the endoscopic appearance of the colonic mucosa.

These signs and symptoms of UC must have occurred ≥2 weeks after receiving the last maintenance dose of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab and are offered only as a benchmark of the minimally acceptable criteria required to designate a subject as having lost response to infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab therapy.

AND

D. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the dates and doses of the failed infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab maintenance therapy.
- Documents that the subject had recurrence of disease activity despite infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab maintenance therapy.

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

III. Current or prior intolerance to therapy with infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab.

Eligible subjects must satisfy criteria A and B.

A. Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (eg, delayed hypersensitivity or serum-sickness-like reaction); or 3) significant injection site reaction. Definitions of these 3 criteria are provided below.

Adverse reactions must have followed ≥1 dose of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab)**, or vedolizumab and, in the treating physician's opinion, precluded continued use of the therapy.**

1) A significant acute infusion/administration reaction is defined as an adverse reaction that was:

- Manifested through ≥1 of the following symptoms.

  a. Fever greater than 100°F (37.8°C)
  b. Chills or rigors
  c. Itching
  d. Rash
  e. Flushing
  f. Urticaria or angioedema
  g. Breathing difficulties (eg, dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor)

h. Clinical hypotension (eg, pallor, diaphoresis, faintness, syncope), blood pressure <90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure >20 mm Hg.

and

- Occurred ≤24 hours after infusion/administration of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab.

and

- Was considered related to the infusion/administration of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab.

2) A significant delayed infusion/administration reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:

  a. Myalgias
  b. Arthralgias
  c. Fever greater than 100°F (37.8°C).
  d. Malaise
  e. Rash

and

- Occurred >24 hours and <15 days after infusion/administration of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab.

and

- Was considered related to the infusion/administration of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab.

3) A significant injection site reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:

  a. Significant bruising
  b. Erythema
  c. Hemorrhage
  d. Irritation
  e. Pain
  f. Pruritus
  g. "Injection site reaction"

and

- Occurred within 24 hours of an SC injection of adalimumab (or approved biosimilar for adalimumab) or golimumab

and

- Was considered related to the injection.

B. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the date of discontinuation of infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab.

- Documents that the subject had intolerance to infliximab, adalimumab, golimumab (or approved biosimilars for infliximab or adalimumab), or vedolizumab.

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

Attachment 2: Definition of Inadequate Response to or Intolerance of Corticosteroids or AZA/6-MP and Corticosteroid Dependence

CORTICOSTEROIDS

Subjects have failed to respond to corticosteroids if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving at least 0.75 mg/kg/day or ≥40 mg/day of prednisone (or corticosteroid equivalent, given orally or intravenously) for 2 weeks; or ≥9 mg/day of budesonide or ≥5 mg/day of beclomethasone dipropionate given orally for at least 4 weeks.

Subjects are intolerant of corticosteroids if:

- They have developed clinically significant adverse events (eg, osteonecrosis or osteoporosis, psychosis, uncontrolled diabetes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of corticosteroids to treat ulcerative colitis (UC).

  OR

- They have a medical condition that precludes the use of corticosteroids as a treatment for UC.

Subjects are corticosteroid dependent if they have failed to successfully taper their corticosteroid (ie, had a flare of disease) within 3 months of starting therapy, or if a relapse occurs within 3 months after stopping corticosteroids or if they are unable to discontinue these agents without flare within 3 months after starting them.

6-MERCAPTOPURINE (6-MP) OR AZATHIOPRINE (AZA):

Subjects have failed to respond to 6-MP or AZA if they have had evidence of an initial inadequate response, recurrent disease, or a relapse despite receiving:

- At least 3 months of therapy with 1 mg/kg/day of 6-MP or 2 mg/kg/day of AZA.

  OR

- A lower dosage of 6-MP or AZA when country or local guidelines specify a different treatment regimen. (In such an event, the country or local guidelines needs to be included in the source document).

  OR

- The dosage of 6-MP or AZA confirmed to be therapeutic for the subject with whole blood thioguanine nucleotide levels >200 pmole/8 x 10^8 RBCs.

  OR

- The highest tolerated dosage due to leukopenia, elevated liver enzymes, or nausea.

Subjects are intolerant of 6-MP or AZA if:

- They have developed clinically significant adverse events (eg, pancreatitis, arthritis accompanied by high fever and/or rash, leukopenia, or persistently elevated liver enzymes) unresponsive to dose reduction that, in the judgment of the investigator, precluded the use of 6-MP or AZA to treat UC within the past 5 years.

  OR

- They have a medical condition that precludes the use of 6-MP or AZA.

Attachment 3: QuantiFERON-TB Gold Testing

The QuantiFERON-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON-TB Gold assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON-TB Gold test (standard format) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON-TB Gold Test

The QuantiFERON-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000 g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the laboratory. The laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In countries in which the QuantiFERON-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required. In Ukraine, the tuberculin skin test is recommended but not required if tuberculin is not available.

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Attachment 4: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Subjects should never be allowed to read their own tuberculin skin test results. If a subject fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a subject who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the subjects may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In Ukraine, the tuberculin skin test is recommended but not required if tuberculin is not available.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

Attachment 5: 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 6: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or nonserious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

Adverse Events Associated with the Study Population

- Adverse events related to symptoms of UC
- Adverse events related to worsening or progression of UC

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of prespecified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Philippe Szapary, MD, MSCE

Institution: Janssen Research & Development

Signature: [redacted] Date: 20-APR-2016
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE