Janssen Research & Development *

Clinical Protocol

A Phase 3b, Multicenter, Randomized, Blinded, Active-Controlled Study to Compare the Efficacy and Safety of Ustekinumab to that of Adalimumab in the Treatment of Biologic Naïve Subjects with Moderately-to-Severely Active Crohn's Disease

SEAVUE: Safety and Efficacy of Adalimumab Versus Ustekinumab for one yEar

Protocol CNTO1275CRD3007; Phase 3b
Amendment 2

Stelara® (ustekinumab); Humira® (adalimumab)

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

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	11 January 2018
Amendment 1	27 February 2019
Amendment 2	14 December 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (14 December 2020)

The overall reason for the amendment: The overall purpose for this amendment is to revise or clarify secondary, other, and patient-reported outcome (PRO) endpoints for this study, adding Type 1 error control for major secondary endpoints, updating several secondary endpoints, adding or revising several PRO endpoints, and clarifying the wording of some endpoints. The added endpoints are to better address patient concerns regarding treatment of Crohn's disease, and Health Authority interest pertaining to efficacy. With this amendment, the updated revisions to the study endpoints will be pre-specified prior to database lock.

More detailed rationales are provided below. Edits to previous text in the protocol are shown in strikeout (for deleted text) or bold (for added text).

Applicable Section(s)	Description of Change(s)
Rationale: Type 1 error control is being added to the analysis of the major secondary endpoints. As a result, they are now being listed in the order with which they will be hierarchically tested, and one new endpoint is being added which focuses on the key Crohn's disease patient symptoms of abdominal pain and diarrhea (ie, stool frequency).	
11.3 Endpoints	**Added text:** In order to control the overall Type 1 error rate, the primary endpoint and major secondary endpoints will be tested in a hierarchical fashion. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive, and the subsequent endpoint(s) will be tested only if the preceding endpoint in the hierarchy is positive.
2.2 Endpoints; 11.3.2 Major Secondary Endpoints	• **Added:** PRO-2 symptom remission at Week 52 (defined as an abdominal pain [AP] mean daily score at or below 1 and also stool frequency [SF] mean daily score at or below 3, ie, AP≤1 and SF≤3). PRO-2 are the stool frequency and abdominal pain scores reported as part of the CDAI. • **Moved up to precede endoscopic remission major secondary endpoint:** Clinical remission (defined as CDAI < 150) at Week 16
Rationale: Endpoints pre-specified as "secondary" are being updated to increase emphasis on key patient symptoms of abdominal pain and diarrhea (ie, stool frequency) and durable response and remission. As the number of these are intended to be limited in number, some endpoints previously listed as secondary are being moved to "other endpoints".	
11.3.3 Secondary Endpoints	**Moved up from Other Endpoints:** • The proportion of subjects with durable clinical remission at Week 52 (defined as CDAI <150 at Week 52 and at ≥80% of all visits between Week 16 and Week 52)
11.3.3 Secondary Endpoints	**Added:** • The proportion of subjects with durable clinical response at Week 52 (defined CDAI>100 decrease from baseline at Week 52 and at ≥80% of all visits between Week 16 and Week 52) • Absence and/or resolution of AP, defined as a mean daily CDAI AP score of 0 in the week prior to the visit among subjects with mean AP >0 at baseline, compared at each postbaseline visit through Week 52

	• Absence and/or resolution of diarrhea, defined as no loose or watery stools in the week prior to the visit (ie, SF CDAI sub-score = 0) among subjects with mean SF >1 at baseline, compared at each postbaseline visit through Week 52 • The proportion of subjects with clinical and biomarker remission, defined as the proportion of subjects with CDAI<150, CRP ≤3 mg/L, and also fecal calprotectin ≤250 μg/g, compared at Weeks 8, 16 and 52
11.3.4 Other Endpoints, Efficacy	**Moved from Secondary to Other Endpoints:** • The change from baseline in SES-CD at Week 52 • The change from baseline in CRP concentration at all postbaseline visits through Week 52 • The proportion of subjects with normalization of CRP (defined as ≤3 mg/L) compared at Weeks 8, 16, and 52 among subjects with abnormal CRP (>3 mg/L) at baseline • The change from baseline in fecal calprotectin concentration, compared at Weeks 8, 16, and 52
11.3.4 Other Endpoints, Efficacy	**Revised analysis:** The change from baseline in the sum of the number of stools and the AP scores in the prior 7 days, **compared individually and combined,** without weighting, at all postbaseline visits through Week 52 **(sum of PRO-2)**
11.3.4 Other Endpoints, Efficacy	**Added:** • Maintenance of clinical remission, defined as CDAI<150 at Week 52, among subjects in remission at Week 16 • Maintenance of clinical response, defined as CDAI decreased at least 100 from baseline at Week 52 among subjects in response [CDAI decrease at least 100 points from baseline] at Week 16 • The change in the weighted (as per the CDAI) sum of the AP and SF subscores of the CDAI from baseline at all postbaseline visits through Week 52 (PRO-2 weighted) • PRO-2 symptom improvement/response, defined as at least a 1 point improvement (or a mean score of zero) in mean daily CDAI AP score from baseline, and also a reduction in SF mean daily score of 3 or more (or a mean score of zero) from baseline, compared at each visit through Week 52 • PRO-2 symptom remission, defined as an AP mean daily score at or below 1 and a SF mean daily score at or below 3, ie, AP≤1 and SF≤3), compared at each visit through Week 52 • AP improvement, defined as a 1 point or greater improvement in mean daily CDAI AP score from baseline, or a mean score of zero, among subjects with mean AP>0 at baseline, compared at each visit through Week 52 • Reduction in frequency of diarrhea, defined as a reduction of at least 3 (or a mean number <1) in SF (ie, mean daily number of liquid or very soft stools from CDAI in the week prior to the visit) from baseline, among subjects with mean SF >1 at baseline, compared at each visit through Week 52

Rationale: All of the other endpoints that are (or may be) based on fecal calprotectin values were reworded to be more clear as to the original intent and precise nature of the analyses to be performed, however, there is no change being made to the planned analyses.	
11.3.4 Other Endpoints, Efficacy	**Example of edits for these endpoints:** • The proportion of subjects with fecal calprotectin ≤ 100 µg/g ~~at all postbaseline visits through Week 52~~ **at Weeks 8, 16, and 52** ~~where fecal calprotectin assessed~~ among subjects with fecal calprotectin >250 µg/g at baseline
11.3.4 Other Endpoints, Efficacy	**Edited for clarity:** • The proportion of subjects with fistula resolution (closure of all **open/draining** perianal/perirectal fistulas) compared at each postbaseline visit through Week 52 among subjects with one or more **open/draining** perianal or perirectal fistulas at baseline • The proportion of subjects with fistula response (defined as closure of 50% of **open/draining** perianal/perirectal fistulas) compared at each postbaseline visit through Week 52 among subjects with one or more **open/draining** perianal or perirectal fistulas at baseline
11.3.4 Other Endpoints, Efficacy	**Deleted (since narcotic use for reason other than Crohn's disease is not being analyzed):** • The proportion of subjects who are on concomitant narcotic pain medications for any reason • The proportion of subjects able to eliminate concomitant narcotic pain medication use for any reason
Rationale: For a number of PRO endpoints based on PROMIS-29 data, the various thresholds for analysis are being revised to better evaluate the extent of improvement, and the wording of several endpoints is being clarified.	
11.3.4 Other Endpoints, PRO Endpoints	**Added:** • The change from baseline in the PROMIS-29 domains of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score, Ability to Participate in Social Roles and Activities Score, Physical Function Score, and Pain Intensity Score compared at Weeks 8, 16, and 52 (results reported separately for each domain) • The proportion of subjects with a T-score decrease of ≥ 5 in the domains of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score at Weeks 8, 16, and 52 (results reported separately for each domain) • The proportion of subjects with a T-score increase of ≥ 5 in the domains of Ability to Participate in Social Roles and Activities Score, and Physical Function Score at Weeks 8, 16, and 52 (results reported separately for each domain) • The proportion of subjects with a T-score decrease of ≥ 3 in the domains of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score at Weeks 8, 16, and 52 (results reported separately for each domain) • The proportion of subjects with a T-score increase of ≥ 3 in the domains of Ability to Participate in Social Roles and Activities Score, and Physical Function Score at Weeks 8, 16, and 52 (results reported separately for each domain) • The proportion of subjects with a score decrease of ≥ ½ baseline standard deviation in Pain Intensity Score at Weeks 8, 16, and 52 • The proportion of subjects with a T-score decrease of ≥5 in Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance

	Score and increase of ≥5 in ability to participate in social roles and activities, and physical function score, at Weeks 8, 16, and 52 • The proportion of subjects with a T-score decrease of ≥ 3 in Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score and increase of ≥ 3 in ability to participate in social roles and activities, and physical function score, at Weeks 8, 16, and 52
Rationale: Healthcare resource utilization endpoint being deleted since all relevant analyses have been prespecified, and this endpoint is not necessary.	
Healthcare resource utilization	**Deleted:** Additional endpoints (not protocol-directed) through Week 52 and based on total available follow up.
Rationale: Text describing the Actigraphy Substudy is being deleted since there has not been a sufficient number of patients enrolled in this optional US Substudy to perform any meaningful analyses, and this Substudy was terminated in July 2019 via a letter to the study sites.	
All sections related to Actigraphy Substudy	Deleted.

Amendment 1 (27 February 2019)

The overall reason for the amendment: The overall reason for the amendment is to clarify the definition of endoscopic remission, update the tuberculosis test being used; add instructions for emergency unblinding; and add a few clarifications.

Applicable Section(s)	Description of Change(s)
Rationale: Definition of endoscopic remission is being clarified to allow for subjects enrolled with SES-CD of 3.	
Synopsis/Endpoints; Definitions of Terms; 2.2 Endpoints; 11.3.2 Major Secondary Efficacy Endpoints	Endoscopic remission (defined as an SES-CD score ≤3**, or = 0 for subjects who enter the study with an SES-CD =3)** at Week 52
Rationale: The tuberculosis test is being updated to include all QuantiFERON-TB tests.	
Throughout protocol	QuantiFERON-TB ~~Gold~~ test
Rationale: CD-related healthcare utilization at screening, which was inadvertently included in the original protocol, is being removed.	
Time and Events Schedule, row for CD-related healthcare utilization	Deleted at Screening visit.
Rationale: Text for emergency unblinding is being added per current Sponsor study practices.	
Section 3.2.1, Overall Rational and Endpoints Chosen for Evaluation (Maintenance of Blind); Section 5.2, Blinding; Section 10.2, Discontinuation of Treatment, 2nd bullet	Procedures to follow for emergency unblinding have been added, following the IWRS unblinding procedures. These include details for treatment discontinuation and subsequent follow-up for subjects whose treatment has been unblinded.
Rationale: Since sites are not asked to calculate the SES-CD score at study entry (it is calculated by the central readers), the reference to the SES-CD score is being clarified to avoid confusion at the sites.	
4.1 Inclusion Criteria, #4	Has one or more ulceration on screening ileocolonoscopy **(**which**, by definition, would** ~~will~~ result in an SES-CD ~~total score~~ of at least 3**)**.
Rationale: Entry requirements pertaining to birth control are recommended to be consistent with local regulations.	
4.1 Inclusion Criteria, #12	Male participants who are not surgically sterilized and are heterosexually active with a woman of childbearing potential, must agree to use a barrier method of contraception, **consistent with local regulations,**….
Rationale: The example of an active stoma is being added as an exclusion criterion to reduce confusion as an active stoma would confound the ability to calculate the CDAI.	
4.2 Exclusion Criteria, #1	Has complications of CD that are likely to require surgery or would confound the ability to assess the effect of ustekinumab or adalimumab treatment using the CDAI, such as: **active stoma;** short-gut syndrome and severe or symptomatic strictures or stenosis.

Applicable Section(s)	Description of Change(s)
Rationale: For clarity, additional details are being added for hepatitis C testing at study entry.	
4.2 Exclusion Criteria, #12	Is seropositive for antibodies to hepatitis C (HCV) without a history of clearance or successful treatment, defined as being negative for HCV RNA in the past year and, if treated, at least 24 weeks after completing antiviral treatment. **Subjects who test positive for anti-HCV antibodies must undergo further testing for HCV RNA. If the HCV RNA test is positive, the subject is not eligible for this study. If the HCV RNA test is negative, the subject is eligible for this study. In the event the HCV RNA test cannot be performed, the subject is not eligible for this study.**
Time & Events Schedule, notes	**Screening for HCV to include anti-HCV antibodies. Subjects are eligible if they are: 1) negative for this test OR 2) positive for anti-HCV antibodies but have a negative HCV RNA test.**
Rationale: A typographical error in the C-reactive protein units is being corrected.	
Definitions of Terms, Normalization of C-reactive protein	C-reactive protein (CRP) ≤ 3 **m**~~u~~g/L
Rationale: Text related to infection details in patient diary cards is being deleted since subjects are not required to write infection information in their diary cards.	
6. Dosage and Administration (last paragraph, 2nd sentence)	Investigators are required to evaluate subjects for any signs or symptoms of infection~~, and also review subjects' diary cards for signs of infection,~~ at scheduled visits (see Time and Events Schedule).
Rationale: Text to clarify that a video ileocolonoscopy at any time 3 months prior to randomization is acceptable is being added.	
9.2.2 Video Ileocolonoscopy, 2nd sentence; Time and Events Schedule (under Notes)	A video ileocolonoscopy recorded during screening and/or within the 3 months prior to randomization may be used. ~~The screening video ileocolonoscopy should be performed at least 8 days before the Week 0 visit.~~
Rationale: Correction of inadvertent omission regarding hepatitis testing.	
9.4.4.1 Tests, 5th bullet	• Serology for HIV antibody, HBsAg, **anti-HBs, anti-HBc,** and hepatitis C virus antibody
Rationale: Clarification is being made to allow for repeat screening laboratory tests in certain cases.	
9.4.4.1 Tests (last paragraph)	**In some cases it may be medically appropriate to repeat screening laboratory tests if test values are outside of the required ranges; contact the Sponsor's medical monitor to discuss specific cases.**
Rationale: A Legally Acceptable Representative is not allowed per the consenting process since a subject must be able to participate on their own accord. In addition, wording is being clarified to avoid any confusion with study entry eligibility, and to allow for Investigators judgment regarding discontinuation for certain cases of latent TB.	

Applicable Section(s)	Description of Change(s)
10.2, Discontinuation of Treatment, 4th and 9th bullets	• The subject is deemed ineligible **to receive further study treatment** according to the following TB screening criteria: Note: **Consideration for study agent discontinuation** ~~Study agent must be discontinued~~ **may be given** for ~~all~~ subjects diagnosed with latent TB in countries with high multidrug-resistant TB burden [eg, South Africa, Bulgaria, and the Russian Federation]). • The subject ~~(or the subject's representative)~~ withdraws consent for further administration of study agent.
Rationale: A section heading is being added for "other" endpoints and the previously listed "other secondary" endpoints were categorized as secondary or other, as appropriate.	
11.3 Endpoints	11.3.3 ~~Other~~ Secondary Endpoints **11.3.4 Other Endpoints**
Rationale: Clarification	
11.3.4 Other Endpoints, Efficacy endpoints at (or through) week 52, 24th bullet	The time to first flare (a flare is defined as an increase in CDAI score of > 100 points at ~~all~~ any subsequent visits through Week 52 [based upon loss of clinical response]) among subjects in clinical response at Week 16
Rationale: Text is being adjusted to reflect that local regulations may require varying return instructions for study medication.	
14.5 Drug Accountability, 4th sentence	**If required per local regulations,** subjects must be instructed to return all original containers, whether empty or containing study drug.
Rationale: Language is being updated to remove requirement for dates of birth, to be aligned with EU Privacy law updates.	
17.3 Subject Identification, Enrollment, and Screening Logs, 2nd paragraph, 3rd sentence	All reports and communications relating to the study will identify subjects by subject identification and **age at initial informed consent** ~~date of birth~~. In cases where the subject is not randomized into the study, the date seen and **age at initial informed consent** ~~date of birth~~ will be used.
Rationale: The cover page footnote is being edited to add the sponsor's affiliate for Russia.	
Cover page	**Janssen Pharmaceutica NV**

SYNOPSIS

Title: A Phase 3b, Multicenter, Randomized, Blinded, Active-Controlled Study to Compare the Efficacy and Safety of Ustekinumab to that of Adalimumab in the Treatment of Biologic Naïve Subjects with Moderately-to-Severely Active Crohn's Disease

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

The primary objective is to compare the efficacy of treatment with ustekinumab to that of adalimumab in biologic naïve subjects with moderately-to-severely active Crohn's Disease (CD) who have previously failed or were intolerant to conventional therapy (corticosteroids and/or immunomodulators, ie, azathioprine, 6-mercaptopurine, or methotrexate), as measured by clinical remission at one year.

Secondary objectives are to evaluate the following in biologic naïve subjects with moderately-to-severely active CD treated with ustekinumab or adalimumab:

- Other measures of clinical efficacy (eg, clinical response) including reductions in frequent concomitant medications associated with adverse outcomes (eg steroids, narcotics)
- Anti-inflammatory efficacy assessed with biomarkers (eg, fecal calprotectin, C-reactive protein)
- Endoscopic endpoints (eg, endoscopic remission)
- Safety (eg, proportions of subjects with serious adverse events, all adverse events, etc.)
- CD-related healthcare utilization (eg, CD-related hospitalizations, surgeries, emergency room [ER] visits) and the need to initiate another biologic treatment
- Patient Reported Outcome (PRO) assessments such as Inflammatory Bowel Disease Questionnaire (IBDQ) and Patient Reported Outcome Measurement Information System (PROMIS), such as quality of life.

Endpoints

The primary endpoint is the proportion of subjects with clinical remission (defined as a Crohn's Disease Activity Index [CDAI] score <150) at Week 52.

Major secondary endpoints are the proportion of subjects with:

- Corticosteroid-free remission at Week 52 (defined as a CDAI score < 150 and not taking any corticosteroids for at least 30 days prior to Week 52)
- Clinical response (defined as a CDAI score decrease ≥100 from baseline) at Week 52
- PRO-2 symptom remission at Week 52 (defined as an abdominal pain [AP] mean daily score at or below 1 and also stool frequency [SF] mean daily score at or below 3, ie, AP≤1 and SF≤3). PRO-2 are the stool frequency and abdominal pain scores reported as part of the CDAI.
- Clinical remission (defined as CDAI < 150) at Week 16
- Endoscopic remission (defined as an SES-CD score ≤3, or = 0 for subjects who enter the study with an SES-CD =3) at Week 52

Other endpoints, including endpoints related to safety and PROs, are listed in Section 11.3.3.

Hypothesis

Ustekinumab is superior to adalimumab as measured by clinical remission after one year of treatment in biologic naïve subjects with moderately-to-severely active CD who have previously failed or were

intolerant to conventional therapy (corticosteroids and/or immunomodulators, ie, azathioprine, 6-mercaptopurine, or methotrexate).

OVERVIEW OF STUDY DESIGN

This is a global, randomized, blinded, parallel-group, active-controlled multicenter study. A target of approximately 350 subjects from up to 200 sites will be randomly allocated in a 1:1 ratio (approximately 175 subjects per treatment arm) to receive study agent (ustekinumab or adalimumab) using approved dosing regimens (specifically, the United States Prescribing Information [USPI] dosing regimens, which are incorporated within approved posology in the European Union [EU] and other regions). The target population consists of subjects with moderately-to-severely active CD of at least 3 months' duration, with a CDAI score ≥ 220 and ≤ 450 and with one or more ulcerations on ileocolonoscopy who have failed conventional therapy but are biologic naïve.

The study is a superiority study examining rates of clinical remission (ie, CDAI <150) after one year of treatment (at Week 52). Study visits are to occur at Screening (within 5 weeks prior to Week 0), and Weeks 0 (baseline), 2, 8, 16, 24, 32, 40, 48, 52 (primary endpoint), and 56, with a final follow-up telephone call (or on-site, of desired) visit at Week 76.

Study assessments include CDAI and video ileocolonoscopy; CD-related healthcare utilization; PROs (IBDQ [Inflammatory Bowel Disease Questionnaire], PROMIS-29 [Patient Reported Outcome Measurement Information System-29], and WPAI [Work Productivity and Activity Index]); laboratory evaluations (including hematology, chemistry with C-reactive protein, pregnancy tests, and fecal calprotectin); biomarkers; physical examinations; vital signs measurements; review of concomitant medications and adverse events (AEs); and evaluation of serum concentrations of study agent as well as development of antibodies to study agent.

SUBJECT POPULATION

Subjects are men or women ≥18 years of age who have moderately-to-severely active CD of at least 3 months duration, a baseline CDAI score ≥ 220 and ≤ 450, and ulcerations on screening ileocolonoscopy, and have failed conventional CD therapy or be steroid-dependent for CD, and be biologic naïve. Subjects with any known malignancy or a history of malignancy or lymphoproliferative disease are to be excluded.

DOSAGE AND ADMINISTRATION

Subjects randomized to ustekinumab will receive a ~6 mg/kg intravenous (IV) induction at Week 0 followed by 90 mg subcutaneous (SC) injections every 8 weeks through Week 56, with the first SC administration occurring at Week 8. Subjects randomized to adalimumab will receive 4 x 40 mg SC injections at Week 0 (160 mg total), followed by 2 SC injections (80 mg total) at Week 2 and then 40 mg SC every 2 weeks (q2w) from Week 4 to Week 56. Further details, including additional placebo administrations needed to preserve the blind, are provided below.

At Week 0, after all study-related procedures have been completed, in order to maintain blinding, subjects will receive medications as follows:

- Group 1 (ustekinumab): An IV infusion of ustekinumab (6 mg/kg) and
  4 SC injections of placebo (to blind for adalimumab)

The approximately 6 mg/kg IV infusion of ustekinumab is given in the weight-based fashion shown below, consistent with labelling:

- 260 mg (weight ≤ 55 kg)
- 390 mg (weight > 55 kg and ≤ 85 kg)
- 520 mg (weight > 85 kg)

- Group 2 (adalimumab): An IV infusion of placebo (to blind for ustekinumab) and 4 SC injections of adalimumab (each 40 mg)

At Week 2, after all study-related procedures have been completed, subjects will receive the following:

- Group 1 (ustekinumab): 2 SC injections of placebo (to blind for adalimumab)
- Group 2 (adalimumab): 2 SC injections of adalimumab (each 40 mg)

All SC study agent administrations at Weeks 0 and 2 will be performed (or supervised) by an unblinded study site staff member (with no other study personnel involved in handling of SC study agent outside of the carton). At these visits, subjects will be trained to self-administer SC study agent by the unblinded study site staff member for subsequent study agent administrations. In contrast, the blinded, double-dummy IV infusion at Week 0 can be administered by blinded study personnel.

Beginning at Week 4 (non-visit week) and continuing through Week 56, subjects will self-administer study agent (generally at home) and will receive:

- Group 1 (ustekinumab): 1 SC injection every 2 weeks (q2w); ustekinumab 90 mg will be administered every eighth week after Week 0, with placebo for adalimumab administered at the other designated q2w dosing intervals
- Group 2 (adalimumab): 1 SC injection of adalimumab 40 mg q2w.

EFFICACY EVALUATIONS

Efficacy evaluations will be based on the results of the CDAI, ileocolonoscopy using the SES-CD scoring system, C-reactive protein and fecal calprotectin, and questionnaires for PROs (IBDQ, PROMIS-29, and WPAI-CD).

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Serum samples will be used to evaluate the serum concentrations of ustekinumab and adalimumab, as well as immunogenicity through assessment of antibodies to both study agents. Serum concentrations and detection and characterization of antibodies will be determined using validated, specific, drug-tolerant and sensitive methods by or under the supervision of the sponsor.

SAFETY EVALUATIONS

Safety will be assessed by evaluating AEs as well as laboratory changes through Week 52 or Week 76. Physical examinations, directed physical examinations (ie, examination for abdominal mass, perianal fistula, and other fistulas), vital signs, and weight, as well as blood sample collection for serum chemistry and hematology will be performed.

STATISTICAL METHODS

Sample Size Determination

The assumptions for sample size and power calculations were based on ustekinumab data from completed Phase 3 studies in the appropriate sub-population of biologic naive CD subjects, as well as in the relevant anti-tumor necrosis factor (TNF) studies, specifically, the adalimumab Phase 3 CHARM study,[7] also confirmed by the infliximab Phase 3b SONIC study,[6] which utilized a similar population and design to the

proposed study. Assuming a 41% clinical remission rate at Week 52 in the adalimumab group and 56% in the ustekinumab group, 175 subjects per treatment group will yield power of approximately 80%, at a significance level of 0.05 (2-sided Mantel-Haenszel test).

Efficacy Analyses

For the primary endpoint, the proportion of subjects in clinical remission at Week 52 will be compared between the ustekinumab treatment group and the adalimumab treatment group using a 2-sided Cochran-Mantel Haenszel chi-square test, stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and the presence of ulcerations >5 mm on screening/baseline ileocolonoscopy (Yes, No) at a significance level of 0.05.

All of the major and other secondary endpoints will be compared between the ustekinumab treatment group and the adalimumab treatment group using a similar method.

Safety Analyses

Safety will be assessed by analyses of the incidence and type of AEs, serious adverse events (SAEs), AEs considered by the investigator to be possibly, probably or very likely related to study agent, AEs leading to discontinuation of study agent, infections, and injection-site and/or infusion reactions. Safety assessments will also include analyses of laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) and incidence of markedly abnormal laboratory parameters (hematology and chemistry).

TIME AND EVENTS SCHEDULE

Study Procedure	Screening Visit (1 to 5 weeks prior to Week 0)	Study Visits (Week)[a]										Early Term[b]	Week 76 Follow-up[c]	Notes
		0	2	8	16	24	32	40	48	52	56			
Screening and Randomization														
Informed consent	X													Must be signed before any study-related activities are performed.
Confirm inclusion/exclusion criteria	X	X												Eligibility should be reconfirmed at Week 0 PRIOR to randomization.
Medical history and other baseline characteristics	X													--
Randomization		X												Subjects are to be randomized after all entry criteria are confirmed.
QuantiFERON-TB test	X													Refer to Inclusion Criterion #9 for further details.
Chest radiograph	X													An adequate chest radiograph taken within 3 months prior to Week 0 visit may be used (ie, is sufficient).
Serum β-hCG pregnancy test	X													To be performed in females of childbearing potential.
Hepatitis B and C serology	X													Screening for HBV, at a minimum, to include HBsAg, anti-HBs, and anti-HBc. Subjects are eligible for study if they are: 1) negative for these tests OR 2) negative for HBsAg; positive only for anti-HBs; or positive for anti-HBc and surface antibody OR 3) positive only for anti-HBc, but with a negative HBV DNA test. Screening for HCV to include anti-HCV antibodies. Subjects are eligible if they are: 1) negative for this test OR 2) positive for anti-HCV antibodies but have a negative HCV RNA test. See Section 4.2.
HIV antibody test	X													Unless negative result in last 3 months is available

Study Procedure	Screening Visit (1 to 5 weeks prior to Week 0)	Study Visits (Week)[a] 0	2	8	16	24	32	40	48	52	56	Early Term[b]	Week 76 Follow-up[c]	Notes
Stool for enteric pathogens	X													Stool studies for enteric pathogens may be performed at either the central or local laboratory and must include a stool culture and *C. difficile* toxin assay performed within 4 months prior to Week 0. Additional testing, such as ova and parasite or *E. coli* O157:H7 assessments, may be performed at the investigator's clinical discretion.
Dispense CDAI diary and train subjects regarding completion	X													Diary to record CDAI components, concomitant medications, and at-home study agent administrations (using adhesive labels from syringe box/kits).
Efficacy (clinical assessments/CD-related healthcare utilization/PROs)														
CDAI (diary collection)		X	X	X	X	X	X	X	X	X	X	X		CDAI must be calculated at Week 0 for eligibility (using screening hematocrit value).
Weight (component of CDAI)	X	X	X	X	X	X	X	X	X	X	X	X		In Kilograms (Kg)
Video ileocolonoscopy	X									X		X		A video ileocolonoscopy recorded during screening and/or within the 3 months prior to randomization may be used. Week 52 procedure should be performed ± 14 days from Week 52 date. In the event that ileocolonoscopies coincide with visit dates or the 7 days prior, CDAI scores should be calculated using the proximate 7 days not impacted by the ileocolonoscopy and/or its preparation.

Study Procedure	Screening Visit (1 to 5 weeks prior to Week 0)	Study Visits (Week)[a] 0	2	8	16	24	32	40	48	52	56	Early Term[b]	Week 76 Follow-up[c]	Notes
Fecal calprotectin	X			X	X					X		X		Samples should not be collected during ileocolonoscopy preparation. Screening sample may be provided at Week 0, or when necessary on different days than study visits (though as close as possible).
Record CD-related healthcare utilization		X	X	X	X	X	X	X	X	X	X	X	X	Items to be recorded are listed in the healthcare resource utilization worksheet.
PROs (IBDQ, PROMIS-29, WPAI)		X		X	X					X		X		After randomization, PROs should be conducted prior to other study-specific procedures.
Safety Procedures														
Laboratory Evaluations														
Hematology and chemistry, including CRP	X	X	X	X	X	X	X	X	X	X	X	X		Laboratory tests (described in Section 9.4.4) at Week 0 are not required if hematology and chemistry tests were performed within 2 weeks before the Week 0 visit. Samples should be collected before study drug administration. Blood samples for chemistry and hematology will be analyzed at a central laboratory unless otherwise specified or approved by the medical monitor.
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X		Only in females of childbearing potential. The Week 0 must be performed prior to randomization, to determine eligibility. At all other visits, perform prior to dispensing study agent.
Blood collection for evaluation of serum concentrations and/or anti-drug-antibodies		X		X	X		X		X	X		X		Samples should be collected before study drug administration.
Blood collection for serum biomarkers		X	X	X	X					X		X		Serum biomarkers will be collected from all participants in the study to assess peripheral

Study Procedure	Screening Visit (1 to 5 weeks prior to Week 0)	Study Visits (Week)[a] 0	2	8	16	24	32	40	48	52	56	Early Term[b]	Week 76 Follow-up[c]	Notes
														proteins related to both Crohn's disease and response to ustekinumab and adalimumab, including (but not limited to) IL-17A and IL-22.
Whole blood sample collection for RNA analysis		X	X		X					X		X		Whole blood for RNA analysis will be collected from all participants in the study to assess the RNA transcriptome related to both Crohn's disease and response to ustekinumab and adalimumab.
Additional Safety Evaluations														
Directed Physical Exam at all visits, with additional Full Physical Exam where noted (Full)	X (Full)	X	X	X	X	X	X	X	X	X	X (Full)	X (Full)		Directed physical exam for abdominal mass and fistulas, (perianal and other) at all visits. Additional full physical exam, including height, where indicated.
Vital signs	X	X										X		Vital signs to include temperature, pulse/heart rate, respiratory rate, and blood pressure. Vital signs to be obtained before, approximately every 30 minutes during, and approximately 30 and 60 minutes after completion of Week 0 IV infusion, and before and approximately 30 minutes after Week 0 SC injections.
Prior and concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	Record all prescribed and OTC medications as specified in the eCRF, including initiation of any biologic therapy outside of that provided in this study.
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	Adverse events are to be recorded beginning after the informed consent form is signed through the end of the study. After a subject's participation in the study has ended, adverse events should be followed as described in Section 12.3.
TB and other infection assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	At each visit, site personnel will monitor subjects for signs or symptoms of TB or other infections. In addition, subjects will be advised on the risks of TB and other infectious disease and will be instructed to monitor themselves on an ongoing-

Study Procedure	Screening Visit (1 to 5 weeks prior to Week 0)	Study Visits (Week)[a] 0	2	8	16	24	32	40	48	52	56	Early Term[b]	Week 76 Follow-up[c]	Notes
														basis while away from the site. If TB is suspected at any time during the study, a chest x-ray and QuantiFERON-TB In-Tube test should be performed.
Study Drug Administration														
Dispense study agent		X[d]	X	X	X	X	X	X	X	X	X			SC study agent administered with the assistance of unblinded site personnel at Weeks 0 and 2. Thereafter study agent self-administered by subjects q2w (generally at home). Study agent should not be administered if subject is experiencing a clinically important active infection. Week 56 study agent to be dispensed only after Week 52 visit assessments (including ileocolonoscopy) have been completed and entered into eCRF. If necessary, subjects may be unblinded after Week 56 study agent dispensed.

a: Study visits should occur at the specified times post-Week 0 +/- 8 days (except Week 2, which should occur +/- 4 days). Note that while visits out of this window should be documented as a protocol deviation, performing them out of window is preferable to not performing them at all, unless so much time has passed that it is time for the next visit.

b: To be performed if subjects wish to terminate study participation (eg withdrawing their consent to participate). When subjects discontinue study agent, the early term visit should be performed 20-24 weeks after last study agent received, unless they refuse to do so in which case this withdrawal of consent results in performance of this visit at that time.

c: This visit, which can occur by phone, applies to all subjects, even those who discontinued study agent prior to Week 56 or who have otherwise terminated study participation (eg, withdrawal of consent) unless they specifically do not consent to this telephone follow up from the site.

d: Both IV and SC study agent are administered at Week 0 (baseline) visit. IV infusions (at Week 0) are to be administered over a period of at least 1 hour, and generally completed within 2 hours. Though not required, it is recommended that Week 0 SC study agent be administered first, prior to the Week 0 IV study agent, for operational efficiency (eg, that way SC injections can be administered after randomization while the IV infusion is prepared). In any case, regardless of whichever treatment is administered first, it is mandatory that at least 1 hour pass between completion of the first study agent and initiation of the second.

Key: CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = c-reactive protein; eCRF = electronic case report form; HBc = hepatitis B virus core; HBs = hepatitis B surface; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; IBDQ = Inflammatory Bowel Disease Questionnaire; IL = interleukin; IV = intravenous; OTC = over-the-counter; PRO = patient-reported outcome; PROMIS-29 = Patient Reported Outcome Measurement Information System; q2w; every 2 weeks; SC = subcutaneous; TB = tuberculosis; WPAI = Work Productivity and Activity Index.

ABBREVIATIONS

Abbreviation	Definition
6-MP	6-mercaptopurine
6-TG	6-thioguinine
β-hCG	β-human chorionic gonadotropin
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
AZA	azathioprine
BCG	Bacille Calmette-Guérin
BUN	blood urea nitrogen
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRP	C-reactive protein
eCRF	electronic case report form
eDC	electronic data capture
ER	emergency room
EU	European Union
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1k	immunoglobulin G1 kappa
IL	Interleukin
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
JAK	Janus kinase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
PFS	pre-filled syringe
PQC	Product Quality Complaint
PRO	patient-reported outcome
PROMIS	Patient Reported Outcome Measurement Information System
q2w	every 2 weeks
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Definition
TB	tuberculosis
TNF	tumor necrosis factor
TPN	total parenteral nutrition
ULN	upper limit of normal
USPI	United States Prescribing Information
WBC	white blood cells
WPAI	Work Productivity and Activity Index

DEFINITIONS OF TERMS

Term	Definition
Clinical remission	CDAI score < 150
Clinical response	Decrease in CDAI score of ≥ 100 from baseline
Corticosteroid-free remission	CDAI score < 150 and not taking any corticosteroids for at least 30 days prior to Week 52
Corticosteroid-free response	Decrease in CDAI score of ≥ 100 from baseline and not taking any corticosteroids for at least 30 days prior to Week 52
Endoscopic improvement	Change in SES-CD score of at least 3 points
Endoscopic remission	SES-CD score ≤3 (or =0 for subjects who enter the study with an SES-CD =3)
Endoscopic response	Reduction in SES-CD score by 50% from baseline
IBDQ remission	Score of > 170
Normalization of C-reactive protein	C-reactive protein (CRP) ≤ 3 mg/L (among subjects with abnormal CRP at baseline)
Perianal/perirectal fistula healing	Complete closure of perianal/perirectal fistulas present at baseline
Time to first flare	Time to an increase in CDAI score of >100 points
Women of non-childbearing potential	Women ≥45 years of age with amenorrhea for at least 18 months or hysterectomy or tubal ligation, or ≥45 years of age with amenorrhea for at least 6 months and a serum follicle-stimulating hormone (FSH) of > 40 IU/mL

1. INTRODUCTION

Ustekinumab is a fully human immunoglobulin (IgG)1k 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 blocking their interaction with their cell surface IL-12Rβ1 receptor protein. Through this mechanism of action, ustekinumab effectively neutralizes all IL-12 (Th1) and IL-23 (Th17) mediated cellular responses tested using in vitro bioassays. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases, including inflammatory bowel disease, and binding the IL 12/23p40 subunit provides effective therapy in Crohn's disease (CD).

Ustekinumab has been approved for multiple indications for immune-mediated diseases. It has been approved in multiple countries for the treatment of patients with moderately-to-severely active CD who:

- Have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker, or
- Have failed or were intolerant to treatment with one or more TNF blockers.[21]

In both populations, treatment was effective for both induction of response at 6 weeks and remission at 8 weeks as well as maintenance of remission and response after a total of one year of treatment.[10]

Adalimumab is a recombinant human IgG1 mAb that binds specifically to human TNFα. This binds soluble TNF, blocking interaction with the p55 and p75 cell surface TNF receptors. It also binds cell surface TNF. Adalimumab has multiple indications for immune-mediated diseases. Adalimumab has been approved for moderately-to-severely active CD in patients who (per the United States Prescribing Information [USPI]).[17]

- Are naïve to TNF blockers,
- Have had an inadequate response to conventional therapy, or
- Have lost response to, or were intolerant of, infliximab.

Adalimumab is also approved for maintenance of clinical remission.

While both ustekinumab and adalimumab are approved and widely used to treat CD, it is not known whether one offers superior clinical results than the other. Comparison of results from previously published trials suggest similar results in induction, but lower response and remission rates in biologic naïve subjects treated with adalimumab maintenance compared to biologic naïve subjects treated with ustekinumab. However, indirect comparisons across studies are problematic due to different study designs, endpoints, populations, and other factors. Since these medications have not been evaluated in a head-to-head trial, this represents an important gap in the scientific literature important for evidence-based practice. This study will fill this gap by providing a prospective, randomized direct comparison of one year of treatment with ustekinumab and adalimumab, evaluating efficacy and safety in biologic naïve subjects with Crohn's disease who have failed conventional therapy.

Note that 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.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives

Primary:

To compare the efficacy of treatment with ustekinumab or adalimumab in biologic naïve subjects with moderately-to-severely active CD who have previously failed or were intolerant to conventional therapy (corticosteroids and/or immunomodulators, ie, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]), as measured by clinical remission at one year.

Secondary:

To evaluate the following in biologic naïve subjects with moderately-to-severely active CD treated with ustekinumab or adalimumab:

- Other measures of clinical efficacy (eg, clinical response) including reductions in frequent concomitant medications associated with adverse outcomes (eg steroids, narcotics)
- Anti-inflammatory efficacy assessed with biomarkers (eg, fecal calprotectin, C-reactive protein)
- Endoscopic endpoints (eg, endoscopic remission)
- Safety (eg, proportions of subjects with serious adverse events, all adverse events, etc.)
- CD-related healthcare utilization (eg, CD-related hospitalizations, surgeries, emergency room [ER] visits) and the need to initiate another biologic treatment
- Patient-reported outcome (PRO) assessments, such as Inflammatory Bowel Disease Questionnaire (IBDQ) and Patient Reported Outcome Measurement Information System (PROMIS).

2.2. Endpoints

Primary Endpoint:

The proportion of subjects with clinical remission (defined as a Crohn's Disease Activity Index [CDAI] score < 150) at Week 52.

Major Secondary Endpoints:

The proportion of subjects with:

- Corticosteroid-free remission at Week 52 (defined as a CDAI score < 150 and not taking any corticosteroids for at least 30 days prior to Week 52)
- Clinical response (defined as a CDAI score decrease ≥100 from baseline) at Week 52

- PRO-2 symptom remission at Week 52 (defined as an abdominal pain [AP] mean daily score at or below 1 and also stool frequency [SF] mean daily score at or below 3, ie, AP≤1 and SF≤3)
- Clinical remission (defined as CDAI < 150) at Week 16
- Endoscopic remission (defined as an SES-CD score ≤3, or SES-CD =0 for subjects who enter the study with an SES-CD =3) at Week 52

Other Endpoints: Refer to Section 11.3.3 for a list of all other endpoints.

2.3. Hypothesis

Ustekinumab is superior to adalimumab as measured by clinical remission after one year of treatment (ie, at the Week 52 visit) in biologic naïve subjects with moderately-to-severely active CD who have previously failed or were intolerant to conventional therapy (corticosteroids and/or immunomodulators).

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a global, randomized, blinded, parallel-group, active-controlled multicenter study. A target of approximately 350 subjects from up to 200 sites will be randomly allocated in a 1:1 ratio (approximately 175 subjects per treatment arm) to receive study agent (ustekinumab or adalimumab) using on-label, approved dosing regimens described further below. The study is a superiority study examining rates of clinical remission (ie, CDAI <150) after one year of treatment (at Week 52).

The target population consists of men or women ≥18 years of age at the time of informed consent with moderately-to-severely active CD of at least 3 months' duration, with a CDAI score of ≥ 220 and ≤ 450 and with ulcerations on ileocolonoscopy who have not previously received biologic therapy (ie, are biologic naïve) and who have failed conventional therapy. For a full list of entry criteria, see Section 4.

Study visits are to occur at Screening (within 1- 5 weeks prior to Week 0), and Weeks 0, 2, 8, 16, 24, 32, 40, 48, 52 (primary endpoint), and 56, with a final follow-up telephone call (or on-site visit, if preferred) at Week 76.

At Week 0, after all study-related procedures have been completed, subjects will receive the following:

- Group 1 (ustekinumab): An intravenous (IV) infusion of ustekinumab (approximating 6 mg/kg per weight-based dosing) and 4 subcutaneous (SC) injections of placebo for adalimumab
- Group 2 (adalimumab): An IV infusion of placebo for ustekinumab and 4 SC injections of adalimumab (each 40 mg)

IV infusions (at Week 0) are to be administered over a period of at least 1 hour, and generally completed within 2 hours. Though not required, it is recommended that Week 0 SC study agent be administered first, prior to the Week 0 IV study agent, for operational efficiency (eg, that way SC injections can be administered after randomization while the IV infusion is prepared). In any case, regardless of whichever treatment is administered first, it is mandatory that at least 1 hour pass between completion of the first study agent and initiation of the second.

At Week 2, after all study-related procedures have been completed, subjects will receive the following:

- Group 1 (ustekinumab): 2 SC injections of placebo
- Group 2 (adalimumab): 2 SC injections of adalimumab (each 40 mg)

All SC study agent administrations at Weeks 0 and 2 will be performed (or supervised) by an unblinded study site staff member (see Section 6). At these visits, subjects will be trained to self-administer SC study agent by the unblinded study site staff member for subsequent study agent administrations. The blinded, double-dummy IV infusion at Week 0 can be administered by blinded study personnel.

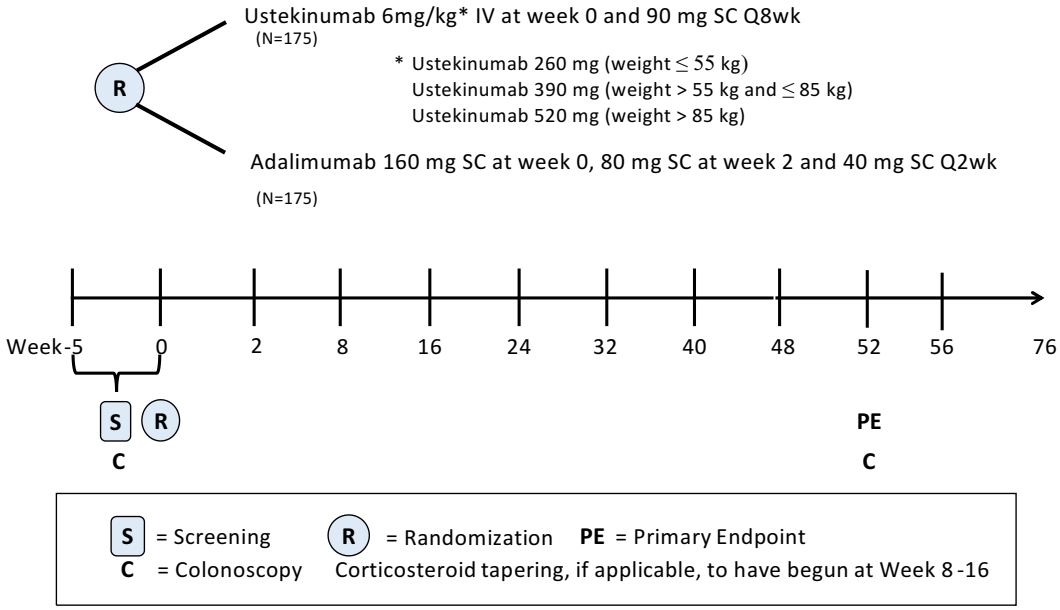
Beginning at Week 4 (non-visit week) and continuing through Week 56, subjects will self-administer study agent, generally at home, and will receive:

- Group 1 (ustekinumab): 1 SC injection every 2 weeks (q2w); ustekinumab 90 mg will be administered every eighth week after Week 0, with placebo for adalimumab administered at the other designated q2w dosing intervals
- Group 2 (adalimumab): 1 SC injection of adalimumab 40 mg q2w.

Study assessments include CDAI, video ileocolonoscopy; CD-related healthcare utilization (eg, CD-related hospitalizations, surgeries, ER visits, initiation of biologic treatment outside of that provided by protocol); PROs (Inflammatory Bowel Disease Questionnaire [IBDQ], Patient Reported Outcome Measurement Information System [PROMIS]-29, and Work Productivity and Activity Index [WPAI]); laboratory evaluations (including hematology, chemistry with CRP, pregnancy tests, and fecal calprotectin); biomarkers; physical examinations; vital signs; weight, review of concomitant medications and adverse events (AEs); and evaluation of serum concentrations of study agent as well as development of antibodies to study agent.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



3.2. Study Design Rationale

3.2.1. Overall Rationale and Endpoints Chosen for Evaluation

Crohn's disease is an autoimmune disorder causing significant symptoms as a result of gut inflammation, which may affect the entire gastrointestinal (GI) tract as well as multiple other organ systems. It is a chronic disease that has a progressive course resulting in both penetrating and fibrotic complications. As many as 70% of patients with CD will develop complications, many of whom will require surgical management during their lifetime, often including multiple bowel resections.[8]

Treatment with anti-TNF mAbs has revolutionized the management of CD and has become the standard therapeutic approach in patients with moderately-to-severely active disease, either after, before, or concomitantly with immunomodulatory medications. Since the approvals of these medications, healthcare utilization such as hospitalizations and surgeries for CD has been decreasing.[11,17] However, approximately one third of patients treated with anti-TNF antibodies do not respond to these agents and of those who do respond, 30-40% lose response within the first year.[18,24]

Two Phase 3 pivotal trials, UNITI-1 (CNTO1275CRD3001) and UNITI-2 (CNTO1275CRD3002), evaluated response and remission after induction with IV ustekinumab.[10] The first trial enrolled subjects who had failed or were intolerant to TNF blockers, while the second enrolled subjects who had failed conventional therapy but not anti-TNF agents. In UNITI-2, the majority of subjects (~2/3) were anti-TNF naïve with the remaining (~1/3) having been exposed

to but not failed any of these medications. A total of 59% of these subjects in UNITI-2 responded to induction with IV ustekinumab after 8 weeks.

Subjects who responded to IV ustekinumab at Week 8 of these induction studies then entered the IM-UNITI (CNTO1275CRD3003) maintenance study in the primary efficacy population, and underwent randomized withdrawal for 44 more weeks, and were randomized 1:1:1 to receive either SC ustekinumab 90 mg q8w, 90 mg q12w, or SC placebo.

As has been seen with other medications, including adalimumab, subjects who had not failed TNF blockers had a greater response to treatment with ustekinumab compared to those who had failed these medications, particularly in induction.[10] The reasons for the more refractory nature of CD in patients who have failed TNF blockers is unknown, but could be due to somewhat shorter disease duration and/or severity seen in the TNF blocker naïve patient population. Among anti-TNF-naïve subjects who had responded to induction treatment, 65% were in remission after a total of 1 year of ustekinumab treatment. Based on these trials, ustekinumab was approved for the treatment of CD in patients who failed TNF blockers as well as those who failed only conventional therapy.

Of note, subjects with CD treated with ustekinumab have been shown to have an anti-drug antibody incidence of <3%, using a newer drug tolerant, high sensitivity assay. This likely means that the practice of adding an immunomodulator such as AZA, 6-MP, or MTX that is common with infliximab likely is neither necessary or helpful. Ustekinumab also has an acceptable safety profile, with a long history of use in psoriasis, having been first approved in 2009, complementing the more recent approvals in CD in 2016.

Response of subjects with CD to induction with adalimumab in TNF blocker-naïve subjects was demonstrated with the CLASSIC I study[12] and a maintenance phase for these subjects was evaluated in the CLASSIC II trial, albeit with a relatively small number of subjects.[19] A third trial, CHARM,[7] was performed in which subjects were given open-label induction with adalimumab and responders entered a randomized withdrawal study where they were randomized 1:1:1 to receive adalimumab SC 40 mg every other week, 40 mg every week, or SC placebo. A total of 41% of induction responder anti-TNF naïve subjects treated with adalimumab 40 mg every other week were in remission after a year of treatment.[7,20]

No direct comparative studies have been performed to evaluate the efficacy and safety of ustekinumab in CD relative to that of adalimumab. The maintenance trials mentioned above were randomized withdrawal studies of induction responders. A treat-through trial design in which all subjects undergo induction therapy and then progress to the maintenance portion of the trial is more aligned with real-world treatment of patients with CD, but is not generally done in Phase 3 registrational studies because of challenges in executing them with a placebo comparison.

This trial will compare one year of continuous treatment with ustekinumab versus adalimumab in subjects who are naïve to treatment with biologic therapies, but have failed conventional therapy (consistent with labelling of both agents). Generating comparative efficacy data will allow development of more informed, evidence-based treatment strategies for patients with potentially progressive and high morbidity disease.

Treatment Groups, Randomization, and Blinding

There will be 2 treatment groups in this study, comparing standard dosing of the TNF blocker, adalimumab, with the anti-IL12/23 p40 mAb, ustekinumab. Randomization will minimize bias, increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and enhance the validity of statistical comparisons across treatment groups, and will be performed 1:1 with the stratification factors described in Section 11.4. Blinded treatment administration is being utilized to reduce potential bias during data collection.

Maintenance of the Blind

The sponsor and site monitors will remain blinded to treatment assignment until after the Week 52 database lock has occurred. The study blind will be maintained for the investigative sites and subjects participating in the study until after they have completed their Week 56 visit and the Week 52 assessments have been completed and entered into the electronic case report form (eCRF). In the event of an emergency, the investigator may also unblind a subject's treatment if such knowledge would change the subject's clinical care (see Section 5.2).

There will be a second database lock after the last subject has completed his or her Week 76 visit/interaction.

Healthcare Resource Utilization

Data pertaining to, eg, CD-related hospitalizations, surgeries, ER visits, medication use, and physician visits will be used to evaluate healthcare resource utilization, which are important considerations when assessing ideal therapy selection in CD patients.

4. PATIENT POPULATION

Screening for eligible subjects will be performed 1-5 weeks before administration of the study drug.

The inclusion and exclusion criteria for this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

A subject must meet the following criteria to be enrolled:

1. Be male or female (according to their reproductive organs and functions assigned by chromosomal complement) ≥18 years of age.
2. Has CD or fistulizing CD of at least 3 months' duration, with colitis, ileitis, or ileocolitis, confirmed at some time in the past by radiography, histology, and/or endoscopy.
3. Has moderately-to-severely active CD with a baseline CDAI score of ≥ 220 and ≤ 450.

4. Has one or more ulceration on screening ileocolonoscopy (which, by definition, would result in an SES-CD of at least 3).

   Note: If a subject had an ileocolonoscopy but then screen failed for another reason, if he/she is rescreened within 3 months, then that ileocolonoscopy is sufficient for inclusion if all other entry criteria are met.

5. Meets the following requirements for prior or current medications for CD:

   a) Has failed conventional therapy:

      i) Is currently receiving corticosteroids and/or immunomodulators (ie, AZA, MTX, or 6-MP) at adequate therapeutic doses;

      OR

      ii) Has a history of failure to respond to, or tolerate, an adequate course of corticosteroids and/or immunomodulators (ie, AZA, MTX, or 6-MP);

      OR

      iii) Is corticosteroid dependent or has a history of corticosteroid dependency;

      AND

   b) Has not previously received an approved biologic for CD (ie, infliximab, adalimumab, certolizumab pegol, ustekinumab, natalizumab, vedolizumab or approved biosimilars of these agents).

6. Subjects on oral corticosteroids (eg, prednisone, budesonide) at a prednisone-equivalent dose of ≤ 40 mg/day or ≤ 9 mg/day of budesonide are permitted provided doses meeting these requirements are stable for 3 weeks prior to baseline (Week 0) or these have been discontinued at least 3 weeks prior to baseline.

7. Subjects on the immunomodulators AZA, 6-MP, or MTX at screening (or recently prior), must discontinue these medications at least 3 weeks prior to baseline.

8. Has screening laboratory test results within the following parameters:

   a) Hemoglobin: ≥ 8.5 g/dL

   b) White blood cells (WBC): > 3.5 x 10^3/μL

   c) Neutrophils: >1.5 x 10^3/μL

   d) Platelets: > 100 x 10^3/μL

   e) Serum creatinine: < 1.7 mg/dL

   f) Aspartate transaminase (AST) and alanine transaminase (ALT) concentrations:

      Within 2 times the upper limit of normal range for the laboratory conducting the test.

   g) Direct (conjugated) bilirubin: < 1.0 mg/dL.

9. Is considered eligible per the following tuberculosis (TB) screening criteria:
    a) Has no history of latent or active TB prior to screening; exceptions are made for a subject who:
        - Is currently receiving treatment for latent TB without evidence of active TB (or has initiated treatment for latent TB prior to Week 0 study agent administration)
        - Has a history of latent TB and documentation of having completed adequate treatment for latent TB within 5 years prior to the first administration of study agent.

        It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide/obtain appropriate documentation.
    b) Has no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    c) Has had no recent, known close contact with a person with active TB or, if there has been such contact, the subject is to be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to, or simultaneously with, the first administration of study agent.
    d) Within 2 months prior to the first administration of study agent, either has:
        - A negative QuantiFERON-TB test, or
        - A newly identified positive QuantiFERON-TB test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to, or simultaneously with, the first administration of study agent.

        A subject whose first QuantiFERON-TB test result is indeterminate should have the test repeated. In the event that additional QuantiFERON-TB test result is persistently indeterminate, the subject should also initiate treatment for latent TB in order to enter the study.

        The QuantiFERON-TB In-Tube test is not required at screening for subjects with a history of latent TB and appropriate treatment as described above.
    e) Has a chest radiograph (at least a posterior-anterior view), taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.
10. If a woman, before randomization she must be:
    a) Postmenopausal, defined as
        i) ≥ 45 years of age with amenorrhea for at least 18 months,

        OR

        ii) ≥ 45 years of age with amenorrhea for at least 6 months and a serum FSH level > 40 IU/mL

        OR

b) Of childbearing potential, in which case she must satisfy at least one of the below:

i) Surgically sterile (has had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or

ii) If heterosexually active, practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, film, gel or suppository), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for a period of 16 weeks after the last administration of study agent,

or

iii) Not heterosexually active.

Note: If a woman participant's childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or if women of childbearing potential who are not heterosexually active at screening become heterosexually active, they must agree to utilize a highly effective method of birth control, as described above.

11. Female participants of childbearing potential (menstrual and not surgically sterile), must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening and a negative urine pregnancy test at Week 0 (prior to randomization) and agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 16 weeks after the last administration of study agent.
12. Male participants who are not surgically sterilized and are heterosexually active with a woman of childbearing potential, must agree to use a barrier method of contraception, consistent with local regulations, (eg, condom with spermicidal foam/gel/film/cream/suppository) and to not donate sperm during the study and for 16 weeks after last receiving study agent. Note that barrier methods must also be used in all male subjects sexually active with pregnant partners for at least 16 weeks after last study agent administration.
13. Sign an informed consent document indicating that he/she understands the purpose of, and procedures required for, the study and are willing to participate in the study.

4.2. Exclusion Criteria

A subject who meets any of the following criteria may not be enrolled in the study:

1. Has complications of CD that are likely to require surgery or would confound the ability to assess the effect of ustekinumab or adalimumab treatment using the CDAI, such as: active stoma; short-gut syndrome and severe or symptomatic strictures or stenosis.

2. Currently has, or is suspected to have, an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained and adequately treated at least 3 weeks prior to baseline, or 8 weeks prior for intra-abdominal abscesses, if there is no anticipated need for any further surgery. Subjects with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses present.

3. Has had any kind of bowel resection within 6 months prior to baseline or other intra-abdominal surgery or a hospital admission for bowel obstruction within 3 months prior to baseline.

4. At any time received any monoclonal antibody (including biosimilars) targeting TNFα, IL-12, or IL-23, or anti-integrin agents approved for CD (ie, vedolizumab or natalizumab) or has received any of the following medications or therapies within the specified periods prior to baseline:

   a) Any other investigational agent for CD (eg other biologics, small molecules or anti-sense RNA such as mongersen), unless at least 3 months or 5 half-lives have elapsed since last dose.

   b) IV corticosteroids as a treatment for CD < 3 weeks prior to baseline.

   c) Oral immunomodulatory agents other than AZA, 6-MP, or MTX (eg, Janus kinase [JAK] inhibitors, 6-thioguanine [6-TG], cyclosporine, tacrolimus, sirolimus, tofacitinib, or mycophenolate mofetil) < 4 weeks prior to baseline.

      (Note that per inclusion criterion 7, typical immunomodulator agents [AZA, 6-MP or MTX] must have been discontinued at least 3 weeks prior to baseline.)

   d) Treatment with apheresis (eg, Adacolumn apheresis) or total parenteral nutrition (TPN) as a treatment for CD < 3 weeks prior to baseline.

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

6. Has received a Bacillus Calmette–Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 2 weeks of baseline.

7. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection, recurrent urinary tract infection (eg, recurrent pyelonephritis or chronic nonremitting cystitis), or infected skin wounds or ulcers.

8. Has current signs or symptoms of infection, or recent (within 8 weeks prior to baseline) history of herpes zoster or serious infection (including any requiring hospitalization).

   Established nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

9. Has evidence of current active infection, including TB, or a nodule suspicious for lung malignancy on screening or any other available chest radiograph, unless definitively resolved surgically or by additional imaging and with source document confirmation.

10. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Refer to inclusion criteria for information regarding eligibility with a history of latent TB.

11. Has ever had a nontuberculous mycobacterial infection or serious opportunistic infection (eg, cytomegalovirus causing colitis, *Pneumocystis jiroveci*, aspergillosis).

12. Is seropositive for antibodies to hepatitis C (HCV) without a history of clearance or successful treatment, defined as being negative for HCV RNA in the past year and, if treated, at least 24 weeks after completing antiviral treatment. Subjects who test positive for anti-HCV antibodies must undergo further testing for HCV RNA. If the HCV RNA test is positive, the subject **is not eligible** for this study. If the HCV RNA test is negative, the subject **is eligibl**e for this study. In the event the HCV RNA test cannot be performed, the subject **is not eligible** for this study.
13. Tests positive for HBV surface antigen (HBsAg), regardless of the results of other hepatitis B tests. Subjects who test positive only for core antibody (anti-HBc) must undergo further testing for hepatitis B DNA (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.
14. Is infected with human immunodeficiency virus (HIV; positive serology for HIV antibody).
15. Has a concomitant diagnosis or any history of congestive heart failure or demyelinating disease.
16. Has current signs or symptoms, or a history of severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, systemic lupus erythematosus, or psychiatric diseases.
17. Has a transplanted organ (except for corneal transplant performed > 3 months prior to screening).
18. Has a 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, supraclavicular, epitrochlear, or paraaortic areas), or splenomegaly.
19. Has any known malignancy or has a history of malignancy (except for 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 prior to screening).
20. Has previously undergone allergy immunotherapy for prevention of anaphylactic reactions.
21. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
22. Has known allergies, hypersensitivity, or intolerance to ustekinumab or adalimumab or their excipients (refer to the ustekinumab Investigator Brochure [IB] and the adalimumab local Prescribing Information).
23. Has a clinically significant substance abuse problem (eg, drugs or alcohol) at screening or during the previous 12 months prior to baseline.
24. Is currently or intending to participate in any other study using an investigational agent or procedure during the first 56 weeks in this study.

25. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, may compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators should ensure that all study enrollment criteria have been met during screening, and in particular, prior to initiating randomization. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) during screening such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study, before initiating randomization (and first study agent administration). Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. Must agree to conform to requirements regarding concomitant, prohibited, and restricted therapy during the study as described in Section 8.

2. Must agree to continue to follow all applicable requirements that must be met for enrollment in the study as described in Section 4.1 and Section 4.2 (eg, contraceptive requirements).

3. Must not receive ustekinumab or adalimumab outside of the protocol. If a subject intends to receive, or receives, ustekinumab or adalimumab or intends to participate, or enrolls, in any other clinical study with an investigational agent, he/she should be discontinued from study agent and also terminate study participation, with procedures to be performed for the Early Termination Visit as shown in the Time and Events Schedule PRIOR to receiving one of these agents.

4. Must agree not to receive a live virus or live bacterial vaccination, including a BCG vaccination, during the study or for 12 months after the last administration of study agent for BCG vaccination and for 15 weeks for other live vaccines.

5. Participants who require treatment for latent TB must continue the appropriate course of therapy to completion.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Treatment Allocation

Allocation to treatment group will be performed using a central randomization center by means of an Interactive Web Response System (IWRS). Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared under the supervision of the sponsor. Permuted block randomization with stratification variables including

the use of steroids at baseline (Yes, No), CDAI score at baseline (≤ 300 or > 300), and ulcerations >5 mm (Yes, No) will be used.

5.2. Blinding

At Week 0, subjects assigned to ustekinumab will receive an IV infusion of ustekinumab and 4 SC injections of placebo to blind for adalimumab; subjects assigned to adalimumab will receive an IV infusion of placebo to blind for ustekinumab and 4 SC injections of adalimumab (each 40 mg). At Week 2, subjects will receive 2 SC injections of placebo (if in the ustekinumab group to blind for ustekinumab) or adalimumab (each 40 mg). Beginning at Week 4 and continuing through Week 56, it is recommended that subjects self-administer SC injections of study agent or placebo, generally at home, q2w. If subjects need to give any injections at the site, eg, additional support or training from unblinded site personnel is necessary, this will be done in a designated area, without involvement of (and out of sight of) blinded personnel.

While the 2 SC study treatments cannot be completely blinded in appearance, every effort is being made in this study to ensure that site personnel and subjects are blinded to the study treatments. To maintain the study blind, the study agent container will have a multilingual label containing the study name, medication number, and reference number. A tear-off label is designed to be separated from the study agent container and attached to the subject's source documents or diary. The label will not identify the study agent in the container. The medication number will be entered in the eCRF when the drug is dispensed.

The ustekinumab and adalimumab placebo syringes will be identical in appearance and packaging; however, the adalimumab and ustekinumab syringes will not be identical. For that reason, the investigator site personnel will not be allowed to see the syringes out of the study agent containers and subjects will be instructed to not discuss the syringes with them. To maintain the blind, at Weeks 0 and 2, study agent will be administered at the study site under the supervision of a site staff member who is not part of the study team and is unblinded to study agent. After Week 2, subjects will self-administer study agent out of sight of the investigator staff. At no time should the site personnel see the syringes, either full or empty. The unblinded site personnel and subjects will track the use of study agent by affixing the tear-off label from the study agent container to the subject's source documents or diary; after Week 2, this will be monitored by study site personnel to assess compliance.

The sponsor and site monitors will remain blinded to treatment assignments until after the Week 52 database lock has occurred. The study blind will be maintained for the investigative sites and subjects participating in the study until after they have completed their Week 56 visit and the Week 52 assessments have been completed and entered into the eCRF. After the Week 52 assessments and visit data are entered, and the subsequent Week 56 visit is completed and Week 56 study agent is dispensed for a subject, study blind can be broken by investigators through the IWRS, if deemed necessary by the investigator (eg, if knowledge of a subject's assigned treatment is needed to ensure his or her welfare by knowing what treatment to continue after last study agent administration at Week 56).

Emergency Unblinding

Under normal circumstances, the blind should not be broken until the subject has had his or her Week 56 medication dose. The investigator may, in an emergency, determine the identity of the intervention if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject, by following the IWRS unblinding procedures. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, 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 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 eCRF 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, Independent Ethics Committee/Institutional Review Board, and site personnel to fulfill regulatory reporting requirements for serious unexpected associated (SUA) adverse reactions.

A separate code break procedure will be available for use by Janssen's Global Medical Safety (GMS) group to allow for unblinding of individual subjects to comply with specific requests from regulatory or health authorities.

Subjects who have had their treatment assignment unblinded by the investigator through the emergency unblinding process will not be eligible to receive further study agent but are encouraged to complete study visits through the next 20 to 24 weeks, at which time an early termination visit should be performed. This early termination visit (20 to 24 weeks after last study agent) is considered mandatory, while attending scheduled study visits up to this time is optional.

6. DOSAGE AND ADMINISTRATION

Subjects randomized to ustekinumab will receive ~6m/kg IV induction at Week 0 followed by 90 mg SC injections every 8 weeks through Week 56, with the first SC administration occurring at Week 8. Subjects randomized to adalimumab will receive 4 x 40 mg SC injections at Week 0 (160 mg total), followed by 2 SC injections (80 mg total) at Week 2 and then 40 mg SC q2w from Week 4 to Week 56. Further details, including additional placebo administrations needed to preserve the blind, are provided below.

At Week 0, after all study-related procedures have been completed, subjects will receive the following:

- Group 1 (ustekinumab): An IV infusion of ustekinumab (approximating 6 mg/kg) and 4 SC injections of placebo for adalimumab

The IV infusion of ustekinumab is weight-based, administered consistent with labelling, as shown below:

- 260 mg (weight ≤ 55 kg)
- 390 mg (weight > 55 kg and ≤ 85 kg)
- 520 mg (weight > 85 kg)

- Group 2 (adalimumab): An IV infusion of placebo for ustekinumab and 4 SC injections of adalimumab (each 40 mg)

IV infusions (at Week 0) are to be administered over a period of at least 1 hour, and generally completed within 2 hours. Though not required, it is recommended that Week 0 SC study agent be administered first, prior to the Week 0 IV study agent, for operational efficiency (eg, that way SC injections can be administered after randomization while the IV infusion is prepared). In any case, regardless of whichever treatment is administered first, it is mandatory that at least 1 hour pass between completion of the first study agent and initiation of the second.

At Week 2, after all study-related procedures have been completed, subjects will receive the following:

- Group 1 (ustekinumab): 2 SC injections of placebo

- Group 2 (adalimumab): 2 SC injections of adalimumab (each 40 mg)

Note: Because it is presumed that subjects will require initial assistance and training as they may be inexperienced and unfamiliar with how to self-administer SC injections, all SC study agent administrations at Weeks 0 and 2 will be performed (or supervised) by an unblinded study site staff member (with no other study personnel involved in handling of SC study agent outside of the carton). At these visits, subjects will be trained to self-administer SC study agent by the unblinded study site staff member for subsequent study agent administrations. The blinded and double dummy Week 0 IV infusion can be administered by blinded study personnel.

Beginning at Week 4 (non-visit week) and continuing through Week 56, subjects will self-administer study agent generally at home and will receive:

- Group 1 (ustekinumab): 1 SC injection q2w (ustekinumab 90 mg will be administered every eighth week after Week 0, with placebo for adalimumab administered at all other designated dosing weeks)

- Group 2 (adalimumab): 1 SC injection of adalimumab 40 mg q2w.

When study agent administration and a study visit occur on the same day, it is generally recommended that subjects administer study agent at home, *after* his/her study visit, or if they need to give it at the site, it must be in a designated area out of sight of blinded study personnel.

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 (see Time and Events Schedule). If a subject develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study treatment must be considered.

7. TREATMENT COMPLIANCE

Study drug administration at Weeks 0 and 2 will be recorded in the subject's source documents or diary with the assistance of an unblinded study site staff member who will be administering or supervising study agent administration at these weeks. Thereafter, subjects will remove the adhesive label from the exterior of the medication kit and place it in the diary, corresponding to the date of administration. Study site personnel will utilize subject diaries at each visit to ensure compliance and record at-home study agent administrations in the eCRF.

Additional details will be provided in a pharmacy manual/study site investigational product manual that is provided separately.

8. CONCOMITANT THERAPY

8.1. Concomitant Therapies

Concomitant therapies must be recorded throughout the study from signing of consent to the last study visit.

All concomitant prescription therapies (including vaccines) must be recorded in the eCRF. Recorded information will include the name of the medication, dose, start and stop dates, and its reason for use.

8.1.1. Crohn's Disease-specific Concomitant Medications

Initiation of standard immunomodulators (MTX, AZA, and 6-MP) or IV/oral corticosteroids (or increases in dose) should be avoided as this will impact the efficacy analyses in this study. If initiated, these treatments should be discontinued or tapered off as soon as medically tolerable and appropriate; however, subjects can (and should) continue to receive study agent and attend all study visits despite initiation (or increasing dose) of any of these CD related medications, except for those described as prohibited medications below (see Section 8.2).

8.1.1.1. Oral Corticosteroids

In order to allow study agent time to provide efficacy, it is recommended that corticosteroid doses be maintained at a stable dose until approximately Week 8, unless a subject has significant disease improvement or experiences corticosteroid side effects. Subjects receiving corticosteroids at Week 0 who are in clinical response at Week 8 may initiate corticosteroid tapering at Week 8 if medically appropriate and tapering should be considered mandatory per the protocol starting at Week 16, unless medically inappropriate. This tapering should follow the below-recommended schedule (Table 1), without exceeding the prescribed magnitude or rate of tapering unless due to medical necessity (eg, subject experiencing corticosteroid-related side effects).

If a subject experiences worsening in his/her disease activity while tapering corticosteroids, further dose decreases may be suspended, and the oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator, to attempt to return to response. For subjects whose corticosteroid taper is interrupted on this basis, investigators should resume tapering as soon as possible thereafter.

Table 1: Recommended Tapering Schedule for Oral Corticosteroids	
Recommended Tapering Schedule for Oral Corticosteroids (Other than Budesonide)	
Dose > 15 mg/day prednisone or equivalent	Taper daily dose by 5 mg/week until receiving 10 mg/day, then continue tapering at 2.5 mg/week until 0 mg/day
Dose 11 to 15 mg/day prednisone or equivalent	Taper daily dose to 10 mg/day for 1 week, then continue at 2.5 mg/week until 0 mg/day
Dose ≤ 10 mg/day prednisone or equivalent:	Taper daily dose by 2.5 mg/week until 0 mg/day
Recommended Tapering Schedule for Oral Budesonide	
Subjects receiving budesonide should have their daily dose tapered by 3 mg every 3 weeks until 0 mg/day.	

If medically necessary (due to worsening disease or symptoms), subjects may initiate oral corticosteroids if needed to manage their disease, but these should be discontinued and/or tapered off, as described above, as soon as clinically possible.

8.2. Prohibited Medications

In contrast to the concomitant medications described above, initiation of any of the following medications is prohibited (until the last study agent administration at Week 56) and if initiated, should result in discontinuation from further study agent, although such subjects should not terminate study participation (unless enrolling in an interventional CD study or initiating a commercial anti-TNF or anti-IL-12 or 23 biologic- as described further below), and are encouraged to complete all visits through the next 20-24 weeks, at which point the mandatory early termination visit should be performed.

- Immunomodulator agents other than AZA, 6-MP, or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, tofacitinib and other JAK inhibitors)

  Note: AZA, 6-MP, and MTX (and corticosteroids) are NOT prohibited medications, so their initiation does NOT necessitate discontinuation of study agent (as described above).

- Immunosuppressant biologic agents (including but not limited to commercial ustekinumab or adalimumab, other TNF-antagonists, natalizumab, vedolizumab, and abatacept)

- Experimental or investigational CD medications

Note: Until study treatment is completed (ie, after Week 56), subjects must not receive ustekinumab or anti-TNF biologics outside of the protocol or participate in any other CD clinical study with an investigational agent. If any of these occur prior to Week 56, subjects must not only discontinue any further study agent, but also must terminate study participation, with performance of the "early termination visit". If the decision or realization that this is about to occur coincides with a scheduled visit, then the early termination visit (and assessments per the Schedule of Events) should be performed in place of the scheduled visit, including the scheduling and performance of the follow-up ileocolonoscopy (as soon as possible). The rationale for handling these circumstances differently (ie, requiring study termination in addition to study agent discontinuation) is that these interventions could result in confounded or uninterpretable subsequent efficacy and safety data.

As protection of human research subjects is paramount, it is recognized that initiating these prohibited therapies may rarely be required due to medical necessity. However, initiation of the above prohibited medications prior to Week 56 should be documented as a deviation from the study protocol (unless study agent has already been discontinued or completed), and subjects must be discontinued from receiving further study agent once these agents are started.

9. STUDY EVALUATIONS

9.1. Overview

The following subsections provide details on the evaluations to be conducted during the study. For the timing of these events, refer to the Time and Events Schedule.

Week 0 Visit

Prior to entering the study, the subject must be evaluated for eligibility. Written informed consent must be obtained from the subject for this study by the principal investigator or designee prior to conducting any protocol-specific procedure.

An assessment of all previous laboratory results, clinical data, and concomitant medication data will be made by the principal investigator or designee to confirm that the subject satisfies all inclusion criteria and does not violate any exclusion criteria prior to randomization.

Postbaseline Visits

Subjects will have clinic visits and assessments performed as indicated in the Time and Events Schedule. Note that the Week 76 follow-up visit is recommended to be performed remotely, by telephone.

Study visits should occur at the week indicated ± 8 days (except Week 2, which should occur ± 4 days). Note that while out of window visits should be recorded as protocol deviations, it is preferable to perform visits and procedures out of window than not perform them at all. One exception may be if sufficient time has passed that it is now in-window for the next, subsequent visit, in which case it is advised to contact the medical monitor for assistance in how to best manage the situation.

Study agent administration should not occur when a subject is experiencing a clinically important, active infection, an example of an appropriate reason to deviate from protocol-specified windows (which should then be documented appropriately).

The subject will be instructed to complete the CDAI diary card daily through Week 56. For all visits where a score needs to be calculated in real-time, the hematocrit value obtained at the previous visit will be used when calculating the CDAI score.

9.2. Efficacy

9.2.1. CDAI

The CDAI will be assessed by collecting information for 8 different CD-related variables (see Attachments 4 and 5): extra-intestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid stools, abdominal pain/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being.[4,9] The last 4 variables are scored over 7 days by the subject on a diary card. Note that at each visit, the most recent hematocrit value (central laboratory) before the current visit will be used for the calculation of CDAI. The CDAI should be completed before subjects begin their preparation for any video ileocolonoscopy to prevent the ileocolonoscopy preparation from interfering with CDAI results. In the event that any of the 7 days that would normally be used for CDAI calculations are impacted by the preparation for, or recovery from, an ileocolonoscopy, these days should be skipped in recording the CDAI for that visit (instead using the closest 7 days that were not impacted).

9.2.2. Video Ileocolonoscopy

During the screening period, prior to randomization, all subjects will have an ileocolonoscopy performed, including attempts at intubation of the terminal ileum, which will be video-recorded for subsequent central reading and scoring. A video ileocolonoscopy recorded within the 3 months prior to randomization may be used. Investigators will determine enrollment eligibility at the screening ileocolonoscopy, based upon presence of ulcerations in at least one segment and also note whether or not any of the ulcers present exceed 0.5 cm in diameter. .At Week 52, within a window ranging from 50 to 54 weeks, all subjects remaining in the study will undergo a second ileocolonoscopy. Subjects who do not remain in the study at Week 52 (due to discontinuation of study agent and/or termination of study participation) will instead have their follow-up ileocolonoscopy at the early termination visit. All of these procedures will be video-recorded, following the more detailed directions provided in the separate study reference (or ileocolonoscopy) manual.

For efficacy endpoints (and to confirm study eligibility) screening and follow-up ileocolonoscopy recordings at Week 52 (or early termination) will be assessed by a central reader blinded to treatment regimens, using the SES-CD scoring system.

SES-CD Scoring System

The SES-CD scoring system, which ranges from 0 to 60, includes 4 variables, each considered in 5 segments of the bowel (the ileum, ascending colon, transverse colon, descending colon, and rectum):

- Ulcer size: 0.1–0.5 cm; 0.5–2 cm; > 2 cm,
- Extent of ulcerated surface: < 10%; 10%–30%; > 30%,
- Extent of affected surface: < 50%; 50%–75%; > 75%, and
- Stenosis: Single or multiple and partially or totally occluded.

9.2.3. Crohn's Disease-related Healthcare Utilization

Crohn's disease-related healthcare utilization, including, but not limited to CD-related hospitalizations, surgery, and/or emergency room visits will be collected and entered into the eCRF by the investigator and study site personnel for all subjects throughout the study.

9.2.4. C-reactive Protein and Fecal Calprotectin

C-reactive protein and fecal calprotectin will be evaluated during the study to monitor efficacy. Stool samples for fecal calprotectin should not be collected on days impacted by ileocolonoscopy preparation.

9.2.5. PROs

During the study, all PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions.

9.2.5.1. IBDQ

The IBDQ is a validated disease-specific instrument composed of 32 Likert-scaled items (see Attachment 1).[16] The total score ranges from 32 to 224 using the 7-point response options, with higher scores indicating better health-related quality of life. A total IBDQ score > 170 is associated with clinical remission. A change of 16 or more points in the total score is considered clinically meaningful. The IBDQ scale contains 4 component subscales: bowel symptoms, systemic symptoms, emotional function, and social function. Each subscale can be computed with total scores ranging from 10 to 70, 5 to 35, 12 to 84, and 5 to 35, respectively.

9.2.5.2. PROMIS-29

The PROMIS-29 Questionnaire will be utilized for this study (see Attachment 2). PROMIS-29 questionnaires are highly reliable, precise measures of subject-reported health status.[5] The PROMIS-29 questionnaire measures physical function, anxiety, depression, fatigue, sleep

disturbance, ability to participate in social roles and activities, and pain interference. The PROMIS-29 also measures pain intensity on a 10-point scale from no pain (0) to worst pain imaginable (10).[13]

9.2.5.3. WPAI-CD

The WPAI-CD is a validated 6-question instrument that measures the effect of CD symptoms on a subject's ability to work and perform normal daily activities (see Attachment 3). The recall period for the WPAI-CD is up to the previous 7 days.[14,23]

9.3. Pharmacology

9.3.1. Serum Concentrations and Antibodies to Study Agent

Serum samples will be used to evaluate the serum concentrations of ustekinumab and adalimumab, and antibodies to ustekinumab and to adalimumab. Serum collected may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

Samples for serum concentrations and antibodies to study agent will be collected at the visits indicated in the Time and Events Schedule for subjects in both groups. Serum concentrations and antibodies to study agent will be assessed at the following timepoints:

- Serum concentrations:
  - Ustekinumab — Weeks 0, 8, 16, 32, 48, 52, and early termination if applicable
  - Adalimumab — Weeks 0, 16, 52, and early termination if applicable

- Antibodies to study agent:
  - Ustekinumab — Weeks 0, 8, 16, 52, and early termination if applicable
  - Adalimumab — Weeks 0, 16, 52, and early termination if applicable

Serum concentrations will be determined using a validated, sensitive, specific, and drug-tolerant method by or under the supervision of the sponsor. Anti-drug assays will be performed for ustekinumab and adalimumab using different, but drug-tolerant, validated assays by the sponsor or their designee. Any comparison of the data will be descriptive, only.

9.4. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

9.4.1. Adverse Events

Adverse events (AEs) will be reported by the subject (or, when appropriate, by a caregiver) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.4.2. Adverse Events Temporally Related to Infusion

Any AE (except laboratory abnormalities) that occurs during or within 1 hour after the IV infusion of study intervention will be carefully evaluated. Minor infusion-related AEs 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 intervention is stopped because of an AE that, in the opinion of the investigator, is not severe or does not result in a serious adverse event (SAE), the infusion may be restarted with caution.

9.4.3. Injection Site Reactions

An injection site reaction is any adverse reaction at a SC study agent injection site. Injection sites will be evaluated for reactions and any injection site reaction will be recorded as an AE.

9.4.4. Clinical Laboratory Tests

9.4.4.1. Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The following tests will be performed by the central laboratory as seen on the Time and Events Schedule, unless otherwise specified or approved by the medical monitor.

- Hematology assessments will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential WBC count.
- Blood chemistry assessments will include but are not limited to the following: chemistry panel (total and direct bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, blood urea nitrogen (BUN)/urea, and creatinine).
- Stool fecal calprotectin
- Serum and urine pregnancy testing for women of childbearing potential only
- Serology for HIV antibody, HBsAg, anti-HBs, anti-HBc, and hepatitis C virus antibody

Additional laboratory or pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation.

For some tests related to screening criteria, existing local or central laboratory results are acceptable to satisfy study requirements (eg, QuantiFERON-TB test, stool pathogens) provided they were performed in the required time windows. Additionally, certain tests that are performed

for study purposes may be performed locally with proper documentation (eg, inclusion on Form 1572). Appropriateness may be discussed with the medical monitor.

A medical monitor or delegate and the clinical site will be notified if prespecified abnormal laboratory values defined in the Laboratory Manual are identified in any subject during the conduct of the study. In some cases it may be medically appropriate to repeat screening laboratory tests if test values are outside of the required ranges; contact the Sponsor's medical monitor to discuss specific cases.

9.4.4.2. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections and refer to the laboratory manual for the collection, handling, storage, and shipment of samples.

9.5. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to adalimumab or ustekinumab treatment and/or CD. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, blood, and/or stool samples collected as specified in the Time and Events Schedule. Data collected from these samples will be used for exploratory research that will include the following objectives:

1. To understand the molecular effects of adalimumab and ustekinumab.
2. To understand CD pathogenesis.
3. To understand why an individual may respond differently to adalimumab or ustekinumab.
4. To develop new laboratory tests that could be used clinically in CD or other conditions.

9.5.1. Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all participants. Assays to be performed 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. These analyses will include but not be limited to IL-17A and IL-22.

9.5.2. Whole Blood-based Biomarkers

Whole blood samples will be collected from all participants to assess the effect of study intervention on RNA expression profiles. Whole blood analyses may also examine RNA expression associated with the pathogenesis of CD.

9.5.3. Physical Examinations, Vital Signs, Weight

Physical examinations, directed physical examinations (ie, examination for abdominal mass, perianal fistula, and other fistulas), vital signs, and weight are to be performed/measured at the

times shown in the Times and Events Schedule. Vital signs are to include temperature, pulse/heart rate, respiratory rate, and blood pressure.

At Week 0, vital signs will be obtained before, approximately every 30 minutes during, and twice (at approximately 30-minute intervals) after completion of the IV infusion, and before as well as approximately 30 minutes after completion of the SC injections.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed the final visit at Week 76.

Subjects will be considered to have completed the primary (blinded) efficacy portion of the study if they have completed the Week 52 visit assessments (or an early termination visit within 35 days of the Week 52 visit target date).

10.2. Discontinuation of Treatment

A subject's study treatment should be discontinued if:

- The investigator or the medical monitor believes that for safety reasons (eg, an AE) it is in the best interest of the subject to stop treatment.
- The subject required emergency unblinding of their study treatment.
- The subject becomes pregnant or plans a pregnancy within the study period or within 16 weeks after the last study agent administration.
- The subject is deemed ineligible to receive further study treatment 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 continued evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB test result and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB is not approved/registered unless active TB can be ruled out and appropriate treatment for latent TB can be initiated either prior to or simultaneously with the next administration of study agent and continued to completion. (Note: Consideration for study agent discontinuation may be given for subjects diagnosed with latent TB in countries with high multidrug-resistant TB burden [eg, South Africa, Bulgaria, and the Russian Federation]).
  - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The subject experiences serious adverse reactions related to either an injection or infusion, he or she should be discontinued from further study injections. Discontinuation of study agent administration must be considered for subjects who develop non-serious, but severe injection site or infusion reaction (as described in Section 12.1.3).
- The subject develops a malignancy including squamous cell skin cancer. Consideration may be given to allow subjects to continue to receive study agent if they develop ≤ 2 basal cell skin cancers that are adequately treated with no evidence of residual disease.
- The initiation of the following protocol-prohibited medications at any time during the study:
  - Immune suppressing immunomodulatory agents other than 6-MP, AZA or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, tofacitinib and other JAK inhibitors)
  - Immunosuppressant biologic agents (including but not limited to commercial ustekinumab or adalimumab, other TNF-antagonists, natalizumab, vedolizumab, and abatacept)
  - Experimental or investigational CD medications
- A serious opportunistic infection occurs.
- The subject withdraws consent for further administration of study agent.
- Subjects who have not experienced any improvement in their symptoms and/or CD disease activity by Week 24 should be considered for discontinuation on the basis of lack of efficacy.
- The subject has CD-related surgeries that will preclude the future ability to assess efficacy through the CDAI. Surgeries that are thought to represent a lack of efficacy of study agent should be considered for discontinuation at the discretion of the Investigator other than minor procedures (eg, placement of a seton or cutaneous drainage of an abscess).

Subjects who discontinue study agent (for the reasons above) before the end of planned study agent treatment (Week 56), should not terminate their study participation (unless enrolling in an interventional CD study or initiating a commercial anti-TNF or anti-IL-12 or 23 biologic, as described further below). Instead, subjects discontinuing study agent are encouraged to complete study visits through the next 20-24 weeks, at which an early termination visit should be performed. This early termination visit (20-24 weeks after last study agent) is considered mandatory, while attending scheduled study visits up to this time is optional.

If subjects refuse to remain in the study to perform this early termination visit at least 20 weeks after last study agent administration, the subject's desire to withdraw their consent for further study participation should be accommodated by performing the early termination visit as soon as necessary/possible. Thus, if possible, the early termination visit should be moved up and performed prior to when the subject might withdraw their consent.

Note: The Week 76 visit, which can occur by phone, applies to all subjects, even those who discontinued study agent prior to Week 56 or who otherwise terminated study participation (eg, withdrawal of consent) unless they specifically do not consent to this telephone follow-up from the site.

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 for study participation (distinct from withdrawal of consent to receive study agent)
- Death
- Sponsor decision (eg, initiating a commercial anti-TNF, anti-IL-12 or anti-IL-23 biologic such as ustekinumab or adalimumab outside of the protocol or plans to receive an investigational agent in an interventional CD study).

Subjects who terminate study participation will not be required to return to the site for any follow-up assessments; however, these subjects should complete the safety and efficacy evaluations specified for Early Termination in the Time and Events Schedule at the time they terminate study participation (including ileocolonoscopy), even if this coincides with a scheduled visit (provided they are willing/consent to do so). Also, of note, the Week 76 visit (which can occur by phone) applies to all subjects, even those who discontinued study agent prior to Week 56 or who otherwise terminated study participation (eg, withdrawal of consent) unless they specifically do not consent to this telephone follow up from the site.

If a subject is 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 eCRF 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.

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 Statistical Analysis Plan.

11.1. Subject Information

The disposition information of all randomized subjects, including the number of subjects who discontinued study agent and terminated study participation, will be summarized by treatment group. The reasons for study agent discontinuation and study participation termination will be also summarized by treatment group. Demographic data and disease characteristics at baseline will be summarized by treatment group.

11.2. Sample Size Determination

As stated above, the primary objective of this study is to explore the hypothesis that one year of treatment with ustekinumab is superior to one year of treatment with adalimumab, as assessed by

the primary endpoint of remission (CDAI<150) after one year of treatment (ie, at the Week 52 visit).

The assumptions that form the basis for sample size and power calculations in this protocol to support the primary endpoint were based on available Phase 3 registrational studies. For ustekinumab, induction data from the UNITI-2 study and maintenance results from IM-UNITI were utilized, focusing on the anti-TNF-naïve subset of subjects.[10] For adalimumab assumptions, data from the open-label induction and then maintenance phase of the CHARM[7] study were utilized, again focusing on the anti-TNF naïve subset of subjects.

In the UNITI-2 trial, 58% of subjects who were anti-TNF naïve responded to induction with ~6 mg/kg IV ustekinumab.[10] Among ustekinumab induction responders, 65% were in remission at Week 44 on 90 mg SC q8w (ie, 38% of the original treated subjects [58% x 65%]). In order to model a treat-through study design, the subjects who were initial non-responders to ustekinumab induction were also incorporated into the estimates. Among the remaining 42% of initial anti-TNF naïve UNITI-2 recipients of IV ustekinumab, 42% of these ustekinumab induction non-responders were in remission at Week 44 (ie, 18% of the original treated subjects [42% x 42%]). Thus, the overall estimate for remission after one year of treatment in the proposed study is 38% + 18%, or **56%** of all treated subjects for the ustekinumab group.

In the Phase 3 adalimumab CHARM study, 59% of the anti-TNF naïve subjects responded to open-label induction therapy with adalimumab;[20] of these induction responders, 42% were in remission with 40 mg of adalimumab every other week at the Week 56 primary endpoint (ie, 25% of the original treated subjects [59% x 42%]).[7] Among the remaining 41% of subjects who did not respond to induction, it is not reported what percentage were in remission at 56 weeks, though remission would typically be notably lower in induction non-responders than in responders. Nonetheless, a similar proportion (40%) of these induction non-responders are assumed to be in remission at one year (representing remission at one year in another 16% of the original treated subjects [41% x 40%]). The resulting overall remission rate after one year of adalimumab treatment is **41%** (25%+16%).

The Phase 3b SONIC study was also examined to evaluate adalimumab assumptions, since it was a one year treat-through study of another anti-TNF (infliximab) in the relevant anti-TNF naïve population. In SONIC, the remission rate in the infliximab monotherapy arm at Week 50 was 39.6,[6] similar to the estimate of 41% calculated above for adalimumab.

Assuming a 41% clinical remission rate at Week 52 in the adalimumab group and 56% in the ustekinumab group (a "delta" of 15%), 175 subjects per treatment group will yield power of approximately 80% for superiority (Table 2), at a significance level of 0.05 (2-sided, Mantel-Haenszel test).

Table 2: Power to detect a treatment effect based on different proportions of subjects achieving clinical remission at Week 52 (n=175 each group)

Clinical remission at Week 52 (%)		Power
Adalimumab	**Ustekinumab**	
41%	54%	68%
	56%	**80%**
	59%	92%
38%	53%	81%
	54%	85%
	55%	89%

11.3. Endpoints

All of the endpoints listed in the following sections are to be compared between the ustekinumab and the adalimumab treatment groups.

In order to control the overall Type 1 error rate, the primary endpoint and major secondary endpoints will be tested in a hierarchical fashion. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive, and the subsequent endpoint(s) will be tested only if the preceding endpoint in the hierarchy is positive.

11.3.1. Primary Efficacy Endpoint

The proportion of subjects with clinical remission (defined as a CDAI score <150) at Week 52.

11.3.2. Major Secondary Efficacy Endpoints

The proportion of subjects with:

- Corticosteroid-free remission at Week 52 (defined as a CDAI score <150 and not taking any corticosteroids for at least 30 days prior to Week 52)
- Clinical response (defined as a CDAI score decrease ≥100 from baseline) at Week 52
- PRO-2 symptom remission at Week 52 (defined as an abdominal pain [AP] mean daily score at or below 1 and also stool frequency [SF] mean daily score at or below 3, ie, AP ≤1 and SF ≤3). PRO-2 are the stool frequency and abdominal pain scores reported as part of the CDAI.
- Clinical remission (defined as CDAI <150) at Week 16
- Endoscopic remission (defined as an SES-CD score ≤3, or SES-CD =0 for subjects who enter the study with an SES-CD =3) at Week 52

11.3.3. Secondary Endpoints

- The proportion of subjects with clinical remission (defined as CDAI < 150), compared at each postbaseline visit through Week 52

- The proportion of subjects with clinical response (defined as a CDAI score decrease ≥100 from baseline), compared at each postbaseline visit through Week 52
- The proportion of subjects with durable clinical response at Week 52 (defined as CDAI>100 decrease from baseline at Week 52 and at ≥80% of all visits between Week 16 and Week 52)
- The proportion of subjects with durable clinical remission at Week 52 (defined as CDAI <150 at Week 52 and at ≥80% of all visits between Week 16 and Week 52)
- Absence and/or resolution of AP, defined as a mean daily CDAI AP score of 0 in the week prior to the visit among subjects with mean AP >0 at baseline, compared at each postbaseline visit through Week 52
- Absence and/or resolution of diarrhea, defined as no loose or watery stools in the week prior to the visit (ie, SF CDAI sub-score = 0) among subjects with mean SF >1 at baseline, compared at each postbaseline visit through Week 52
- The proportion of subjects with clinical and biomarker remission, defined as the proportion of subjects with CDAI<150, CRP ≤3 mg/L, and also fecal calprotectin ≤250 μg/g, compared at Weeks 8, 16 and 52
- The proportion of subjects with at least one AE, and subcategories of AEs including infections, SAEs, and serious infections
- The proportion of subjects with anti-drug antibodies

11.3.4. Other Endpoints

Efficacy Endpoints at (or through) Week 52:

- The change in CDAI score from baseline at all postbaseline visits through Week 52
- Maintenance of clinical remission, defined as CDAI <150 at Week 52, among subjects in remission at Week 16
- Maintenance of clinical response, defined as CDAI decreased at least 100 from baseline at Week 52 among subjects in response [CDAI decrease at least 100 points from baseline] at Week 16
- The time to first flare (a flare is defined as an increase in CDAI score of > 100 points at any subsequent visits through Week 52 [based upon loss of clinical response]) among subjects in clinical response at Week 16
- The change from baseline in the sum of the number of stools and the AP scores in the prior 7 days, compared individually and combined (sum PRO-2), without weighting, at all postbaseline visits through Week 52
- The change in the weighted (as per the CDAI) sum of the AP and SF subscores of the CDAI from baseline at all postbaseline visits through Week 52 (PRO-2 weighted)
- PRO-2 symptom improvement/response, defined as at least a 1 point improvement (or a mean score of zero) in mean daily CDAI AP score from baseline, and also a reduction in SF mean daily score of 3 or more (or a mean score of zero) from baseline, compared at each visit through Week 52

- PRO-2 symptom remission, defined as an AP mean daily score at or below 1 and a SF mean daily score at or below 3, ie, AP ≤1 and SF ≤3), compared at each visit through Week 52
- AP improvement, defined as a 1 point or greater improvement in mean daily CDAI AP score from baseline, or a mean score of zero, among subjects with mean AP >0 at baseline, compared at each visit through Week 52
- Reduction in frequency of diarrhea, defined as a reduction of at least 3 (or a mean number <1) in SF (ie, mean daily number of liquid or very soft stools from CDAI in the week prior to the visit) from baseline, among subjects with mean SF >1 at baseline, compared at each visit through Week 52
- The proportion of subjects with corticosteroid-free response at Week 52 (defined as a CDAI score decrease ≥100 from baseline and not taking any corticosteroids for at least 30 days prior to Week 52)
- The proportion of subjects with corticosteroid-free remission at Week 52 (defined as a CDAI score <150 and not taking any corticosteroids for at least 30 days prior to Week 52) among subjects who were on corticosteroids at baseline
- The proportion of subjects with corticosteroid-free response at Week 52 (defined as a CDAI score decrease ≥100 from baseline and not taking any corticosteroids for at least 30 days prior to Week 52) among subjects who were on corticosteroids at baseline
- The total number of visits subjects are in steroid-free remission through Week 52
- The proportion of subjects with endoscopic response (defined as a reduction in SES-CD score by 50% from baseline, or SES-CD score ≤3. For subjects with SES-CD=3 at baseline, SES-CD=0) at Week 52
- The change from baseline in SES-CD at Week 52
- The proportion of subjects with endoscopic improvement (change in SES-CD score of at least 3 points) at Week 52
- The proportion of subjects with a minimum of 25% improvement from baseline in SES-CD score at Week 52
- The proportion of subjects with fistula resolution (closure of all open/draining perianal/perirectal fistulas) compared at each postbaseline visit through Week 52 among subjects with one or more open/draining perianal or perirectal fistulas at baseline
- The proportion of subjects with fistula response (defined as closure of 50% of open/draining perianal/perirectal fistulas) compared at each postbaseline visit through Week 52 among subjects with one or more open/draining perianal or perirectal fistulas at baseline
- The change from baseline in CRP concentration at all postbaseline visits through Week 52
- The proportion of subjects with normalization of CRP (defined as ≤3 mg/L) compared at each postbaseline visit through Week 52 among subjects with abnormal CRP (>3 mg/L) at baseline
- The change from baseline in fecal calprotectin concentration, compared at Weeks 8, 16, and 52
- The proportion of subjects with fecal calprotectin ≤250 µg/g, compared at Weeks 8, 16, and 52 among subjects with baseline fecal calprotectin at >250 µg/g at baseline

- The proportion of subjects with fecal calprotectin ≤100 µg/g at Weeks 8, 16 and 52 among subjects with fecal calprotectin >250 µg/g at baseline
- The proportion of subjects with clinical remission and a ≥50% reduction from baseline in CRP or fecal calprotectin compared at Weeks 8, 16, and 52
- The proportion of subjects with clinical remission and a ≥50% reduction from baseline in CRP or fecal calprotectin, compared at Weeks 8, 16, and 52, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 µg/g at baseline
- The proportion of subjects with clinical and biomarker remission, defined as CDAI < 150, CRP ≤3 mg/L, and also fecal calprotectin ≤250 µg/g, compared at Weeks 8, 16, and 52, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 µg/g at baseline
- The proportion of subjects with clinical and biomarker response (clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin) compared at Weeks 8, 16, and 52
- The proportion of subjects with clinical and biomarker response (clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin) compared at Weeks 8, 16, and 52, among participants with elevated CRP (>3 mg/L) or fecal calprotectin (>250 µg/g) at baseline
- The proportion of subjects with clinical response, CRP ≤3 mg/L, and fecal calprotectin ≤250 µg/g at Weeks 8, 16 and 52
- The proportion of subjects with clinical response, CRP ≤3 mg/L, and fecal calprotectin ≤250 µg/g at Weeks 8, 16, and 52, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 µg/g at baseline
- The proportion of subjects who are on concomitant narcotic pain medications for CD
- The proportion of subjects able to eliminate concomitant narcotic pain medication use for CD
- The total number of days subjects are off narcotic pain medications for CD through Week 52 among subjects who are on narcotic pain medication for CD at baseline

PRO Endpoints:

- The change from baseline in the IBDQ score (including IBDQ domains), compared at Weeks 8, 16, and 52
- The proportion of subjects with IBDQ response (≥16-point improvement from baseline), compared at Weeks 8, 16, and 52
- The proportion of subjects with IBDQ remission (IBDQ score >170), compared at Weeks 8, 16, and 52
- The change from baseline in the PROMIS-29 domains of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score, Ability to Participate in Social Roles and Activities Score, Physical Function Score, and Pain Intensity Score compared at Weeks 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a T-score decrease of ≥5 in the domains of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score at Weeks 8, 16, and 52 (results reported separately for each domain)

- The proportion of subjects with a T-score increase of ≥5 in the domains of Ability to Participate in Social Roles and Activities Score, and Physical Function Score at Weeks 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a T-score decrease of ≥3 in the domains of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score at Weeks 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a T-score increase of ≥3 in the domains of Ability to Participate in Social Roles and Activities Score, and Physical Function Score at Weeks 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a score decrease of ≥½ baseline standard deviation in Pain Intensity Score at Weeks 8, 16, and 52
- The proportion of subjects with a T-score decrease of ≥5 in Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score and increase of ≥5 in ability to participate in social roles and activities, and physical function score, at Weeks 8, 16, and 52
- The proportion of subjects with a T-score decrease of ≥3 in Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score and increase of ≥3 in ability to participate in social roles and activities, and physical function score, at Weeks 8, 16, and 52
- Change from baseline in combined pain score from PROMIS-29 and number of liquid or soft stools from CDAI, compared at Weeks 8, 16, and 52
- The change from baseline in the WPAI questionnaire, compared at Weeks 8, 16, and 52

Healthcare resource utilization endpoints:

- The proportion of subjects with CD-related hospitalization, surgeries, or initiation of non-study alternate biologic for CD through Week 52
- The proportion of subjects with CD-related hospitalization or surgeries through Week 52
- The proportion of subjects initiating a non-study alternate biologic for CD through Week 52
- The proportion of subjects with CD-related hospitalization through Week 52
- The proportion of subjects with CD-related surgeries through Week 52
- The proportion of subjects with a CD-related ER visit through Week 52
- The total number of days a subject has a CD-related hospitalization through Week 52
- The proportion of subjects with an endoscopic procedure related to CD (not protocol-directed) through Week 52

Endpoints to be compared at Week 56 and/or 76:

- The proportion of subjects with CD-related hospitalization, surgeries, or initiation of biologic therapy for CD outside of the protocol through Week 76
- The proportion of subjects with CD-related hospitalization or surgeries through Week 76

- The proportion of subjects initiating a non-study alternate biologic for CD through Week 76
- The proportion of subjects with CD-related hospitalization through Week 76
- The proportion of subjects with CD-related surgeries through Week 76
- The proportion of subjects with clinical response at Week 56
- The proportion of subjects with clinical remission at Week 56
- The change from baseline in CDAI at Week 56
- The proportion of subjects with at least one AE, and subcategories of AEs including infections, SAEs, and serious infections through Week 76
- Normalization of CRP (defined as ≤3 mg/L) at Week 56 among subjects with abnormal CRP (>3 mg/L) at baseline
- The total time in steroid-free remission through Week 56
- The time to first flare among subjects in clinical response at Week 16 (defined as an increase in CDAI score of >100 points) through Week 56 (based upon loss of clinical response).

11.4. Efficacy Analyses

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. Graphical data displays (eg, line plots) may also be used to summarize the data whenever appropriate. Listings may also be utilized to present data at a subject level.

All endpoints will be based on a superiority comparison between the 2 randomized groups (ustekinumab treatment and adalimumab treatment). All randomized subjects will be included in the efficacy analyses. All efficacy analyses will be based on intent-to-treat principle.

For the primary endpoint, the proportion of subjects in clinical remission at Week 52 will be compared between the ustekinumab treatment group and the adalimumab treatment group using a 2-sided Cochran-Mantel-Haenszel chi-square test, stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No) at a significance level of 0.05.

The endpoints listed Sections 11.3.2 - 11.3.4 will be compared between the ustekinumab treatment group and the adalimumab treatment group.

Treatment failure rules will override the response status (eg, clinical response, clinical remission, and mucosal healing). Subjects who meet any of the following criteria for treatment failure will be considered to not have achieved their dichotomous efficacy endpoints from the time the treatment failure occurs onwards:

- Had a CD-related surgery due to lack of efficacy

OR

- Discontinued study agent due to an AE of worsening CD or due to lack of efficacy

OR

- Had a prohibited change in concomitant medications (to be detailed in the Statistical Analysis Plan).

For continuous efficacy endpoints, the baseline value will be carried forward from the time the treatment failure occurs onwards.

Subjects with missing data, defined as those who terminated the study prior to the designated visit or subjects who have a missing value at the designated visit, will be considered to not have achieved their dichotomous efficacy endpoints. For continuous endpoints, the last available value will be carried forward for subjects with missing data.

Crohn's disease-related healthcare utilization for each subject will be analyzed according to the assigned treatment regardless of the actual treatment received.

11.5. Pharmacokinetic and Immunogenicity Analyses

Descriptive statistics of the serum study agent concentrations will be calculated at each sampling time point. Serum study agent concentrations over time will be summarized for each treatment group.

Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

The incidence of antibodies to study agent (immunogenicity) will be summarized for all subjects who receive any study agent and have appropriate samples for detection of antibodies to ustekinumab.

11.6. Safety Analyses

Safety will be assessed by evaluating AEs as well as laboratory changes through Week 76. All subjects who receive at least 1 administration of study agent will be included in the safety analyses. Subjects will be analyzed according to the actual treatment received.

11.6.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a serious AE.

Adverse events will be assessed by evaluating summaries of the following:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Reasonably related AEs (very likely, probable, possible as assessed by the investigator)
- Discontinuation of study agent due to AEs
- Infections and serious infections
- Injection site reactions
- Infusion-related AEs (during or within 1 hour of an ustekinumab infusion)
- Malignancies.

11.6.2. Clinical Laboratory Tests

The following will be used to assess the safety of subjects:

- Laboratory parameters (hematology and chemistry) and change from baseline in these laboratory parameters
- The incidence of markedly abnormal laboratory parameters

Definitions for markedly abnormal results for each laboratory parameter will be defined in the Statistical Analysis Plan.

11.7. Interim Analysis

No interim analysis is planned for this study.

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 Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE 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 AEs starting with the signing of the Informed Consent Form (ICF; refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Events (SAEs)

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, and whether these should be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction (SUSAR) even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Events/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an AE will be determined by whether or not it is listed in the ustekinumab IB or adalimumab local prescribing information.

Adverse Events Associated with the Use of the Drug

An AE 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, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related: An AE that is not related to the use of the drug.

Doubtful: An AE 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 AE 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 AE 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 AE 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 drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug

- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious AE should be recorded on the serious AE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, 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. Serious AEs, including those spontaneously reported to the investigator within 20 weeks after the last dose of study drug, 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.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SAEs that are unlisted (unexpected) and associated with the use of the drug with the exception of events of CD and related common manifestations (eg, abdominal pain, diarrhea, nausea, vomiting, fistula, and rectal bleeding). The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Serious AEs relating to lack of efficacy (eg, events attributed to CD or related symptoms such as abdominal pain, diarrhea, nausea, vomiting, fistula, and rectal bleeding) or progression of the disease under study (ie, stenosis, stricture, ileus, or bowel obstruction) will not be individually unblinded for expedited reporting (with the exception of fistula complications or fistulas events that are indicated by the investigator to represent infections).

Cases will be collectively assessed with all events (including those assessed as unrelated by investigators) at sponsor database locks from this and other ongoing sponsor studies. If such an assessment were to conclude that an association with ustekinumab is at least a reasonable possibility, that assessment would then result in changes to the ICF and/or the protocol consistent

with assessment of the AE as an unanticipated problem and/or an adverse drug reaction to ustekinumab. This assessment, as well as any resultant ICF or protocol changes, would promptly be communicated to appropriate global health authorities and Ethics Committees/Institutional Review Boards under whose auspices this protocol is being conducted.

The investigator (or sponsor where required) must report SUSARs consistent with the above 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 will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- 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 contact telephone number (for medical staff only)
- 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 and Safety Report Form of the eCRF, which must be completed and reviewed 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 transmitted electronically or 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 drug 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 AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). 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 AE 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 within 20 weeks of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects 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, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) 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.

Female subjects of childbearing potential should not donate eggs during the study and for 16 weeks after the last study drug administration. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

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

12.3.4. Adverse 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, Serious Adverse Events. 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 a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event 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 DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The ustekinumab and ustekinumab placebo (for IV infusion) supplied for this study will be manufactured and provided under the responsibility of the sponsor.

Ustekinumab for IV infusion will be supplied as a clear liquid containing 5 mg/mL per vial. Each 1 mL of ustekinumab solution contains 5 mg ustekinumab, L-histidine, L-histidine monohydrochloride monohydrate, sucrose, L-methionine, Ethylenediaminetetraacetic acid disodium salt dihydrate, and polysorbate 80 at pH 6.0. No preservatives are present.

Ustekinumab for SC injection will be supplied in a 90 mg/mL prefilled syringe (PFS). Each 1 mL of ustekinumab solution in the PFS contains 90 mg ustekinumab, L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0. No preservatives are present.

Ustekinumab placebo for IV infusion is supplied as single-use, sterile solution in 30 mL vials with a 26 mL nominal volume. The composition of the placebo is 10 mM L-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. No preservatives are present.

Ustekinumab placebo for SC injection will have the same appearance as the respective ustekinumab administrations. Liquid placebo will also be supplied in a 1 mL PFS, and have a composition 10 mM L-histidine, 8.5% (w/v) sucrose, 0.004% (w/v) polysorbate 80, at pH 6.0. No preservatives are present.

Adalimumab is manufactured by Abbvie and will be purchased commercially and provided by the sponsor. Adalimumab is supplied as a liquid containing 40 mg/0.4 mL per vial for SC injection in a PFS. Each vial includes mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water.[15]

There will be no matching placebo for adalimumab. The ustekinumab placebo for SC injection will be used for the adalimumab placebo.

14.2. Packaging

The study agent will be packaged in individual subject kits. Each kit will contain enough study drug for treatment q2w for 6 weeks (when given at Week 2) or 8 weeks (when given at each subsequent visit).

The ustekinumab 5 mg/mL liquid formulation is intended for IV infusion after being diluted to an appropriate concentration using an appropriate diluent.

Ustekinumab 90 mg/mL PFS is supplied as a single-use, sterile solution in a BD Hypak™ 1 mL, type 1 glass syringe with a 27-gauge, 1/2-inch fixed needle. The needle cover on the PFS contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Adalimumab will be supplied as a PFS, purchased commercially by the sponsor.

Study treatment will not be dispensed in child-resistant packaging. Blinded study treatment will be administered by a qualified site personnel within an inpatient facility.

14.3. Labeling

Each vial or PFS of study drug or placebo will contain information and be labeled as required per country regulatory requirements. For PFS, the label must remain affixed to the carton until the subject removes it to adhere into their diary.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C).

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject at Week 0 must be documented on the drug accountability form. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. If required per local regulations, subjects must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug 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. Since subjects will be self-administering study drug at home between Weeks 4 and 56, they will receive detailed instructions for study drug storage and disposal of used syringes and handling of unused study material. Subjects will receive a sharps container to dispose of used syringes. Unused syringes must also be disposed of in the sharps container in order to maintain the blind at the study site. Subjects will be instructed to return the sharps container and/or cartons. Subjects will record study drug administrations with time and date information in the subject Diary.

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.

Study drug 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 drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug 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:

- IB for ustekinumab
- Local prescribing information for adalimumab
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual(s)
- PRO questionnaires and PRO completion guidelines
- IWRS Manual
- Electronic data capture (eDC) Manual

- Sample ICF or Information Sheet (as applicable per country)
- Subject 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 from each study participant will not exceed 150 mL over approximately 56 weeks, an amount that is far less than the American Red Cross standard limit for whole blood donation (approximately 475 mL every 8 weeks) and is, therefore, considered an acceptable amount of blood to be collected over this time period.[2]

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)
- New edition(s) of the IB for ustekinumab and local prescribing information for adalimumab
- 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, unless required locally), 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.

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 for ustekinumab and local prescribing information for adalimumab
- 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 drug
- 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, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

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/are 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 disease. 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 access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

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.

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.

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 and adalimumab, to understand differential drug responders, and to develop tests/assays related to ustekinumab or adalimumab and CD. 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.

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 if the need for the product persists, 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 IEC/IRB (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 listed in the Contact Information page(s), which will be provided as a separate document. 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 eCRF 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 drug 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)

- 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 age at initial informed consent. In cases where the subject is not randomized into the study, the date seen and age at initial informed consent 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 documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: 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 drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods 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.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms (CRFs) are prepared and provided by the sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

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 documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All patientive measurements (eg, questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and 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).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and 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, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data and video ileocolonoscopy from a central vendor 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 CRF 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 CRF 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 use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

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 per the study monitoring plan. At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. 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 documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review 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 documents 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.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last contact for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject contact 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 drug 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. 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 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 data from all study sites that participated in the study as per protocol. 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. Study subject identifiers will not be used in publication of results. Any work created in connection with 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 disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: SAMPLE INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

Updated from: IBDQ - United Kingdom-English - Version of 09 May 08 - Mapi Research Institute.
ID4529/IBDQ_AU2.0_eng-GB.doc
IBDQ (enGB) 03JUN2016 FINAL – ICON Language Services

INSTRUCTIONS FOR SELF-ADMINISTERED INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has graded response choices numbered from 1 to 7. Please read each question carefully and answer the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS THE MOST FREQUENT YOU HAVE EVER EXPERIENCED
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a toilet? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no toilet close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of wind? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the toilet even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or an upset stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

ATTACHMENT 2: SAMPLE PROMIS-29 QUESTIONNAIRE

PROMIS–29 Profile v2.0

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.0

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep118	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.0

Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst pain imaginable

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ATTACHMENT 3: SAMPLE WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: CROHN'S DISEASE (WPAI-CD)

Work Productivity and Activity Impairment Questionnaire:
CROHN'S DISEASE (WPAI-CD)

The following questions ask about the effect of your Crohn's disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____NO _____YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your Crohn's disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your Crohn's disease. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your Crohn's disease affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Crohn's disease affected your work only a little, choose a low number. Choose a high number if Crohn's disease affected your work a great deal.

Crohn's disease had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Crohn's disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your Crohn's disease affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If Crohn's disease affected your activities only a little, choose a low number. Choose a high number if Crohn's disease affected your activities a great deal.

Crohn's disease had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Crohn's disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

ATTACHMENT 4: CROHN'S DISEASE ACTIVITY INDEX

DISEASE ACTIVITY INDEX	SUM	X FACTOR	SUBTOTAL
Total number of liquid or very soft stools in the previous 7 days	_____	x 2 =	_____
Sum abdominal pain/cramps ratings (total for previous 7 days): 0 = none 2 = moderate 1 = mild 3 = severe	_____	x 5 =	_____
General well being (total for previous 7 days): 0 = generally well 3 = very poor 1 = slightly under par 4 = terrible 2 = poor	_____	x 7 =	_____
Categories currently present and presumed to be related to Crohn's disease: 0 = no; 1 = yes			
☐ = arthritis/arthralgia	_____	x 20 =	_____
☐ = iritis/uveitis	_____	x 20 =	_____
☐ = erythema nodosum/pyoderma gangrenosum/aphthous stomatitis	_____	x 20 =	_____
☐ = anal fissure, fistula or abscess	_____	x 20 =	_____
☐ = other fistula	_____	x 20 =	_____
☐ = fever over 100° F (37.8° C) during the previous 7 days.	_____	x 20 =	_____
During the previous 7 days has subject received antidiarrheal therapy at least once: **OR** During the previous 7 days has subject received opiate therapy on each of the 7 days: 0 = no 1 = yes	_____	x 30 =	_____
Abdominal mass: 0 = none 2 = questionable 5 = definite	_____	x 10 =	_____
Hematocrit: Males: (47-Hct) = SUM Females: (42-Hct) = SUM	_____ (add or subtract by sign)	x 6 =	_____
(Standard Weight - Actual Body Weight) / Standard Weight x 100 =	_____ *	x 1 =	_____ (add or subtract by sign, round to 3 decimal places)

* If this value is less than -10 then enter -10 here.
Standard weight and actual weight must be in same units (kg or lb)

TOTAL = _____
(round total to integer)

ATTACHMENT 5: STANDARD WEIGHT TABLE

Actual Height Inches (cm)	Standard Weight in Pounds Men (kg)	Standard Weight in Pounds Women (kg)
58.0 (147.3)		115.0 (52.2)
58.5 (148.6)		116.0 (52.6)
59.0 (149.9)		117.0 (53.1)
59.5 (151.1)		118.3 (53.6)
60.0 (152.4)		119.5 (54.2)
60.5 (153.7)		120.8 (54.8)
61.0 (154.9)		122.0 (55.3)
61.5 (156.2)		123.5 (56.0)
62.0 (157.5)	136.0 (61.7)	125.0 (56.7)
62.5 (158.8)	137.0 (62.1)	126.5 (57.4)
63.0 (160.0)	138.0 (62.6)	128.0 (58.0)
63.5 (161.3)	139.0 (63.0)	129.5 (58.7)
64.0 (162.6)	140.0 (63.5)	131.0 (59.4)
64.5 (163.8)	141.3 (64.1)	132.5 (60.1)
65.0 (165.1)	142.5 (64.6)	134.0 (60.8)
65.5 (166.4)	143.8 (65.2)	135.5 (61.4)
66.0 (167.6)	145.0 (65.8)	137.0 (62.1)
66.5 (168.9)	146.5 (66.4)	138.5 (62.8)
67.0 (170.2)	148.0 (67.1)	140.0 (63.5)
67.5 (171.5)	149.5 (67.8)	141.5 (64.2)
68.0 (172.7)	151.0 (68.5)	143.0 (64.9)
68.5 (174.0)	152.5 (69.2)	144.5 (65.5)
69.0 (175.3)	154.0 (69.8)	146.0 (66.2)
69.5 (176.5)	155.5 (70.5)	147.5 (66.9)
70.0 (177.8)	157.0 (71.2)	149.0 (67.6)
70.5 (179.1)	158.5 (71.9)	150.5 (68.3)
71.0 (180.3)	160.0 (72.6)	152.0 (68.9)
71.5 (181.6)	161.8 (73.4)	153.5 (69.6)
72.0 (182.9)	163.5 (74.1)	155.0 (70.3)
72.5 (184.2)	165.3 (75.0)	
73.0 (185.4)	167.0 (75.7)	
73.5 (186.7)	169.0 (76.6)	
74.0 (188.0)	171.0 (77.5)	* Height in shoes with one-inch heels
74.5 (189.2)	172.8 (78.4)	* Indoor clothing weighing 5 pounds for men and 3 pounds for women
75.0 (190.5)	174.5 (79.1)	
75.5 (191.8)	176.8 (80.2)	* Centimeters x 0.3937 = inches
76.0 (193.0)	179.0 (81.2)	* Pounds x 0.4535 = kilograms

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): Andrew Greenspan, MD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____
(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.

Signature

User	Date	Reason
GREENSPAN ANDREW 194058	14-Dec-2020 21:13:23 (GMT)	Document Approval

Janssen Research & Development

Clinical trial CNTO1275CRD3007 (SEAVUE)

COVID-19: Measures taken for ongoing study

Amendment to CTA as part of Urgent Safety Measure

EudraCT numbers: 2017-004209-41

Status:	Approved for Dossier Use
Date:	21 April 2020
Prepared by:	Janssen Research & Development, LLC

1. INTRODUCTION

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study, CNTO1275CRD3007, due to, for example, self-isolation/quarantine by patients and study-site personnel; travel restrictions/limited access to public places, including hospitals; and/or study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related patient management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of patient and site staff. If, at any time, a patient's safety is considered to be at risk, study interventions will be discontinued or delayed, and study follow-up will be conducted. As appropriate, impacted study site Investigators will need to assess the risk of continuing the study balanced with the risk of discontinuing study agent. A gap in active treatment may lead to a disease-flare. This could lead to disease progression as well as a possible hospital admission. Multiple professional societies, including the International Organization for the Study of Inflammatory Bowel Disease (IOIBD), United European Gastroenterology (UEG), and European Crohn's and Colitis Organization (ECCO), have advised all patients with inflammatory bowel disease (IBD) to remain on current treatments, where possible, given the risk of worsening disease if they are stopped (IOIBD https://www.gastrojournal.org/article/S0016-5085(20)30465-0/fulltext; Danese, et al, Management of IBD during the COVID-19 outbreak: resetting clinical priorities. Nature Reviews Gastroenterology & Hepatology [25 March 2020]). Notably, the study protocol clearly states (in Section 6) that in the event of a clinically important, active infection, which COVID-19 certainly represents, all study treatment should be held until that infection clears and, that discontinuation of study agent should be considered if patients develop a serious infection.

In light of COVID-19, the sponsor is now providing guidance to study sites on potential modifications, provided they are consistent with local regulations, patient privacy practices, and are otherwise feasible. They include remote study visits, guidance on performing efficacy and safety assessments, study agent dispensing alternatives (including direct to patient [DTP] shipping), and the tracking of COVID-related protocol deviations that occur. Notably, for this study, the performance of remote visits and provision of study drug directly to patients are in alignment with the protocol, which does not stipulate the location of visits and refers to the study pharmacy manual for mechanism and methods of study agent dispensing (protocol Section 7). However, these operational changes do represent urgent safety measures (USM), per regional (e.g., European Medicines Agency) and local guidance, and may impact other related clinical trial application documents. Study CNTO1275CRD3007 will continue under the currently approved protocol with appropriate modifications as described below.

1.1 STUDY BACKGROUND

CNTO1275CRD3007, A Phase 3b, Multicenter, Randomized, Blinded, Active-Controlled Study to Compare the Efficacy and Safety of Ustekinumab to that of Adalimumab in the Treatment of Biologic Naïve Subjects with Moderately-to-Severely Active Crohn's Disease, also known as

SEAVUE, is an ongoing study. This one-year study began in 2018 and completed enrollment in December 2019. Patients are followed for 1 year; we anticipate completion of the primary efficacy portion of the study, with a database lock when all patients complete their Week 52 primary endpoint, at the end of 2020.

As a Phase 3b study, SEAVUE is comparing approved medications (ustekinumab and adalimumab) using labelled dosing. Per protocol, patients are trained to inject themselves with study agent and after week 2, they self-administer the study agent at home. Subsequent to week 2, study visits are scheduled every 8 weeks. Medication is dispensed to patients for the following 8 weeks at each visit. To date, all patients have been in the study for at least 8 weeks, therefore, per protocol, all patients are currently self-administering study agent at home.

2. REMOTE STUDY VISITS

Given restrictions on travel and on-site visits, patients may not be able to be seen at the study site for evaluation. Guidance is being provided to sites that remote study visits can be performed by telephone, or if possible, as a video telemedicine/telehealth visit, provided this is consistent with local regulations, patient privacy practices, and is otherwise feasible. Further, the possibility to perform home health visits, and specific relevant guidance, is being explored. Sites are being provided guidance on best practices for the collection of efficacy and safety data under these circumstances. Adverse events (AE), serious AEs and concomitant medications will continue to be reported and documented, per protocol, even during these modified visits. In addition, any deviations that result from assessments that cannot be performed remotely (eg, physical examination for abdominal mass per the CDAI key efficacy measure) will be captured (see Section 4 below).

Laboratory Studies

Local laboratory studies may be performed if patients cannot come to the site, as a part of standard of care for safety monitoring purposes. This is permitted per protocol, as approved by the medical monitor, which has been granted during the COVID-19 pandemic. Any local laboratory result that represents a clinically relevant change, in the investigator's opinion, should be reported as an Adverse Event. Because local laboratory results are not incorporated into the study database they are not interchangeable with central laboratory results, which should therefore be resumed as soon as conditions permit. In addition, for selected measures (eg, urine pregnancy), home testing may be employed.

3. DIRECT TO PATIENT SHIPMENT

In exceptional circumstances, other study agent dispensing solutions may be considered by site staff, depending on the Health Authority's country requirements, medical disease management, and the need to maintain protocol-specified treatment schedule. Specifically, DTP shipping may be requested on a per-patient level with a written request to the sponsor. Once a request is made, DTP processes will be initiated by the sponsor including the use of an approved courier (ie, World Courier) who will then manage the distribution of study agent between the study site and patient, including mandatory temperature tracking for these products and traceability of the transport.

As a part of this process, all personal patient information remains confidential and is not disclosed to the sponsor. The sponsor will activate the courier and will provide the courier contacts to the study site. As such there will be direct communication between the study site and courier and only the site communicates the patient's details to the courier. The patient should verbally consent to share home address with the courier for this purpose, which will be recorded in patient source records. The site must retain courier documentation, track the shipment and confirm successful delivery to the patient. The site must maintain drug accountability records.

Full details describing the dispensing and distribution of study agent are included in the Site Investigational Product Procedures Manual (SIPPM), which will be updated with these procedures specific to the DTP process. This information is only presented in the SIPPM and not described in the protocol.

4. COVID-RELATED DEVIATIONS

Any missing data, including missed central laboratory tests and assessments that cannot be performed remotely (eg physical examination for abdominal mass per the CDAI key efficacy measure), will be documented as protocol deviations by the investigator and sponsor as due to COVID-19, and tracked for future reporting and analysis purposes. The occurrence of remote visits will also be recorded in the source documents. All COVID-related deviations will be fully discussed in the CSR, including their potential impact on the study.

5. SITE MONITORING

With regards to site monitoring visits at sites where these are not currently allowed, Site Managers will perform remote monitoring with investigative staff, as allowed and appropriate. On-site monitoring, per study monitoring guidelines, will be resumed when Site Managers are permitted to return to the sites.

6. CONCLUSION/SUMMARY

The sponsor is committed to the protection of patient safety in-light of the COVID-19 pandemic and providing sites and patients alternative solutions under the current circumstances, provided they are consistent with local regulations, patient privacy practices, and are otherwise feasible. Study CNTO1275CRD3007 will continue under the currently approved protocol with appropriate modifications as described above. These exceptions to the current protocol, to allow for safe, continued study treatment and remote visits, are adjustments considered on an exceptional basis and the clinical trial will return to previous conditions at the end of the health crisis. All protocol deviations and missing data as a result of COVID-19 will be tracked and documented. The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study Statistical Analysis Plan (SAP). Further, the sponsor will continue to monitor the conduct and progress of the clinical study with respect to the COVID-19 pandemic and any additional changes will be communicated to the sites and health authorities, as needed, according to local guidance.