Janssen Scientific and Medical Affairs*

Clinical Protocol

Protocol Title

A Phase 3b, Randomized, Double-blind, Multicenter Study to Evaluate the Safety and Efficacy of Intravenous Re-induction Therapy With Ustekinumab in Patients with Moderately to Severely Active Crohn's Disease

Patient Optimization With ustEkinumab Re-induction (POWER)

Short Title

Efficacy and Safety of Ustekinumab Re-induction Therapy in Patients With Moderately to Severely Active Crohn's Disease With Secondary Loss of Response

Protocol CNTO1275CRD3008; Phase 3b
AMENDMENT 4

STELARA (ustekinumab)

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	5 August 2020
Amendment 3	19 May 2020
Amendment 2	8 April 2020 (COVID-19 amendment)
Amendment 1	19 July 2019
Original Protocol	17 August 2018

The changes in Amendment 4 are summarized in the table below. Changes in previous protocol amendments are presented in Section 10.9, Appendix 9.

Amendment 4, 5 August 2020

Overall Rationale for the Amendment: To increase enrollment into the study, through allowing patients who have previously received a dose interval shortening of 90mg SC ustekinumab less than every 8 weeks and clarify ileocolonoscopy as an exploratory endpoint for participants who agree to this procedure.

Section Number and Name	Description of Changes and Brief Rationale
5.1 Inclusion Criteria OR 5.2 Exclusion Criteria; 10.2 Definition of Ustekinumab Initial Response and Current Therapy.	**Description of Change:** Allowed for inclusion of patients who have previously received a dose interval shortening of 90 mg SC ustekinumab less than every 8 weeks, provided they have since received specified per label doses. Evidence of prior ustekinumab treatment and response/remission should be documented by medical records, if available. If such documentation is unavailable, the investigator can confirm the ustekinumab doses, and initial response/remission in the eCRF to their best knowledge and clinical judgement.
	Rationale: To enable recruitment of patients.
Synopsis; 9.5 Interim Analyses.	**Description of Change:** Included an overview of interim analysis to test for futility.
	Rationale: To test for futility and assess/confirm sample size.
Synopsis; 1.3 Schedule of Activities; 3 Objectives and Endpoints; 4.1 Overall Design; 8 Study Assessments and Procedures	**Description of Change:** Clarified that ileocolonoscopy should be performed only at the physician's discretion and where participants agree for this procedure, for evaluation of this exploratory endpoint. Where this is not performed, this will not be considered a protocol deviation. **Rationale:** To enable recruitment and patient retention.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3b, Randomized, Double-blind, Multicenter Study to Evaluate the Safety and Efficacy of Intravenous Re-induction Therapy With Ustekinumab in Patients with Moderately to Severely Active Crohn's Disease

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human IL-12/23p40 that binds with high affinity to human IL-12 and IL-23. Ustekinumab prevents IL-12 and IL-23 bioactivity by preventing their interaction with the cell surface IL-12Rβ1 receptor protein, thereby effectively neutralizing all IL-12 (Th1) and IL-23 (Th17) mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases, including psoriasis, psoriatic arthritis, and inflammatory bowel disease. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

OBJECTIVES AND ENDPOINTS

Objectives

The primary objective is to evaluate the achievement of clinical response at Week 16 following a single IV re-induction dose of ~6 mg/kg ustekinumab, compared with continuing regular SC q8w 90 mg ustekinumab administration, in participants with secondary loss of response (LoR) to SC q8w 90 mg ustekinumab maintenance therapy.

The secondary objectives are to:

- Evaluate the achievement of clinical response and clinical remission, as well as the reduction in inflammatory biomarkers (serum C-reactive protein [CRP] and fecal calprotectin [fCal] levels), after IV ustekinumab re-induction.
- Assess the overall safety of IV ustekinumab re-induction.

Other objectives are to assess endoscopy and patient-reported assessment of bowel inflammation following IV ustekinumab re-induction, and to assess the steroid-sparing effect and pharmacokinetics following a single IV re-induction dose of ~6 mg/kg ustekinumab.

Endpoints

The primary endpoint is clinical response at Week 16, defined as a ≥100-point reduction from the baseline Crohn's Disease Activity Index (CDAI) score or a CDAI score <150 points.

The major secondary endpoints, listed in order of testing, are as specified below:

- Clinical remission at Week 16, defined as a CDAI score of <150 points.
- Clinical response at Week 8, defined as a ≥100-point reduction from the baseline CDAI score or a CDAI score <150.
- Clinical remission at Week 8, defined as a CDAI score of <150 points.
- Normalization of CRP and/or fCal concentration(s) at Week 16, among participants with elevated CRP and/or fCal at baseline.

Other secondary endpoints are:

- Clinical remission at Week 24, defined as a CDAI score of <150 points.
- Clinical response at Week 24, defined as a ≥100-point reduction from the baseline CDAI score or a CDAI score <150.
- Normalization of CRP and/or fCal concentration(s) at Week 24, among participants with elevated CRP and/or fCal at baseline.
- Safety endpoints, including the proportion of participants with at least one adverse event and subcategories of adverse events (all infections, all serious adverse events and serious infections), as well as changes in clinical laboratory test results.

Other endpoints are described in Section 3 of the protocol.

Hypothesis

The study hypothesis is that in patients with secondary LoR to SC q8w 90 mg ustekinumab maintenance treatment, a single weight-tiered based IV ustekinumab re-induction dose of ~6 mg/kg (ie, IV ustekinumab/SC placebo at Week 0) followed by q8w 90 mg ustekinumab maintenance will result in a higher clinical response rate (defined as a ≥100-point reduction from the baseline CDAI score, or a CDAI score <150) compared with continuous SC q8w 90 mg ustekinumab maintenance treatment (ie, IV placebo/SC ustekinumab at Week 0) after 16 weeks.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, 24-week, Phase 3b study in adult patients with moderately to severely active Crohn's disease who initially responded (as defined in Section 10.2, Appendix 2 of the protocol) to ustekinumab induction therapy per label followed, at any time, by secondary LoR to SC q8w ustekinumab maintenance therapy. The benefit of a single weight-tiered based IV re-induction dose of ~6 mg/kg body weight ustekinumab versus continuous SC q8w maintenance treatment will be evaluated.

Secondary LoR is defined as a CDAI score of ≥220 and ≤450 plus at least one of the following:

- Elevated CRP (>3.0 mg/L); and/or
- Elevated fCal (>250 mg/kg); and/or
- Endoscopy (ileocolonoscopy) performed ≤3 months before baseline with evidence of active Crohn's disease (defined as one or more ulcerations in the ileum and/or colon).

Eligible participants will be randomly assigned to 1 of the following 2 intervention groups in a 1:1 ratio, using permuted block randomization stratified at the study level by participant's baseline CDAI score (≤300 or >300) and prior biologic failure (yes or no) at baseline:

- **Ustekinumab re-induction:** IV ustekinumab and SC placebo at Week 0.
- **Continuous maintenance:** IV placebo and SC ustekinumab at Week 0.

At baseline (Week 0), approximately 8 weeks (±2 weeks) after the previous per label dose of SC 90 mg ustekinumab maintenance, participants will undergo clinical assessments. Following randomization, participants will receive either IV ustekinumab ~6 mg/kg and SC placebo or IV placebo and SC ustekinumab 90 mg in a double-blind manner (IV administration will be as an infusion and SC administration will be as an injection). Either the IV infusion or the SC injection may be administered first at Week 0, based on the standard-of-care practices at the study site; there must be no concurrent administration of IV and SC study intervention.

At Week 8 and Week 16, all participants will receive SC ustekinumab 90 mg and undergo clinical assessments. The SC injections at Week 8 and Week 16 should be administered by qualified study site staff during the study visit. In exceptional cases, where a site visit is not possible, participants who have appropriate experience or have received required training may self-administer SC study intervention at the times instructed by the investigator.

At Week 24, all participants will undergo study assessments before resuming their standard-of-care therapy at the discretion of the treating physician. All participants will have a follow-up for evaluation of safety approximately 20 weeks after their last study intervention administration (ie, Week 36 for participants who complete the final study intervention visit at Week 16); this may be conducted at a site visit or by telephone.

A participant will be considered to have completed the study if he/she has completed assessments through the 24-week treatment period and the Week 36 safety follow up. Participants will be considered to have completed the primary efficacy period of the study if they have completed the study assessments through Week 16 (or at an early termination visit). The end of study is considered the last scheduled study assessment for the last participant in the study.

Key efficacy assessments will include clinical response (CDAI reduction ≥100), clinical remission (CDAI value <150) and biomarker normalization. Safety assessments will include the monitoring of adverse events, vital signs, and clinical laboratory tests.

NUMBER OF PARTICIPANTS

The study will include approximately 200 participants, with approximately 100 participants in each of the 2 intervention groups.

INTERVENTION GROUPS AND DURATION

Administration of Interventions

Study intervention will start at baseline (Week 0), approximately 8 weeks (±2 weeks) after the previous dose of per label SC 90 mg ustekinumab maintenance treatment. The date of the previous dose of ustekinumab will be recorded in the case report form (CRF).

To maintain the double-blind, at Week 0 all participants will receive one IV infusion of study intervention (ustekinumab ~6 mg/kg or placebo) plus one SC administration of study intervention (ustekinumab 90 mg or placebo).

At Week 8 and Week 16, all participants will receive SC maintenance injections of 90 mg ustekinumab. Following study assessments at Week 24, all participants will resume their standard-of-care therapy with either ustekinumab maintenance therapy per label or another treatment modality at the discretion of their physician.

Description of Interventions

Study intervention should be dispensed under the supervision of the investigator, a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention in glass vials and PFS will be ready to use. The required volume of study intervention will be prepared using the appropriate vials or PFS. Aseptic procedures must be used during the preparation and administration of the ustekinumab solution for IV infusion.

For IV administration, the study intervention will be administered to each participant as an infusion over a period of not less than 1 hour by qualified staff. The infusion should be completed within 8 hours of preparation. Details of each infusion will be recorded in the CRF (including date, start and stop times of the IV infusion, and volume infused).

Subcutaneous injections at Week 0 will be administered by qualified staff at the study site. At Week 8 and Week 16, SC injections should be administered by qualified study site staff during the study visit. In exceptional cases, where a site visit is not possible, participants who have appropriate experience or have received required training may self-administer SC study intervention at the times instructed by the investigator. The study site staff must ensure that those participants have the appropriate experience or have received the required training to perform self-administration of SC injections. Details of each administration will be recorded in the CRF (including date and time of administration).

EFFICACY EVALUATIONS

Efficacy evaluations will include the following:

- CDAI (the primary tool for assessing disease activity response to ustekinumab).
- PRO-2 (the CDAI components of the total number of liquid or very soft stools and the abdominal pain score).
- Inflammatory Bowel Disease Questionnaire (IBDQ).
- Inflammatory markers including serum CRP and fCal.
- Fistula assessment.
- Endoscopic assessments of the intestinal mucosa based on the presence and absence of mucosal ulcerations and the SES-CD in the subset of patients with endoscopies performed.

Other endpoints are described in Section 3 of the protocol.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Serum samples will be used to evaluate the PK of ustekinumab and to detect and characterize anti-ustekinumab antibodies. Serum collected for PK and immunogenicity evaluations may additionally be used to explore safety or efficacy aspects arising during or after the study period.

The blood sample for trough serum PK must be collected at all study visits prior to the administration of **ANY** study intervention (ie, IV or SC ustekinumab) as well as prior to the administration of standard-of-care therapy at Week 24. The post-IV infusion PK blood sample at Week 0 should be drawn approximately 60 minutes after completion of the IV infusion.

BIOMARKERS

Biomarker assessments will be conducted to examine the biologic response to treatment and to identify biomarkers that are relevant to ustekinumab treatment and/or Crohn's disease. Assessments may include the evaluation of relevant biomarkers in serum, blood, and/or stool samples collected as specified in the Schedule of Activities. Data collected from these samples will be used for exploratory research purposes**.**

SAFETY EVALUATIONS

Safety will be assessed through Week 24 by evaluating adverse events, clinical laboratory changes, physical examination, and vital signs. Adverse events will also be evaluated at a safety follow up performed at a site visit or by telephone approximately 20 weeks after the last study intervention administration (ie, Week 36 for participants who complete the final study intervention visit at Week 16).

STATISTICAL METHODS

The assumptions that form the basis for sample size and power calculations incorporated into this protocol to support the primary endpoint are based on the dose adjustment data from the IMUNITI Phase 3 study. In IMUNITI, 17 of 29 (59%) participants attained clinical response 16 weeks after LoR in the q12w adjusted to q8w group, while 11 of 28 (39%) participants attained clinical response 16 weeks after LoR in the sham dose adjustment group (ie. continually remaining on SC q8w dosing). The hypothesis for the sample size determination is that the IV ustekinumab group in this study will perform similarly to, if not better than, the q12w adjusted to q8w group in the IMUNITI study, given that the participants in this group will receive a higher dose of ustekinumab than those in the IMUNITI study, who received an adjustment from q12w to q8w.

Assuming a 60% clinical response rate at Week 16 in the IV ustekinumab group and 40% in the continuous SC q8w 90mg group, 100 participants per intervention group will yield an overall power above 80%, at a significance level of 0.05 (2-sided, Mantel-Haenszel test).

Efficacy analyses will be based on an intent-to-treat principle; the efficacy data for each participant will be analyzed according to the assigned treatment regardless of the actual treatment received.

For the primary endpoint, the proportion of participants in clinical response at Week 16 will be compared between the IV ustekinumab group and the continuous SC q8w group using a 2-sided Cochran-Mantel-Haenszel-chi-square test, stratified by baseline CDAI score (≤300 or >300) and prior biologic failure status at baseline (yes or no) at a significance level of 0.05.

Participants with missing data, defined as those participants who terminate the study before the designated visit or participants who have (a) missing value(s) 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 participants with missing data.

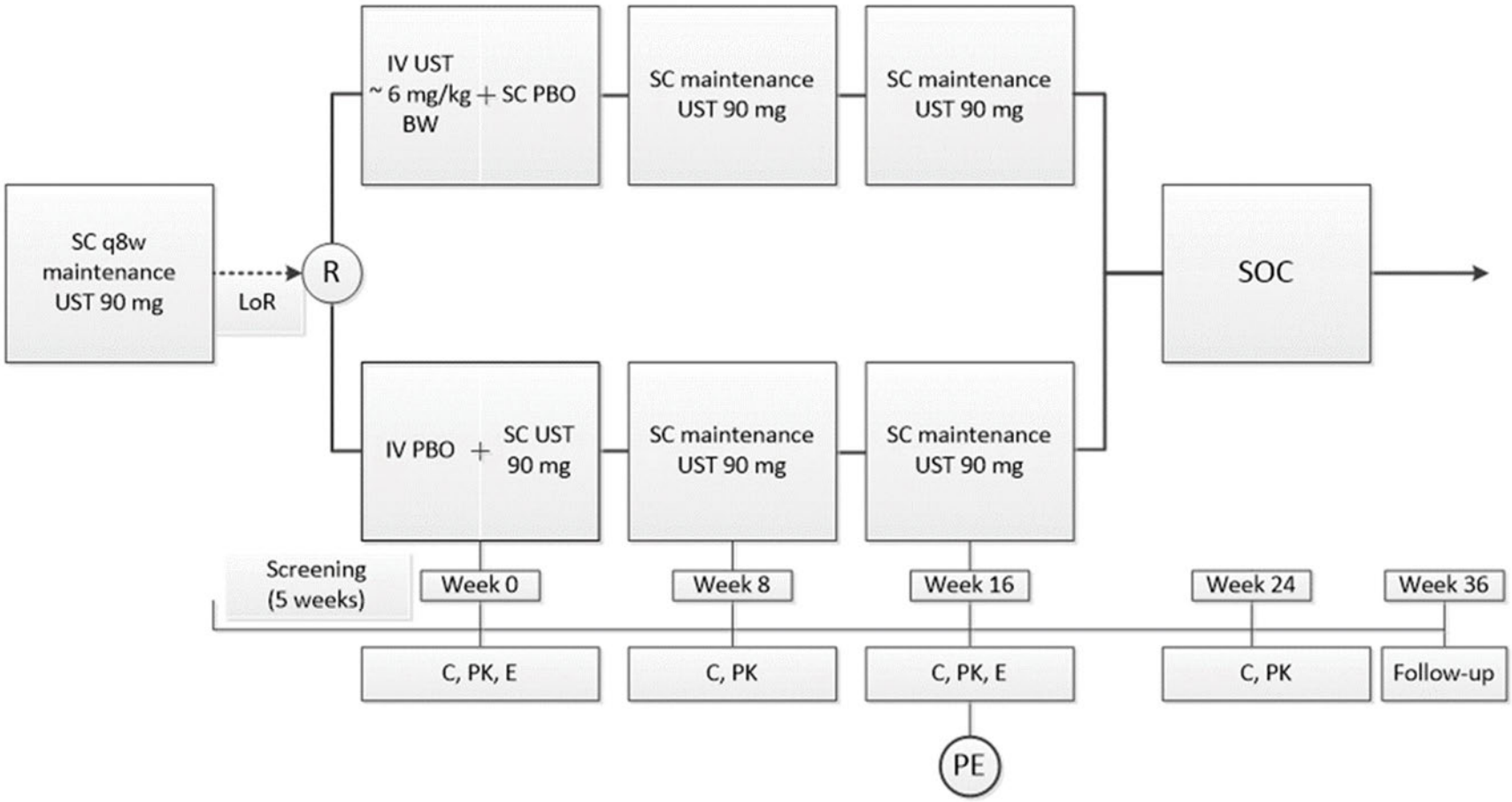
Treatment failure rules will override the response status (eg, clinical response, clinical remission, and mucosal healing). Participants who meet any of the following criteria for treatment failure will be considered to not have achieved their dichotomous efficacy endpoints from the time the treatment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

- Had a Crohn's disease-related surgery due to lack of efficacy; OR
- Discontinued study intervention due to an adverse event of worsening Crohn's disease 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.

An interim analysis will be performed in the study to test for futility after 40 randomized participants have completed the efficacy assessment at Week 16, and to assess sample size.

1.2. Schema



C=clinical assessment; E=endoscopy (where applicable); IV=intravenous (infusion); LoR=Loss of response; PBO=Placebo; PE=primary endpoint; PK=pharmacokinetic sampling (for immunogenicity + ustekinumab concentration); q8w=dosing every 8 weeks; R=randomization; SC=subcutaneous (injection); SOC=Standard of care (participants will resume their standard-of-care therapy after study assessments at Week 24); UST=ustekinumab; BW=body weight. Follow-up for evaluation of safety approximately 20 weeks after the last study intervention administration (ie, Week 36 for participants who complete the final study intervention visit at Week 16) may be conducted at a site visit or by telephone.

1.3. Schedule of Activities

	Study Period[a]							
Study Procedure	**Screening**	**Baseline (Week 0)**	**Week 8**	**Week 16**	**Week 24**	**Early termination**	**Follow-up[b] (Week 36)**	Notes:
Screening/Administrative								
Informed consent form	X							Signed before any study-related activities.
Inclusion/exclusion criteria	X	X						Eligibility should be reconfirmed at Week 0 before randomization.
Medical history/demographics	X	X						
Initial response criteria	X							
Provide daily diary cards	X							For recording CDAI components and concomitant medications.
Preplanned surgery/ procedure(s)		X						
Tuberculosis and Infection Screen								
Chest radiograph	X							A prior chest radiograph taken within 6 months before Week 0 may be used.
QuantiFERON-TB test	X							If TB is suspected at any time during the study, a chest radiograph should be obtained, and a QuantiFERON®-TB test performed.
Stool sample (for enteric pathogens)[c]	X							Tests to be performed by central lab.
HIV, HBV and HCV testing[d]	X							
Pregnancy Testing								
Serum pregnancy test	X							Only in females of childbearing potential. Tests to be performed by central lab.
Urine pregnancy test		X	X	X	X	X		Before every study intervention administration in female participants of childbearing potential only. Tests to be performed by local lab.
Study Intervention								
Randomization		X						After all study entry criteria are confirmed.
Dispense/administer study intervention		X	X[e]	X[e]				Participants will resume their standard-of-care therapy after the Week 24 study assessments.

	Study Period[a]							
Study Procedure	**Screening**	**Baseline (Week 0)**	**Week 8**	**Week 16**	**Week 24**	**Early termination**	**Follow-up[b] (Week 36)**	Notes:
Efficacy Evaluations								
Collect and review daily diary cards		X	X	X	X	X		Diary cards should be collected for every day before each study visit.
CDAI assessment (including PRO-2)		X	X	X	X	X		Hematocrit value obtained during screening will be used to calculate CDAI at baseline.
Height (cm)	X							
Body weight (kg)		X	X	X	X	X		Required as part of the CDAI assessment
CRP[f]	X	X	X	X	X	X		
Stool sample (fecal calprotectin)[f]	X	X	X	X	X	X		Stool samples should be obtained before the start of bowel preparation for the video ileocolonoscopy (where applicable, see below)
Fistula exam	X	X	X	X	X	X		
Inflammatory Bowel Disease Questionnaire (IBDQ)		X		X		X[g]		Should be administered before any other study-specific procedures.
Video ileocolonoscopy		X		X		X		Where participants agree for this procedure, ileocolonoscopy should be performed as close to the visit as possible but within 14 days before Week 0 and within 14 days before or 28 days after Week 16. If ileocolonoscopy coincides with visit dates or the 7 days before the visit dates, CDAI scores should be calculated using the closest previous 7 days not impacted by the ileocolonoscopy and/or its preparation.

	Study Period[a]							
Study Procedure	**Screening**	**Baseline (Week 0)**	**Week 8**	**Week 16**	**Week 24**	**Early termination**	**Follow-up[b] (Week 36)**	Notes:
Safety Evaluations								
Physical examination	X				X	X		
Vital signs		X	X	X	X	X		Temperature, pulse/heart rate, blood pressure must be obtained before the IV infusion, approximately 30 minutes during the infusion, and twice (approximately 30-minute intervals) after completion of the IV infusion. Vital signs must also be obtained before and approximately 30 minutes after completion of each SC injection.
Hematology, chemistry[f]	X	X	X	X	X	X		Laboratory tests at Week 0 are not required if screening lab tests were performed within 2 weeks before Week 0. Blood samples for laboratory safety tests should be collected before administration of any study intervention and will be analyzed at a central laboratory; see Section 10.5, Appendix 5 of the protocol.
Pharmacokinetics/Immunogenicity								
Ustekinumab serum concentration[h]		X	X	X	X	X		At baseline, blood samples for PK and antibody determination should be drawn before administration of any study intervention (IV or SC), except for the post-IV infusion PK sample which should be drawn approximately 60 minutes after completion of the IV infusion. At post-baseline visits, all blood samples should be collected before administration of study intervention.[h]
Antibodies to ustekinumab[h]		X	X	X	X	X		
Biomarkers		X	X	X	X	X		
Ongoing Review								
Adverse events	X	X	X	X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X	

Footnotes:

a. Visit window should be ±4 days for each visit up to and including Week 16 and ±7 days for Week 24 and Week 36.
b. Participants should complete the safety follow up approximately 20 weeks after their last study intervention administration; for participants who complete the final study intervention visit at Week 16, this will occur at Week 36. The safety follow up may be conducted at a site visit or by telephone and applies to all participants, including those who discontinued study intervention before Week 24 or otherwise terminated study participation (eg, through withdrawal of consent), unless they do not consent to this follow up by study-site staff.
c. Stool test for enteric pathogens must include a stool culture and C. difficile toxin assay performed within 4 months before Week 0. Additional testing may be performed at the investigator's discretion.
d. Screening for HBV to include HBsAg, anti-HBs, and anti-HBc. Participants are eligible 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.
   HIV antibody test need not be performed if a negative result in last 6 months is available.
e. In exceptional cases, where a site visit is not possible, participants who have appropriate experience or have received required training may self-administer SC study intervention at Week 8 and/or Week 16.
f. Clinical laboratory tests for assessment of screening criteria and for study evaluations are further described in Section 10.5, Appendix 5 of the protocol.
g. The IBDQ at the early termination visit is required only for participants who did not remain in the study at Week 16 (due to early discontinuation of study intervention and/or early termination of study participation) or did not perform the IBDQ at Week 16.
h. All reasonable attempts should be made to collect samples at the scheduled timepoints and record the actual times of PK sample collections.
   At each time point, one venous blood sample of sufficient volume should be collected. Each serum sample will be divided into 3 aliquots (for ustekinumab serum concentration, antibody assessment, and a back-up), except for the post-infusion blood sample at Week 0 which will be for PK evaluation only.
   Determination of ustekinumab serum concentrations and antibody assessments will be performed by a central laboratory.

CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IV=intravenous; PK=pharmacokinetic.

2. INTRODUCTION

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human IL-12/23p40 that binds with high affinity to human IL-12 and IL-23. Ustekinumab prevents IL-12 and IL-23 bioactivity by preventing their interaction with the cell surface IL-12Rβ1 receptor protein, thereby effectively neutralizing all IL-12 (Th1) and IL-23 (Th17) mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases, including psoriasis, psoriatic arthritis, and inflammatory bowel disease. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

STELARA® (ustekinumab)[27] was initially approved for the treatment of adults with moderate to severe chronic plaque psoriasis in the European Union (EU) in January 2009 and in the United States (US) in September 2009, and gained subsequent approvals for psoriatic arthritis and adolescent psoriasis, followed by approval for the treatment of adult patients with moderately to severely active Crohn's disease on 23 September 2016 in the US and 11 November 2016 in the EU.

For the most comprehensive nonclinical and clinical information regarding ustekinumab, refer to the latest version of the Investigator's Brochure for STELARA (ustekinumab).

The term 'study intervention' used throughout this document refers to ustekinumab administered as a ~6 mg/kg intravenous (IV) infusion or as a 90 mg subcutaneous (SC) injection.

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.

2.1. Study Rationale

Crohn's disease is a chronic debilitating inflammatory disease of the digestive tract with a remitting and relapsing course. For the last decade, Crohn's disease has been most effectively treated with monoclonal antibodies to tumor necrosis factor (TNF); however, approximately one-third of patients do not respond to anti-TNFs initially, and a further third lose response during their course of treatment, requiring dose adjustment or switch to another medication.[16] There is a significant medical need for new safe and effective therapies for moderate to severe, active Crohn's disease as well as to optimize the limited treatment options currently available.

The approved dosing regimen for ustekinumab in the treatment of Crohn's disease comprises an initial weight-tiered based induction dose of approximately 6 mg ustekinumab per kg body weight (~6 mg/kg) administered intravenously followed by maintenance doses of 90 mg administered subcutaneously from Week 8. In the EU, the approved maintenance dosing regimen is 90 mg SC every 12 weeks (q12w) after Week 8, although patients who have not demonstrated an adequate response at Week 16 or who subsequently lose response may be dosed every 8 weeks (q8w). In the US, patients receive maintenance doses of 90 mg SC q8w from Week 8 per label.

While the clinical development program for ustekinumab established that both of the approved maintenance doses maintained clinical response through Week 44 (Section 2.2.1), it was demonstrated that a proportion of patients on maintenance dosing with ustekinumab will lose their response over time (Section 2.2.2). In a proportion of patients, the loss of response (LoR) to ustekinumab maintenance treatment is associated with low serum levels of ustekinumab (Section 2.2.3). Patients commonly lose response to biologics for the treatment of Crohn's disease, requiring dose intensification to regain response.[20] Similarly, patients in the EU with LoR to q12w maintenance dosing with ustekinumab may regain the response following dose adjustment to q8w maintenance dosing. However, there is no option for dose adjustment for patients in the US or EU who have lost response to q8w maintenance dosing. It is expected that a proportion of patients with LoR to q8w maintenance dosing will regain response employing a strategy of increasing serum concentrations. The approved IV dose provides a logical option to rapidly increase the serum concentrations of ustekinumab.

The aim of this study is to demonstrate the efficacy of a single weight-tiered based ustekinumab IV re-induction dose of ~6 mg/kg versus continuous ustekinumab SC maintenance treatment in adult patients with moderately to severely active Crohn's disease demonstrating a secondary LoR to ustekinumab q8w maintenance treatment.

2.2. Background

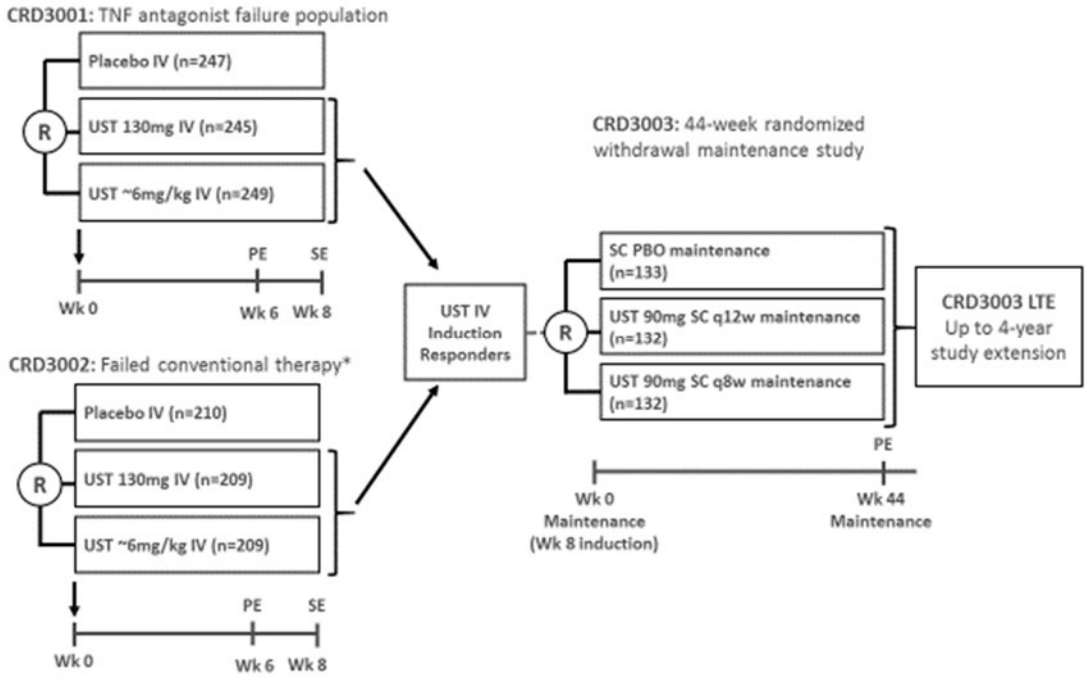
2.2.1. Development of the Current Ustekinumab Dosing Regimen in Crohn's Disease

The Phase 3 development program for ustekinumab in Crohn's disease consisted of three Phase 3 trials: two 8-week induction studies (CNTO1275CRD3001 [UNITI-1] and CNTO1275CRD3002 [UNITI-2]) that fed into one 44-week maintenance study (CNTO1275CRD3003 [IMUNITI]) (Figure 1).

Participants in the UNITI-1 and UNITI-2 studies who met the criteria for clinical response to IV induction with ustekinumab at Week 8 (defined as a reduction from baseline in CDAI score ≥100 points or total CDAI score <150 points) were randomized to receive either placebo maintenance or ustekinumab maintenance of q8w or q12w through Week 40 in the IMUNITI study, in which the primary endpoint was clinical remission at Week 44 (CDAI<150). The IMUNITI protocol allowed for blinded crossover to dose escalation for participants who qualified due to LoR; participants with LoR on placebo maintenance or q12w ustekinumab maintenance were switched to q8w ustekinumab maintenance, while participants with LoR on q8w maintenance received a sham dose escalation of continued q8w maintenance.

Based on the results of these studies, a weight-tiered based IV dose of ~6 mg/kg body weight was selected as the approved induction dose and 90 mg SC was selected as the approved maintenance doses, starting at Week 8. Patients in the US are to be maintained on q8w maintenance dosing from Week 8 per label. While q12w maintenance injections are recommended in the EU from Week 8, patients who have not shown adequate response at Week 16 or who subsequently lose response may be switched to q8w maintenance dosing. Indeed, the flexibility to optimize results is recognized as an important option in the treatment of Crohn's disease.

Figure 1: Study Designs for the Ustekinumab Phase 3 Development Program in Crohn's Disease



* Conventional therapy is defined as corticosteroids and/or immunomodulator. IV=intravenous; LTE=long-term extension, q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous; TNF=Tumor necrosis factor; PE=primary endpoint; SE=secondary endpoint; UST=ustekinumab

2.2.2. Loss of Response to Ustekinumab Maintenance Dosing

While the results of the IMUNITI study established that both the q12w and q8w doses of ustekinumab maintenance therapy were superior to placebo and maintained clinical response through Week 44, by Week 32 approximately 20% of participants in each ustekinumab maintenance arm met the criteria for dose escalation due to LoR (defined as CDAI ≥220 points and an increase in CDAI score from baseline of maintenance of ≥100 points).[9] Of those who entered the long-term extension, an additional approximately 10% were no longer in response by Week 92.[21] The results were similar between the 2 maintenance dosing regimens at both timepoints.

The observation of patients losing response over time has been observed with all biologics in the treatment of Crohn's disease, including 3 TNF inhibitors[1,5,13] and an integrin receptor antagonist[29]. A recent systematic review and meta-analysis of 86 studies of patients with Crohn's disease found that approximately 30% of primary anti-TNF responders experienced a LoR and required dose adjustment to regain and maintain response.[20] Rates of LoR after up to 1 year of treatment with vedolizumab have been reported to be around 50% in normal clinical practice.[3,26]

Considerable research has been conducted on the reasons for patients losing their initial response to biologic therapy. The causes for LoR, known as secondary nonresponse, fall into 2 general categories[8]: causes linked to the disease (eg, changes in disease pathology or progression) and causes linked to the drug's ability to treat the disease (eg, an increase in the level of inflammation and/or an increase in drug clearance, leading to inadequate levels of drug to maintain activity).

2.2.3. Dose Adjustment in Patients with Loss of Response to Ustekinumab

Pharmacokinetic (PK) analysis from the IMUNITI study showed that participants who lost response to q12w dosing had lower serum ustekinumab concentrations than those who did not lose response, suggesting that lower drug levels may be associated with LoR.[2] Similarly, participants with LoR to q8w dosing were also observed to have lower serum levels of drug compared with q8w participants who did not lose response. Median serum ustekinumab concentrations at Weeks 8 and 16 of q8w maintenance were 1.63 µg/mL and 1.19 µg/mL, respectively, for participants who met the criteria for dose adjustment, and 2.21 µg/mL and 2.04 µg/mL, respectively, for participants who did not need dose adjustment.[28]

Consistent with the hypothesis that patients with LoR have lower levels of drug than those with sustained response and considering the PK characteristics and exposure-response (E-R) relationship of ustekinumab, a potential strategy to address LoR is a dose escalation to raise serum drug levels, either in the form of an increase in dose or a shortening of the interval of ustekinumab administration. In IMUNITI, use of dose escalation to address LoR was studied only in the q12w group; participants with LoR to q8w dosing received blinded sham dose escalation of continued q8w maintenance. Upon dose escalation from q12w to q8w, 55% regained their response and 42% achieved remission by Week 16. Regaining of response was accompanied by a 4-fold increase in serum drug levels.[28] Thus, the concept of dose escalation for LoR is established for the q12w dose and was accordingly included in the approved European posology; however, for patients losing response to the q8w dose there is currently no established or approved strategy to address the LoR.

During induction and maintenance, ustekinumab concentration was inversely related to concentrations of C-reactive protein (CRP). At Week 8 in both induction studies, serum ustekinumab concentration was positively correlated with normalization of CRP. This suggests that ustekinumab clearance, and therefore ustekinumab concentration, is associated with baseline CRP, presumably as a function of the higher underlying inflammatory activity for which CRP is a marker.[2] These data suggest that ustekinumab clearance could slow as inflammation is suppressed and response is regained in these patients. Consequently, a permanent increase in dose might not be necessary to sustain adequate drug levels once response has been regained. Indeed, studies with other biologics have demonstrated that patients can return to standard doses after regaining response. Schnitzler et al[23] reported that more than 70% of patients who underwent infliximab dose optimization could return to their original treatment regimen during follow-up. Furthermore, as Crohn's disease is characterized by periodic flares, permanently high doses might not be needed to sustain response once regained, rather increased doses of drug would be required only until the flare quiesces or subsides.

There is evidence demonstrating that a strategy of re-induction can be as effective as long-term dose increase or interval shortening. Srinivasan et al[25] compared re-induction with shortened dosing intervals in patients who had lost response to standard maintenance dosing with either infliximab or adalimumab and found no significant difference in the incidence of treatment failure at 12 months follow-up (24% vs 15%, p=0.27). Although there were few patients and the dosing regimens varied, Heron[12] reported on 11 patients with Crohn's disease on SC 90 mg q4w ustekinumab with either clinical or endoscopic LoR who were dose adjusted with either SC (n=3)

or IV re-induction (n=8). The IV re-induction dose used was 260 mg IV in 2 patients and 390 mg IV in 6 patients. Five of the 8 (62.5%) participants receiving IV re-induction were in clinical remission or endoscopic response at follow-up (2 months and 7 months, respectively). Additional evidence supporting the efficacy of re-induction has been demonstrated in a small number of patients (n=3) who had been initially treated with non-weight-based SC induction and had not demonstrated an adequate clinical response to ustekinumab.[19]

Pharmacokinetic modeling of ustekinumab shows that IV re-induction with the approved ~6 mg/kg dose would achieve an approximately 10-fold higher peak concentration than would be achieved with even more frequent SC doses of 90 mg, such as q4w, the attained serum ustekinumab exposure being similar to the exposure following the initial induction. Based on the PK analysis, re-induction would not result in a meaningfully higher ustekinumab exposure than with the initial induction dose, since at the time of the re-induction serum concentrations would be at relatively low levels (1.19 µg/mL to 1.63 µg/mL). The C_{max} after re-induction would be expected to be only marginally higher than the C_{max} observed in the UNITI-1 and UNITI-2 induction studies (126.1 µg/mL and 124.4 µg/mL, respectively). Thereafter, serum concentrations would likely return to levels typically expected with ustekinumab maintenance dosing within 16 weeks, since median serum concentrations of ustekinumab are undetectable 16 weeks after infusion of the induction dose.

2.3. Benefit/Risk Assessment

The safety profile of ustekinumab is well documented, based on information from clinical trials and postmarketing experience. As of 31 December 2017, an estimated 11,557 participants have been exposed to ustekinumab in the clinical development program, including 2,742 patients with Crohn's disease. The estimated cumulative exposure to ustekinumab from launch through 31 December 2017 is 1,036,701 person-years across all disease indications.

The benefits of ustekinumab in patients with moderate to severe Crohn's disease have been well characterized, with a significant improvement in control of disease and a potential for decreased colectomy, lower frequency of hospitalization, and improved quality of life.

Re-induction dosing for LoR employs the currently approved initial IV induction dose that was demonstrated to be safe and effective in clinical trials. This incremental, short-term increase in serum levels of ustekinumab is unlikely to have safety consequences compared with the initial induction; indeed, no dose response was observed for safety between the different induction doses tested in clinical trials with ustekinumab. In Crohn's disease induction studies, no events of anaphylaxis or other serious infusion reactions were reported following the single IV dose; 2.4% of 466 participants who received placebo and 2.6% of 470 participants who received the recommended dose of ustekinumab reported adverse events occurring during or within an hour of the infusion.

As described in Section 2.2.3, it is likely that serum concentrations after re-administration of the IV induction dose in patients on q8w maintenance would be similar to those after the initial IV induction dose administration. Use of the approved maintenance dose and dosing interval after IV

re-induction would avoid increased long-term exposure to ustekinumab and present a lower treatment administration burden on patients than more frequent injections.

There is evidence in the literature demonstrating that a strategy of re-inducing therapy can be as effective as long-term dose increases or interval shortening with reduced safety considerations.[6,11,12,15,16,18,32] Of particular interest is the most recent of these reports (Heron 2018[12]), in which 8 patients with Crohn's disease who were on SC 90 mg q4w ustekinumab, with either clinical or endoscopic LoR, were dose adjusted with IV re-induction. Of the 8 patients who received IV re-induction, 5 (62.5%) were in clinical remission or endoscopic response at follow-up.

In this study, the potential risks of treatment with ustekinumab (eg, serious infections, including tuberculosis [TB] and hypersensitivity reactions) are addressed in multiple ways:

- The inclusion/exclusion criteria set appropriate limits regarding, for example, infections or predisposition to infections, history of reactions to biologic agents, and baseline laboratory abnormalities (see Sections 5.1 and 5.2, respectively).
- Comprehensive medical monitoring of data by the sponsor during the conduct of this study includes regular assessment of adverse events and serious adverse events, vital signs, physical examination, and laboratory test results to evaluate individual cases as well as potential emerging safety trends (see Schedule of Activities and Section 8.2).
- Certain concomitant medications have been prohibited and limitations set on dose levels of permitted concomitant medications in this study, such as high dose glucocorticoids and use of multiple biologics simultaneously, which could introduce safety risks due to over-suppression of the immune system (see Section 6.5).
- Finally, the steroid-sparing effects of ustekinumab are evaluated by implementation of a glucocorticoid taper from Week 8 (see Section 6.5.2). This may benefit participants by reducing risk of infection and other glucocorticoid-related complications; however, if a participant experiences a worsening in their disease activity while tapering corticosteroids, further dose decreases can be suspended, and/or the participant's oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator.

The benefit risk ratio is considered favorable, given the potential benefit of a re-induction strategy to regain response to ustekinumab with a single intervention, and considering the current understanding of the safety profile of ustekinumab and the cumulative ongoing safety evaluations.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objective

The primary objective is to evaluate the achievement of clinical response at Week 16 following a single IV re-induction dose of ~6 mg/kg ustekinumab, compared with continuing regular SC q8w 90 mg ustekinumab administration, in participants with secondary LoR to SC q8w 90 mg ustekinumab maintenance therapy.

Secondary Objectives

The secondary objectives are to:

- Evaluate the achievement of clinical response and clinical remission, as well as the reduction in inflammatory biomarkers (serum CRP and fecal calprotectin [fCal] levels), after IV ustekinumab re-induction.
- Assess the overall safety of IV ustekinumab re-induction.

Other Objectives

Other objectives are to assess endoscopy and patient-reported assessment of bowel inflammation following IV ustekinumab re-induction, and to assess the steroid-sparing effect and pharmacokinetics following a single IV re-induction dose of ~6 mg/kg ustekinumab.

ENDPOINTS

Primary Endpoint

The primary endpoint is clinical response at Week 16, defined as a ≥100-point reduction from the baseline CDAI score or a CDAI score <150 points.

Secondary Endpoints

The major secondary endpoints, listed in order of testing, are as specified below:

- Clinical remission at Week 16, defined as a CDAI score of <150 points.
- Clinical response at Week 8, defined as a ≥100-point reduction from the baseline CDAI score or a CDAI score <150.
- Clinical remission at Week 8, defined as a CDAI score of <150 points.
- Normalization of CRP and/or fCal concentration(s) at Week 16, among participants with an elevated CRP and/or fCal at baseline.

Other secondary endpoints are:

- Clinical remission at Week 24, defined as a CDAI score of <150 points.
- Clinical response at Week 24, defined as a ≥100-point reduction from the baseline CDAI score or a CDAI score <150.

- Normalization of CRP and/or fCal concentration(s) at Week 24, among participants with an elevated CRP and/or fCal at baseline.
- Safety endpoints, including the proportion of participants with at least one adverse event and subcategories of adverse events (all infections, all serious adverse events and serious infections), as well as changes in clinical laboratory test results.

Other Endpoints

The following other endpoints will be assessed:

- Endoscopy
  - Reduction of ≥50% from baseline in simple endoscopic score for Crohn's disease (SES-CD) at Week 16.
  - Reduction of ≥3 points from baseline in SES-CD at Week 16.
  - SES-CD score ≤3 at Week 16.
  - Complete absence of mucosal ulcerations in any ileocolonic segment at Week 16
  - Change from baseline in simple endoscopic score for SES-CD score at Week 16.
  - Proportion of participants with a minimum of 25% improvement from baseline in SES-CD score at Week 16.
- Patient-reported outcomes
  - Change from baseline in the sum of the number of stools and the abdominal pain scores in the prior 7 days, without weighting (PRO-2), at Week 16.
  - Change from baseline in the weighted sum of the abdominal pain and stool frequency subscores of the CDAI (PRO-2 weighted) at Week 16.
  - Change from baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ) score (including IBDQ domains) at Week 16.
  - Proportion of participants with IBDQ remission (IBDQ score >170) at Week 16.
- Steroids
  - Proportion of participants with corticosteroid-free response at Week 24, defined as a CDAI score decrease ≥100 from baseline.
  - Proportion of participants with corticosteroid-free response at Week 24, defined as a CDAI score decrease ≥100 from baseline, among participants who were on corticosteroids at baseline.
  - Proportion of participants with corticosteroid-free remission at Week 24, defined as a CDAI score <150, among participants who were on corticosteroids at baseline.
- Pharmacokinetics
  - Serum ustekinumab concentrations and PK parameters.
  - Proportion of participants with anti-ustekinumab antibodies.

Additionally, the following other combined endpoints will be assessed at Week 16:

- Proportion of participants with clinical remission and ≥50% reduction from baseline in CRP or fCal.
- Proportion of participants with clinical remission and ≥50% reduction from baseline in CRP or fCal, among participants with elevated CRP (>3 mg/L) or elevated fCal (>250 mg/kg) at baseline.
- Proportion of participants with clinical remission and CRP <3 mg/L and fCal ≤250 mg/kg.
- Proportion of participants with clinical remission and CRP <3 mg/L and fCal ≤250 mg/kg, among participants with elevated CRP (>3 mg/L) or elevated fCal (>250 mg/kg) at baseline.
- Proportion of participants with clinical biomarker response (clinical response and ≥50% reduction from baseline in CRP or fCal).
- Proportion of participants with clinical biomarker response (clinical response and ≥50% reduction from baseline in CRP or fCal), among participants with elevated CRP (>3 mg/L) or elevated fCal (>250 mg/kg) at baseline.
- Proportion of participants with clinical response and CRP <3 mg/L and fCal ≤250 mg/kg.
- Proportion of participants with clinical response and CRP <3 mg/L and fCal ≤250 mg/kg, among participants with elevated CRP (>3 mg/L) or elevated fCal (>250 mg/kg) at baseline.

Refer to Section 8, Study Assessments and Procedures, for evaluations related to endpoints.

HYPOTHESIS

The study hypothesis is that in patients with secondary LoR to SC q8w 90 mg ustekinumab maintenance treatment, a single weight-tiered based IV ustekinumab re-induction dose of ~6 mg/kg (ie, IV ustekinumab/SC placebo at Week 0) followed by q8w 90 mg ustekinumab maintenance will result in a higher clinical response rate (defined as a ≥100-point reduction from the baseline CDAI score, or a CDAI score <150) compared with continuous SC q8w 90 mg ustekinumab maintenance treatment (ie, IV placebo/SC ustekinumab at Week 0) after 16 weeks.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, 24-week, Phase 3b study in adult patients with moderately to severely active Crohn's disease who initially responded to ustekinumab induction therapy per label followed, at any time, by secondary LoR to SC q8w ustekinumab maintenance therapy. The benefit of a single weight-tiered based IV re-induction dose of ~6 mg/kg body weight ustekinumab versus continuous SC q8w maintenance treatment will be evaluated.

Initial response criteria are described in Section 10.2, Appendix 2.

Secondary LoR is defined as a CDAI score of ≥220 and ≤450 plus at least one of the following:

- Elevated CRP (>3.0 mg/L); and/or
- Elevated fCal (>250 mg/kg); and/or
- Endoscopy (ileocolonoscopy) performed ≤3 months before baseline with evidence of active Crohn's disease (defined as one or more ulcerations in the ileum and/or colon).

The study will include approximately 200 participants. Eligible participants will be randomly assigned to one of the following 2 intervention groups, in a 1:1 ratio, using permuted block randomization stratified at the study level by participant's baseline CDAI score (≤300 or >300) and prior biologic failure (yes or no) at baseline.

- **Ustekinumab re-induction:** IV ustekinumab and SC placebo at Week 0.
- **Continuous maintenance:** IV placebo and SC ustekinumab at Week 0.

At baseline (Week 0), approximately 8 weeks (±2 weeks) after the previous per label dose of SC 90 mg ustekinumab maintenance, participants will undergo clinical assessments. Following randomization, participants will receive IV ustekinumab ~6 mg/kg and SC placebo or IV placebo and SC ustekinumab 90 mg in a double-blind manner. Either the IV infusion or the SC injection may be administered first at Week 0, based on the standard-of-care practices at the study site; there must be no concurrent administration of IV and SC study intervention (see Section 6.1).

At Week 8 and Week 16, all participants will receive SC ustekinumab 90 mg and undergo clinical assessments.

At Week 24, all participants will undergo study assessments before resuming their standard-of-care therapy at the discretion of the treating physician. All participants will have a follow-up for evaluation of safety approximately 20 weeks after their last study intervention administration (ie, Week 36 for participants who complete the final study intervention visit at Week 16); this may be conducted at a site visit or by telephone.

Key efficacy assessments will include clinical response (CDAI reduction ≥100), clinical remission (CDAI value <150) and biomarker normalization. Safety assessments will include the monitoring of adverse events, vital signs, and clinical laboratory tests.

A diagram of the study design is provided in Section 1.2, Schema. The timing of study interventions and clinical assessments is summarized in Section 1.3, Schedule of Activities.

4.2. Scientific Rationale for Study Design

Study Population

The population for this study includes only adult patients with moderately to severely active Crohn's disease who experience a secondary LoR to SC q8w ustekinumab maintenance treatment, representative of the population of patients with Crohn's disease in which ustekinumab is approved. Since anti-TNF agents are often the first-line biologics used in the treatment of patients with Crohn's disease, based on recommended treatment algorithms[11,17], and the relatively recent approval of ustekinumab for the treatment of Crohn's disease, these patients likely have few remaining therapeutic options; hence regaining and preserving the response to ustekinumab is essential for the long-term management of their disease. While the current EU labeling for ustekinumab provides the option for dose adjustment in patients with LoR to q12w maintenance, there is no option for patients with LoR to q8w maintenance. Since dose adjustment using IV re-induction has not yet been studied in a controlled manner in these patients, this represents an important gap in the scientific literature that is important for evidence-based practice. This study will fill this gap by providing a prospective, randomized direct comparison of IV re-induction with continuous q8w maintenance therapy.

To mimic normal clinical practice and consistent with other studies, enrolled participants will be permitted to receive concomitant immunosuppressants or oral corticosteroids for the treatment of Crohn's disease during the study, provided they were on a stable dose for a specified period prior to baseline and will maintain a stable dose throughout the trial, with the exception of oral corticosteroids which will be tapered in Week 8 CDAI-70 responders.

Blinding, Control

This study is double-blind and utilizes a double-dummy design to maintain blinding and prevent bias. Placebo is included in each intervention group for blinding purposes, rather than for determination of the effect of the study intervention (IV re-induction with ustekinumab versus continuous SC ustekinumab maintenance therapy). All participants will receive ustekinumab treatment until Week 24, at which time they will receive standard-of-care therapy.

Dosing, Study Duration

The dosage and dosing interval are designed to align with the currently approved label for ustekinumab for Crohn's disease in both the EU and the US.

The relatively short duration of the study (24 weeks, with a safety follow up at Week 36) is intended to provide evidence for the effectiveness of re-induction without requiring prolonged treatment, should a patient not respond to the therapeutic intervention. Based on PK modeling, it

is expected that serum concentrations of ustekinumab will have nearly normalized by Week 16 with complete normalization by Week 24.

Study Endpoints

The primary endpoint at Week 16 aligns with the current recommendations to evaluate the response to initial induction or dose escalation after 16 weeks of therapy. The primary endpoint of clinical response is designed to mimic the real-world treatment of patients with Crohn's disease. The population of patients enrolled in this trial (ie, with LoR despite high dose ustekinumab maintenance therapy and a likely history of previous, inadequate response to biologic agents) is expected to be difficult to treat. In this refractory setting the primary goal is to achieve a clinical response, rather than clinical remission or endoscopic response. In addition, it is not clear if patients who experience LoR necessarily have associated endoscopic recurrence, nor has it been established for any biologic that endoscopic response can be regained with dose adjustment for LoR in patients with Crohn's disease. The use of the CDAI to assess response to treatment has been demonstrated in clinical trials for recently approved therapeutics for Crohn's disease.[9,21]

This study will also evaluate patient-reported outcomes (PROs), recognizing the important information these tools can provide to help clinicians evaluate response to therapies. The evaluation of endoscopic outcome measures at Week 16 will seek to provide additional information on the efficacy of IV re-induction and of mucosal inflammation in the setting of LoR. Additional evaluations will examine the pharmacodynamics of IV re-induction, correlating the PK with clinical outcomes (eg, CDAI, changes in CRP and fCal, and endoscopic measures where applicable); these evaluations may provide further information to enable clinicians to make informed treatment decisions for patients with a secondary LoR to ustekinumab.

Database Locks

Two database locks are planned for this study. The first (the primary endpoint database lock) will occur when all participants have completed Week 16 or have terminated study participation prior to Week 16. The second (the final database lock) will occur when all participants have completed Week 36 or have terminated study participation prior to Week 36.

At the time of the Week 16 database lock, the sponsor (except for site monitors, who have interactions with the investigative sites) will become unblinded to treatment assignment. The study blind will be maintained for investigators, site personnel, participants, and sponsor site monitors until the final assessments have been completed for all study participants at Week 36. This measure will mitigate the potential bias in the remaining investigator and participant assessments.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study. During the study, participants 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 participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and who provide their consent voluntarily will be enrolled.

The efficacy and safety profile for ustekinumab in the treatment of moderately to severely active Crohn's disease is well-established. All participants will receive active treatment for their disease throughout the study, including those patients who receive IV placebo. Additionally, the dosage and dosing interval used in this study are designed to align with the currently approved label for ustekinumab for Crohn's disease in both the EU and the US.

The total blood volume to be collected in this study (see Section 8) is considered an acceptable amount for the study duration and study population based upon the standard of the World Health Organization (450 mL once every 2 months, up to a maximum of 3 L over 12 consecutive months for blood donation).

4.3. Justification for Dose

The IV ustekinumab re-induction dose (~6 mg/kg) is the approved dose for the initial induction with ustekinumab in patients with Crohn's disease, which is being investigated in this study for re-induction in patients with secondary LoR to ustekinumab.

The maintenance dose of ustekinumab (90 mg) SC q8w is the approved dose for maintenance treatment in patients with Crohn's disease in the US and for EU patients who have not responded adequately to ustekinumab induction treatment or q12w treatment. All participants must have demonstrated secondary LoR to current SC q8w ustekinumab maintenance therapy to qualify for this study (see Section 4.1); any patients who initially did not respond adequately to ustekinumab q12w treatment must also have not responded to q8w treatment before being considered eligible for this study.

The rationale for re-induction rather than dose interval shortening to address LoR in patients on q8w maintenance is supported by 2 key arguments:

- Ustekinumab PK analysis shows that ustekinumab clearance is increased with increased levels of underlying inflammation, as measured by CRP. This raises the possibility that ustekinumab clearance could slow as inflammation is suppressed and response is regained and, if so, that a longer-term increase in dose might not be necessary to sustain adequate ustekinumab levels once response has been regained.
- Crohn's disease is characterized by periodic flares, which suggests that increased doses of drug would be required only until the flare is quiesced or has subsided, after which maintenance dosing can be continued.

The therapeutic intervention takes advantage of an approved induction dose and route of administration with known PK characteristics and safety, minimizing risk to the study participants, particularly over an extended time since no safety data exist for long-term use of 90-mg SC q6w or q4w dosing.

4.4. End of Study Definition

A participant will be considered to have completed the study if he/she has completed assessments through the 24-week treatment period and the Week 36 safety follow up. Participants will be considered to have completed the primary efficacy period of the study if they have completed the study assessments through Week 16 (or at an early termination visit).

The end of study is considered the last scheduled study assessment for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible participants will be performed within 5 weeks before the first administration of study intervention at Week 0. Refer to Section 5.4 for information on repeat of any screening procedures.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about any of these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed. For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

5.1. Inclusion Criteria

Each potential participant must satisfy all the following criteria to be enrolled in the study:

1. Male or female aged ≥18 years (or the legal age of consent in the jurisdiction in which the study is taking place if older than 18 years).

2. A history of Crohn's disease or fistulizing Crohn's disease of at least 3 months' duration, with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography, histology, and/or endoscopy.

3. Criterion changed per Amendment 4.

3.1 Initially responded to ustekinumab induction therapy[a], administered according to the local label, followed by secondary LoR to ustekinumab[b].

[a] *Initial response to ustekinumab as defined in Section 10.2, Appendix 2.*

[b] *Secondary LoR to ustekinumab is defined as active disease at study baseline, proven by a CDAI score of ≥220 and ≤450 with at least one of the following:*

- *Elevated CRP (>3.0 mg/L); and/or*
- *Elevated fCal (>250 mg/kg); and/or*
- *Endoscopy (performed ≤3 months before baseline) with evidence of active Crohn's disease (defined as one or more ulcerations in the ileum and/or colon).*

Participants must currently be on a SC 90 mg ustekinumab q8w maintenance dose regimen and have received at least 2 doses of SC 90 mg ustekinumab treatment 8 weeks apart prior to enrollment.

4. The following medications for the treatment of Crohn's disease are permitted providing the doses indicated are stable for at least 3 weeks before baseline or have been discontinued at least 3 weeks before baseline:

- Oral 5-aminosalicylic acid (5-ASA) compounds.
- Oral corticosteroids (eg, prednisone, budesonide) at a prednisone-equivalent dose of ≤40 mg/day or ≤9 mg/day of budesonide.
- Antibiotics used as the primary treatment of Crohn's disease.

Any participants receiving conventional immunomodulators (ie, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) must have been taking them for ≥12 weeks and must have been on a stable dose for a least 4 weeks before baseline.

5. The following laboratory test results are within the specified limits at screening:

- Hemoglobin ≥8.5 g/dL (≥85 g/L).
- White blood cell (WBC) count ≥3.5 x 10^3/μL (≥3.5 GI/L).
- Neutrophils ≥1.5 x 10^3/μL (≥1.5 GI/L).
- Platelets ≥100 x 10^3/μL (≥100 GI/L).
- Serum creatinine <1.7 mg/dL (≤150 μmol/L).
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels ≤2 times the upper limit of normal for the laboratory conducting the test.
- Direct (conjugated) bilirubin <1.0 mg/dL (<0.01 g/L).

NOTE: A repeat of these screening laboratory tests is allowed during the screening phase. The investigator may consider the participant eligible if the previously abnormal laboratory test result is within the acceptable range on repeat testing in the laboratory.

6. Criterion changed per Amendment 1.

6.1 Meet the following TB screening criteria:

- No history of latent or active TB before screening. An exception is made for participants who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB prior to first administration of study intervention, or have documentation of having completed appropriate treatment for latent TB within 5 years prior to the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation.
- No signs or symptoms suggestive of active TB upon medical history and/or physical examination.

- No recent close contact with a person with active TB. If there has been such contact, the participant will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, will receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study intervention.
- Within 5 weeks before the first administration of study intervention, has a negative QuantiFERON®-TB test result, 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 prior to the first administration of study intervention. If the QuantiFERON-TB test is not approved or is not registered in a country or if the tuberculin skin test is mandated by local health authorities, a negative tuberculin skin test (see Section 10.3, Appendix 3), or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study intervention, is additionally required within 5 weeks prior to the first administration of study intervention.
- Participants who have an indeterminate result should have the test repeated. Participants with persistently indeterminate QuantiFERON-TB test results may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor, recorded in the participant's source documents, and initialed by the investigator.

  NOTE: The QuantiFERON-TB test and/or the tuberculin skin test is/are not required to be performed at screening for participants with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above. Participants with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.
- Has a chest radiograph (at least a posterior-anterior view) or computed tomography of the chest, taken within 6 months before the first administration of study intervention and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

7. A female participant must be:

   - Not of childbearing potential (as defined in Section 10.8, Appendix 8)

   OR

   - If heterosexually active, must be practicing a highly effective method of birth control, consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies, for the duration of their participation in the study and for 15 weeks after the last dose of study intervention, the end of relevant systemic exposure.

     NOTE: If the participant's childbearing potential changes after the start of the study, that participant must begin practicing a highly effective method of birth control as described above.

OR

- Not be heterosexually active and agrees to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.

Examples of highly effective methods of contraception are presented in Section 10.8, Appendix 8.

8. All female participants of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) pregnancy test at screening and a negative urine pregnancy test at baseline and prior to each administration of study intervention.

9. A male participant who is heterosexually active with a woman of childbearing potential and is not surgically sterile must agree to use a double-barrier method of birth control and not donate sperm during the study and for 15 weeks after receiving study intervention.

10. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

11. Sign an informed consent document indicating that he/she understands the purpose of and procedures required for the study and is willing to participate in the study.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Complications of Crohn's disease, such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation that might be anticipated to require surgery, could preclude the use of the CDAI to assess response to therapy, or would possibly confound the ability to assess the effect of treatment with ustekinumab.

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 before baseline (or 8 weeks before baseline for intra-abdominal abscesses) provided there is no anticipated need for any further surgery. Participants with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses identified.

3. Any kind of bowel resection within 6 months or any other intra-abdominal surgery within 3 months before baseline.

4. A draining (ie, functioning) stoma or ostomy.

5. Criterion changed per Amendment 4:

5.1 Received any of the following prescribed medications or therapies within the specified period:

- Use of IV ustekinumab re-induction after the initial weight-tiered-based IV induction dose of ustekinumab.
- Any known history of shortened frequency of SC dose administration (<q8w) for a secondary loss of response where the participant did not, in the opinion of the treating physician, benefit from the dose interval shortening.
- Intravenous corticosteroids as a treatment for Crohn's disease within 3 weeks before baseline.
- 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) within 4 weeks before baseline.
  NOTE: See Inclusion Criterion 4 for restrictions on typical immunomodulator agents (AZA, 6-MP or MTX).
- Any other investigational agent for Crohn's disease (eg other biologics, small molecules or anti-sense RNA such as mongersen), unless at least 3 months or 5 half-lives (whichever is longer) have elapsed since the last dose.
- Treatment with apheresis (eg, Adacolumn apheresis) or total parenteral nutrition as a treatment for Crohn's disease within 3 weeks before baseline.

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

7. Received a Bacille Calmette-Guérin (BCG) vaccination within 12 months before baseline or any other live bacterial or live viral vaccination within 2 weeks before baseline.

8. 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 open, draining, or infected skin wounds or ulcers.

9. Any current signs or symptoms of infection. Established non-serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

10. A history of serious infection (eg, sepsis, pneumonia, or pyelonephritis), including any infection requiring hospitalization or IV antibiotics, for 8 weeks before baseline.

11. Evidence of a herpes zoster infection ≤8 weeks before baseline.

12. A history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening; refer to Inclusion Criterion 6 for information regarding eligibility with a history of latent TB.

13. 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.

14. A current or (lifetime) history of a nontuberculous mycobacterial infection or serious opportunistic infection (eg, Cytomegalovirus colitis, Pneumocystis carinii, aspergillosis).

15. Known to be infected with human immunodeficiency virus, hepatitis B, or hepatitis C.

16. Severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or any signs or symptoms thereof.

17. A transplanted organ, with the exception of a corneal transplant performed >12 weeks before screening.

18. A known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.

19. Any known malignancy or a history of malignancy, with the exception of: basal cell carcinoma; squamous cell carcinoma in situ of the skin; cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that was treated with no evidence of recurrence within 5 years before screening.

20. Previous allergy immunotherapy for prevention of anaphylactic reactions.

21. Unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.

22. Known to have had a substance abuse (drug or alcohol) problem within the 12 months before baseline.

23. Known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients (refer to the Investigator's Brochure for further details).

24. Currently is participating in or is intending to participate in any other study using an investigational agent or procedure during participation in this study.

25. A woman who is pregnant, or breastfeeding, or planning to become pregnant, or is a man who plans to father a child while enrolled in this study or within 15 weeks after the last dose of study intervention.

26. Any condition that, in the opinion of the investigator, would make study participation not in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

27. Criterion added per Amendment 3:
During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection.

- Exception: may be included with a documented negative result for a validated SARS-CoV-2 test
  - obtained at least 2 weeks after conditions (a), (b), or (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

    AND
  - with absence of ALL conditions (a), (b) and (c) above during the period between the negative test result and the baseline study visit.

Notes on COVID-19-related Exclusion:

- If a patient is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form (CRF) under the exclusion criterion of having a condition for which study participation would not be in the patient's interest or could confound study assessments.
- The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations, guidance from authorities, or standards of care.

Precautions:

For those patients who may carry a higher risk for severe COVID-19 illness (eg, patients aged over 65 years), follow the guidance from local health authorities when considering the potential benefits and risks of enrolling patients into the study and during study participation.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he/she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are indicated in Section 10.6, Appendix 6.

5.3. Lifestyle Considerations

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

1. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

2. Must not receive ustekinumab outside of the study or participate in any other clinical study with an investigational agent while in this study. If a participant intends to receive ustekinumab or participate in any other clinical study with an investigational agent, they must terminate study participation and an early termination visit should occur.

3. Must agree to adhere to the restrictions/prohibitions regarding concomitant therapies during the study (see Section 6.5).

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 receiving study intervention for BCG vaccination and for at least 15 weeks for other live vaccines.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent (as allowed by local regulations). In cases where the participant is not randomized into the study, the date seen and age at initial informed consent (as allowed by local regulations) will be used.

If a participant does not meet all inclusion and exclusion criteria as listed in Sections 5.1 and 5.2 (ie, is a screen failure), but at some point is expected to meet the study eligibility criteria, the participant may be rescreened. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

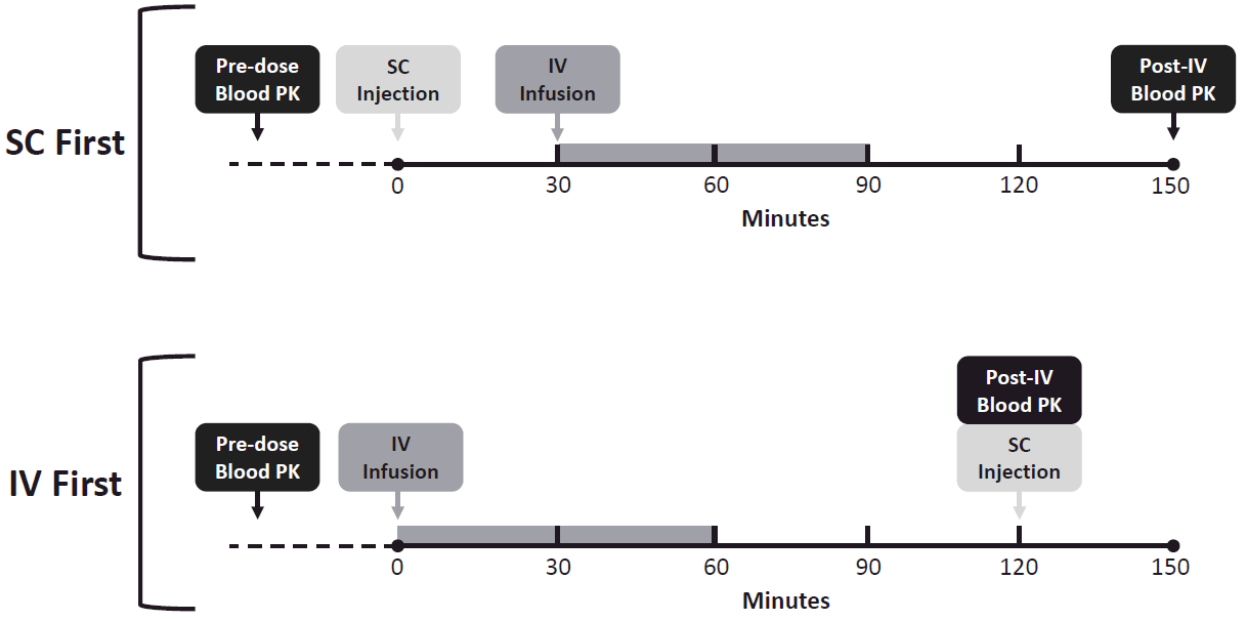
Study intervention will start at baseline (Week 0), approximately 8 weeks (±2 weeks) after the previous dose of per label SC 90 mg ustekinumab maintenance treatment. The date of the previous dose of ustekinumab will be recorded in the case report form (CRF).

To maintain the double-blind, at Week 0 all participants will receive one IV infusion of ustekinumab ~6 mg/kg or placebo **plus** one SC injection of ustekinumab 90 mg or placebo. Either the IV infusion or the SC injection may be administered first at Week 0, based on the standard-of-care practices at the study site, but there must be no concurrent administration of study intervention (ie, IV and SC). The minimum required time windows between administration of IV infusion and SC injection at Week 0 are indicated below and in Figure 2:

- If the SC injection is administered first, the IV infusion must not begin until at least 30 minutes after completion of the SC injection.
- If the IV infusion is administered first, the SC injection must not begin until at least 120 minutes after the start of the IV infusion, or at least 60 minutes after completion of the IV infusion.

The blood sample for trough serum PK must be collected at all study visits prior to the administration of **ANY** study intervention (ie, IV or SC) as well as prior to the administration of standard-of-care therapy at Week 24. The post-IV infusion PK blood sample at Week 0 should be drawn approximately 60 minutes after completion of the IV infusion.

Figure 2: Minimum Required Time Windows Between Administration of Study Intervention (IV or SC) at Week 0



At Week 8 and Week 16, all participants will receive SC maintenance injections of 90 mg ustekinumab. Following study assessments at Week 24, all participants will resume their standard-of-care therapy with either ustekinumab maintenance therapy per label or another treatment modality at the discretion of their physician.

For IV administration, the study intervention will be administered to each participant as an infusion over a period of not less than 1 hour by qualified staff. The infusion should be completed within 8 hours of preparation. Details of each infusion will be recorded in the CRF (including date, start and stop times of the IV infusion, and volume infused).

Subcutaneous injections at Week 0 will be administered by qualified staff at the study site. At Week 8 and Week 16, SC injections should be administered by qualified study site staff during the study visit, if possible. However, in cases where a site visit is not possible, participants who have appropriate experience or have received required training may self-administer SC study intervention at the times instructed by the investigator. The study site staff must ensure that those participants have the appropriate experience or have received the required training to perform self-administration of SC injections. Details of each administration will be recorded in the CRF (including date and time of administration).

Study-site personnel will instruct participants on how to store study intervention for at-home use during Weeks 8 and 16. For each administration of study intervention, the time and date of injection, whether study intervention was self-administered, and if so, whether SC administration was complete (based on the returned syringe[s]) will be recorded in the CRF.

Detailed instructions on the administration of study interventions are provided in the site investigational product procedures manual.

Ustekinumab will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Storage and Preparation

All study intervention must be stored at controlled temperatures ranging from 2°C to 8°C, must not be frozen, and must be protected from light. The solution in the vial or prefilled syringe (PFS) should not be shaken. Prior to administration, the solution should be visually inspected for particulate matter and discoloration, and should not be used if it is discolored, cloudy, or if foreign particulate matter is present.

Study intervention should be dispensed under the supervision of the investigator, a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention in glass vials and PFS will be ready to use. The required volume of study intervention will be prepared using the appropriate vials or PFS. Aseptic procedures must be used during the preparation and administration of the ustekinumab solution for IV infusion.

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

6.2.2. Drug Accountability

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

Study intervention must be handled in strict accordance with the protocol and container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Any study participant who will be self-administering study intervention at home during Week 8 and Week 16 will receive detailed instructions for study intervention storage, disposal of used syringes, and handling of unused study material. Participants will receive a sharps container to dispose of used syringes and will be instructed to return the sharps container and cartons to the study site. Participants will record SC administrations with time and date information in the participant's diary. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

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 intervention accountability purposes.

Study intervention 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 intervention will be supplied only to participants participating in the study. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Following clinical assessments at baseline, all enrolled participants will be randomized in a 1:1 ratio to 1 of 2 intervention groups to receive either IV ustekinumab ~6 mg/kg and SC placebo or IV placebo and SC ustekinumab 90 mg in a blinded manner.

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of the 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Permuted block randomization with stratification variables, including the participant's baseline CDAI score (≤300 or >300) and whether the participant had failed a prior biologic at baseline (yes or no), will be used. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, together with the relevant unique participant details to identify the participant.

Blinding

At Week 0 participants will receive a single IV infusion of study intervention (ustekinumab ~6 mg/kg or placebo) **plus** a single SC injection of study intervention (ustekinumab 90 mg or placebo) in a double-blind, double-dummy manner. During study visits at Week 8 and Week 16, all participants will receive SC maintenance injections of 90 mg ustekinumab.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant. Appropriate sponsor representatives will also have access to the IWRS to break the blind for an individual participant, if needed.

Data that may potentially unblind the intervention assignment (ie, treatment allocation, study intervention preparation/accountability, and administration of study intervention; see details in Sections 6.1, 6.2 and 6.3) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding (at Weeks 16 and 36, see Section 4.2).

Under normal circumstances, the blind should not be broken until the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. 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 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 by the IWRS in the appropriate section of the CRF. The documentation received from the IWRS, indicating the code break, must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

6.4. Study Intervention Compliance

Study intervention will be administered at the study site throughout the study, whenever possible, and study personnel will maintain a log of all study intervention administrations. Study intervention supplies for each participant will be inventoried and accounted for. All ongoing therapies administered at the time of screening must be recorded.

Each administration of study intervention performed will be recorded in the participant's source documents or diary. Study intervention at Week 0 will be administered with the assistance of a staff member at the study site who will be supervising study intervention administration at this visit. Study intervention at Week 8 and Week 16 will be administered at the study visit, whenever possible, with the assistance of a staff member. For any study intervention administration performed by the participant outside of a study site, participants will keep the syringe carton and return the empty carton to the study site with the diary at their next visit. The participant will record the corresponding date and time of the administration in the diary. Study site personnel will utilize participant's diaries to ensure compliance and record at-home study intervention administrations in the eCRF. Additionally, a sharps container to dispose of used syringes will be provided to participants who will administer any study intervention outside of the study site. Participants will be instructed to return the sharps container, the syringe cartons and diaries to the study site at their next visit.

Additional details will be provided in the pharmacy manual/study site investigational product manual provided separately.

6.5. Concomitant Therapy

Concomitant medications will be reviewed at each visit. All concomitant therapies (including vaccines) must be recorded throughout the study, from signing of the informed consent form (ICF) to the last study visit. Recorded information will include a description of the type of the therapy, treatment period, dosing regimen, route of administration, and its indication.

6.5.1. Crohn's Disease-specific Concomitant Medications

During the study, participants are permitted to receive oral 5-ASA compounds, the immunomodulators AZA, 6-MP and MTX, oral corticosteroids, and/or antibiotics for the treatment of Crohn's disease, provided the participant was on a stable dose for a specified period before baseline (as defined in the inclusion criteria, Section 5.1). Participants receiving these medications at baseline should maintain a stable dose throughout the study, except for oral corticosteroids which must be tapered in participants with a CDAI-70 response at Week 8 (see Section 6.5.2).

Enrolled participants should not initiate any of the following concomitant Crohn's disease-specific medical therapies during the study:

- Oral or rectal 5-ASA compounds.
- Immunomodulators (AZA, 6-MP, or MTX).
- Oral, parenteral, or rectal corticosteroids.

- Antibiotics as a treatment of Crohn's disease.
- Total parenteral nutrition as a treatment of Crohn's disease.

If the above medications are initiated or doses/regimens are modified, participants should complete all efficacy visits and the final safety visit in this study. If the above medications are initiated or increased due to medical necessity, in the opinion of the investigator, this does not represent a deviation from the study protocol but may be considered a treatment failure (details will be presented in the statistical analysis plan).

6.5.2. Oral Corticosteroids

Participants will be allowed to enter the study on oral corticosteroids at a prednisone-equivalent dose of ⩽40 mg/day or ⩽9 mg/day of budesonide. For participants receiving corticosteroids and achieving a CDAI-70 response at Week 8 or later, corticosteroid tapering is mandatory. This tapering should follow the recommended schedule (Table 1). Tapering is only to exceed this schedule if warranted by medical necessity (eg, due to corticosteroid-related side effects).

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	
Study participants receiving budesonide should have their daily dose tapered by 3 mg every 3 weeks until 0 mg/day.	

If a participant experiences a worsening in their disease activity while tapering corticosteroids, further dose decreases can be suspended, and/or the participant's oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator. The oral corticosteroid dose, however, may not be increased above the baseline dose unless needed due to medical necessity. For participants whose corticosteroid taper is interrupted on this basis, investigators are encouraged to resume tapering within 4 weeks.

6.5.3. Prohibited Medications

Enrolled participants must not initiate any of the following prohibited medications until the Week 24 visit at which time participants will receive standard-of-care therapy. If prohibited medications are initiated before Week 24, study intervention must be discontinued, and participants must complete early termination assessments and the final safety follow-up visit.

- Immunomodulatory agents other than 6-MP, AZA or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil).
  Note: AZA, 6-MP, and MTX (and corticosteroids) are NOT prohibited medications, so their initiation does NOT necessitate discontinuation of study intervention.

- Immunomodulatory biologic agents (including but not limited to TNF antagonists, vedolizumab, natalizumab, abatacept).
- Experimental or investigational Crohn's disease medications (including but not limited to thalidomide, briakinumab, traficet, AMG 827).

NOTE: Participants must not receive ustekinumab outside of the study or participate in any other clinical study with an investigational agent while in this study. If they intend to receive ustekinumab or participate in any other clinical study with an investigational agent, an early termination visit should occur beforehand. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.6. Dose Modification

Dose/dosage adjustment of study intervention is not permitted within this study.

6.7. Intervention After the End of the Study

Participants will be instructed that study intervention will not be made available to them after they have completed or discontinued the study and that they should return to their primary physician to determine the standard of care at the end of the study period.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention (ie, ustekinumab IV infusion and/or SC injection) must be discontinued if:

- The investigator believes that for safety or tolerability reasons (eg, an adverse event) it is in the best interest of the participant to stop study intervention.
- The participant becomes pregnant, plans a pregnancy within the study period, or plans a pregnancy within 15 weeks after the last study intervention administration; refer to Section 10.8, Appendix 8 for further information.
- The participant is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A participant 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 participant undergoing continued evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB test result (or a positive tuberculin skin test result in countries in which the QuantiFERON-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated before the next administration of study intervention and continued to completion. Participants who have an indeterminate result should have the test repeated. Participants with persistently indeterminate QuantiFERON-TB test results may continue without treatment for latent

TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor's medical monitor, recorded in the participant's source documents, and initialed by the investigator.

  - A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The participant experiences a serious adverse event related to either an injection or infusion. Discontinuation of ustekinumab administration must also be considered for participants who develop a non-serious but severe infusion or injection site reaction (as defined in Section 10.7, Appendix 7).
- The participant is diagnosed with a malignancy, including squamous cell skin cancer. Consideration may be given to allow participants to continue to receive study intervention if they develop 1 to 2 basal cell skin cancers that are adequately treated with no evidence of recurrence or residual disease.
- The participant initiates the following prohibited medications before Week 24:
  - Immunomodulatory agents other than 6-MP, AZA or MTX.
  - Immunomodulatory biologic agents.
  - Experimental or investigational Crohn's disease medications.
- The participant receives ustekinumab outside of the protocol.
- A serious opportunistic infection occurs.
- The participant withdraws consent for administration of study intervention.
- The participant is unable to adhere to the study visit schedule or comply with protocol requirements.
- The participant has Crohn's disease-related surgeries that precludes the ability to further assess efficacy through the CDAI. Surgeries that are thought to represent a lack of efficacy of study intervention 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).

Consideration should also be given to discontinuing treatment in participants who show no evidence of therapeutic benefit 16 weeks after the IV re-induction.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up.
- Withdrawal of consent.
- Death.
- Sponsor decision (eg, receiving ustekinumab outside of the protocol or participating in any other clinical study with an investigational agent).
- Investigator decision (eg, because of an adverse event or lack of efficacy).

Participants who terminate study participation will not be required to return for any follow-up assessments but should complete the safety and efficacy evaluations specified for early withdrawal (see Schedule of Activities) at the time they terminate study participation. Additionally, the safety follow up approximately 20 weeks after the last study intervention administration, which may be conducted at a site visit or by telephone, applies to all participants, including those who discontinued study intervention before Week 24 or who have otherwise terminated study participation (eg, through withdrawal of consent), unless they do not consent to this follow up by study-site staff.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study intervention assigned to a withdrawn participant may not be assigned to another participant. Participants who withdraw will not be replaced. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

If a participant is withdrawn from the study for any reason, the early termination assessments indicated in the Schedule of Activities should be performed as close as possible to the time of study discontinuation. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

7.2.1. Withdrawal From the Use of Research Samples

A participant may withdraw consent for research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the appropriate sponsor representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

A participant may also withdraw consent for use of samples in future research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.6, Appendix 6). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. Refer to Section 7.2 for further details on participant discontinuation/withdrawal from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The eligibility of participants will be assessed during a 5-week screening period, at which written informed consent must be obtained prior to conducting any protocol-specific assessments or procedures. Study assessments will be conducted at baseline (Week 0) and at Weeks 8, 16 and 24, or at early termination. All participants will have a follow-up for evaluation of safety performed at a site visit or by telephone approximately 20 weeks after their last study intervention administration (ie, Week 36 for participants who complete the final study intervention visit at Week 16). The Schedule of Activities summarizes the frequency and timing of safety, efficacy, ileocolonoscopy, PK, and immunogenicity measurements at screening and during the study. The following sections provide additional details on the evaluations to be conducted during the study.

During the screening period, participants will receive training in diary card completion for recording CDAI and information on concomitant medications. For calculation of CDAI at Week 0, the hematocrit value obtained during screening will be used.

Where participants agree for this procedure, a baseline, video ileocolonoscopic evaluation should be performed within 14 days before Week 0 (see Section 8.1.7). An ileocolonoscopy performed ≤3 months before baseline may be used as a measure of secondary LoR (in combination with CDAI score; see Section 5.1, Inclusion Criterion 3), and may also be used as the baseline ileocolonoscopy, provided a video recording of the procedure is available . For these participants, a final endoscopy should be performed at the Week 16 visit.

All study-specific PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions. The PRO instruments will be provided in the local language in accordance with local guidelines.

Study site personnel must remind participants of the need to provide stool samples at the visits indicated in the Schedule of Activities.

All female participants of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline and prior to each administration of study intervention. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or as required by local regulation, to establish the absence of pregnancy at any other time during study participation.

The total blood volume to be collected from each participant will be approximately 180 mL.

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

Sample Collection and Handling

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

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure for ustekinumab.
- EU SmPC/US Package Insert for ustekinumab.
- Pharmacy Manual/Site Investigational Product and Procedures Manual.
- Laboratory Manual.
- IWRS Manual.
- Manual for electronic data capture (eDC).
- Sample ICF.
- Contact information page.
- Participant diary cards.
- Participant study card.
- Paper PRO questionnaires.

8.1. Efficacy Assessments

8.1.1. Overview

The Schedule of Activities summarizes the frequency and timing of efficacy assessments during the study.

Efficacy evaluations will include the following:

- CDAI (the primary tool for assessing disease activity response to ustekinumab).
- PRO-2 (the CDAI components of the total number of liquid or very soft stools and the abdominal pain score).
- IBDQ.

- Inflammatory markers including serum CRP and fCal.
- Fistula assessment.
- Endoscopic assessments of the intestinal mucosa based on the presence and absence of mucosal ulcerations and the SES-CD.

8.1.2. Crohn's Disease Activity Index

The CDAI will be assessed by collecting information on 8 specific Crohn's disease-related variables[4]: 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. The last four variables are scored over 7 days by the participant on a diary card. At each visit, the most recent hematocrit value before the current visit will be used for the calculation of CDAI.

For participants who agree for the ileocolonoscopy procedure, the CDAI should be completed before participants begin their preparation for this procedure, to prevent the ileocolonoscopy preparation from interfering with the CDAI results. If ileocolonoscopies coincide with visit dates or the 7 days before, the CDAI scores should be calculated using the closest previous 7 days not impacted by the ileocolonoscopy and/or its preparation.

The PRO-2 includes the unweighted CDAI components of the total number of liquid or very soft stools and the abdominal pain score.

Note: Fistulas that are only visible during an ileocolonoscopy procedure should not be included in the calculation of the CDAI score, as fistulas seen only on endoscopy cannot be evaluated at all visits (ie, not at Week 8 or Week 24).

A sample CDAI is presented in Section 10.10, Appendix 10. A standard weight table for CDAI is presented in Section 10.11, Appendix 11.

8.1.3. C-reactive Protein

C-reactive protein has been demonstrated to be useful as a marker of inflammation in patients with inflammatory bowel disease. In Crohn's disease, elevated CRP concentrations have been associated with severe clinical activity, elevated sedimentation rate, and active disease as detected by colonoscopy.[24,30]

Blood samples for the measurement of CRP will be collected from all participants at visits indicated in the Schedule of Activities. C-reactive protein will be assayed by the central laboratory using a validated, high sensitivity CRP assay. Results of postbaseline CRP measurements will not be released to the investigators.

8.1.4. Calprotectin

Fecal calprotectin has been demonstrated to be a sensitive and specific marker in identifying intestinal inflammation and response to treatment in patients with inflammatory bowel disease.[7]

Stool samples for determination of fCal concentrations will be collected from all participants at visits indicated in the Schedule of Activities; those stool samples should not be collected on days impacted by ileocolonoscopy preparation.

The assay for fCal concentration will be performed using a validated method by the central laboratory. Additional tests may also be performed on the stool samples for additional markers related to intestinal inflammation and treatment response. Results of post-baseline fCal tests will not be released to the investigators.

8.1.5. Inflammatory Bowel Disease Questionnaire

The IBDQ[14] is a validated, 32-item self-report questionnaire for participants with inflammatory bowel disease to evaluate PROs across 4 dimensions: bowel symptoms (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). Scores range from 32 to 224, with higher scores indicating better outcomes.

The IBDQ should be administered before any other study-specific procedures are performed.

Participants who do not remain in the study at Week 16, due to discontinuation of study intervention and/or termination of study participation, should have their follow-up IBDQ at the early termination visit.

A sample IBDQ is presented in Section 10.12, Appendix 12.

8.1.6. Fistula Assessment

All participants will be assessed for fistulas. For participants with fistulizing disease, fistula closure will be assessed. Enterocutaneous fistulas (eg, perianal and abdominal) will be considered no longer draining (ie, closed) when there is absence of drainage despite gentle compression. Rectovaginal fistulas will be considered closed based on either physical examination or absence of relevant symptoms (eg, passage of rectal material or flatus from the vagina). Only those fistulas that can be assessed during a normal physical examination should be included as part of the fistula assessment.

8.1.7. Video Ileocolonoscopy

At the physician's discretion, where participants agree for this procedure, ileocolonoscopy should be performed at baseline and at Week 16, for exploratory assessment of SES-CD and to determine the presence or absence of mucosal inflammation and ulceration.

All ileocolonoscopies should be performed as close to the applicable study visit as possible. The baseline (Week 0) ileocolonoscopy should be performed within 14 days before or at the Week 0 visit. The Week 16 ileocolonoscopy should be performed within 14 days before or 28 days after

the Week 16 visit. Where ileocolonoscopy impacts the 7 days used for CDAI evaluations, see Section 8.1.2 for details on how those CDAI scores should be calculated.

Participants who do not remain in the study at Week 16 (due to discontinuation of study intervention and/or termination of study participation) should have their follow-up ileocolonoscopy at the early termination visit, where possible.

The ileocolonoscopy procedures should be video-recorded, following the more detailed directions provided in the separate study reference (or ileocolonoscopy) manual. Video endoscopies will be assessed by a central facility that will be blinded to intervention group.

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%.
Stenosis:	Single or multiple and partially or totally occluded.

8.2. Safety Assessments

Safety and tolerability evaluations will be performed as summarized in the Schedule of Activities. In cases of self-administration of SC study intervention, participants are requested to contact their treating physician as soon as possible to consider reporting of an adverse event.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and in Section 10.7, Appendix 7.

Any clinically relevant changes occurring during the study must be recorded in the adverse event section of the CRF.

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 condition is reached.

8.2.1. Physical Examination

Physical examinations will be performed as specified in the Schedule of Activities. Any abnormalities or changes in severity noted during the review of body systems should be documented in the source document.

8.2.2. Vital Signs

Vital signs (temperature, pulse/heart rate, and systolic and diastolic blood pressure) will be obtained immediately before the initial IV infusion, approximately every 30 minutes during the IV infusion, and twice (at approximately 30-minute intervals) after the completion of the IV infusion.

Vital signs will also be obtained before and approximately 30 minutes after completion of each SC injection.

8.2.3. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.5, Appendix 5. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

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. Appropriateness may be discussed with the medical monitor.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, 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.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Anticipated events will be recorded and reported as described in Section 10.4, Appendix 4.

For further details on adverse events and serious adverse events (definitions and classifications; attribution definitions; severity criteria; special reporting situations; procedures) as well as product quality complaints, refer to Section 10.7, Appendix 7.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events 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 participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 20 weeks after the last dose of study intervention (ie, up to Week 36), 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.

Serious Adverse Events

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

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the participant is specifically questioned, and which are noted by participants in their diary.

Unsolicited Adverse Events

Unsolicited adverse events are adverse events for which the participant is not specifically questioned in the participant diary.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.7, Appendix 7.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator’s assessment. The

sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants 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 serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Infusion/Injection Site Reactions and Allergic Reactions

Infusion Reactions

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

Injection Site Reactions

An injection site reaction is any adverse reaction at a study intervention injection site. The injection sites will be evaluated for reactions and any injection site reactions will be recorded as an adverse event.

Allergic Reactions

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

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

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

Participants who receive an incomplete administration of the IV dose, due to any safety observation requiring intervention, should be discontinued from further injections of study intervention.

Participants who experience any systemic reaction following an IV infusion or SC injection of ustekinumab that requires ventilatory support or treatment with epinephrine will not be permitted to receive additional injections.

8.3.7. Infections

Study intervention should not be administered to a participant with a clinically important, active infection. Investigators are required to evaluate participants for any signs or symptoms of infection, and also review participants' diary cards for signs of infection, at scheduled visits.

If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study treatment must be considered. For active varicella-zoster infection or a significant exposure to varicella-zoster infection in a participant without a history of chickenpox, study intervention should be interrupted until the symptoms have resolved and no active infection is present.

Assessments for TB infection will be performed at the visits specified in the Schedule of Activities. Refer to Section 10.3, Appendix 3 for details of tuberculin skin testing.

8.3.8. Malignancies

Any participant who develops a malignancy, including squamous cell skin cancer, will be withdrawn from study intervention. Consideration may be given to allow participants who develop 1 to 2 basal cell skin cancers to continue to receive study intervention if they are adequately treated with no evidence of recurrence or residual disease.

8.3.9. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments or not.

8.4. Treatment of Overdose

Single IV doses of ustekinumab up to approximately 6 mg/kg have been administered in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

8.5. Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the PK of ustekinumab and to detect and characterize anti-ustekinumab antibodies. Serum collected for PK and immunogenicity evaluations may additionally be used to explore safety or efficacy aspects arising during or after the study period. Participant confidentiality will be maintained.

At all visits, PK and immunogenicity blood samples must be drawn **PRIOR** to the administration of **ANY** study intervention (IV or SC), except for the Week 0 post-infusion PK sample which should be drawn approximately 60 minutes after completion of the IV infusion. Pharmacokinetic and immunogenicity blood samples must also be drawn prior to the administration of any standard-of-care therapy at Week 24.

8.5.1. Evaluations

A venous blood sample of sufficient volume will be drawn at each blood sampling time point. At Week 0, a pre-dose PK blood sample must be drawn before **ANY** study intervention (IV or SC) and approximately 60 minutes after completion of the IV infusion. At all other times, blood samples should be collected before administration of study intervention.

With the exception of the post-infusion blood sample at Week 0, which will be for PK evaluation only, each serum sample will be divided into 3 aliquots (1 each for pharmacokinetics, antibodies to study intervention, and a back-up sample).

8.5.2. Analytical Procedures

All PK serum samples collected will be evaluated by a central laboratory for ustekinumab serum concentrations and anti-ustekinumab antibodies to enable interpretation of the data.

Pharmacokinetics

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

Immunogenicity

The detection and characterization of anti-ustekinumab antibodies will be performed using a validated, drug-tolerant assay method by or under the supervision of the sponsor.

8.5.3. Pharmacokinetic Parameters and Evaluations

Serum samples will be used to evaluate various pharmacokinetic parameters, including trough and peak ustekinumab concentrations.

8.6. Genetics

Pharmacogenomics or other genetic measures are not evaluated in this study.

8.7. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.8. Biomarkers

Biomarker assessments will be conducted to examine the biologic response to treatment and to identify biomarkers that are relevant to ustekinumab treatment and/or Crohn's disease. Assessments may include the evaluation of relevant biomarkers in serum, blood, and/or stool samples collected as specified in the Schedule of Activities. Data collected from these samples will be used for exploratory research, which will include the following objectives:

- To understand the molecular effects of ustekinumab.
- To understand the pathogenesis of Crohn's disease.
- To develop new laboratory tests that could be used clinically in Crohn's disease or other conditions.
- Genetic analyses will not be performed on biological samples obtained for this study.

8.8.1. 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.

8.8.2. 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 Crohn's disease.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be conducted 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.

9.1. Statistical Hypothesis

The study hypothesis is that in patients with secondary LoR to SC q8w 90 mg ustekinumab maintenance treatment, a single weight-tiered based IV re-induction dose of 6 mg/kg ustekinumab will result in a higher clinical response rate (defined as a ≥100-point reduction from the baseline CDAI score, or a CDAI score <150) after 16 weeks of treatment, compared with continuous SC q8w 90 mg ustekinumab maintenance treatment.

It is expected that the difference in the proportion of participants who achieve a clinical response after receiving the ~6 mg/kg IV re-induction of ustekinumab compared with participants receiving continuous SC q8w 90 mg ustekinumab maintenance treatment will be at least 20 percentage points. The study is powered based on this difference in the level of response.

9.2. Sample Size Determination

The assumptions that form the basis for sample size and power calculations incorporated into this protocol to support the primary endpoint are based on the dose adjustment data from the IMUNITI Phase 3 study. In IMUNITI, 17 of 29 (59%) participants attained clinical response 16 weeks after LoR in the q12w adjusted to q8w group, while 11 of 28 (39%) participants attained clinical response 16 weeks after LoR in the sham dose adjustment group (ie. continually remaining on SC q8w dosing). The hypothesis for the sample size determination is that the IV ustekinumab group in this study will perform similarly to, if not better than, the q12w adjusted to q8w group in the IMUNITI study, given that the participants in this group will receive a higher dose of ustekinumab than those in the IMUNITI study, who received an adjustment from q12w to q8w.

Assuming a 60% clinical response rate at Week 16 in the ustekinumab IV re-induction group and 40% in the continuous SC q8w 90mg group, 100 participants per intervention group will yield an overall power above 80%, at a significance level of 0.05 (2-sided, Mantel-Haenszel test).

Table 2 provides the power for detecting a treatment difference between the IV ustekinumab group and the continuous SC q8w 90mg ustekinumab group (for 100 participants per group) under varying assumptions for the clinical response rates.

Table 2: Power to Detect a Treatment Effect Based on Different Proportions of Participants Achieving Clinical Response at Week 16 (Each Group)

Clinical response at Week 16 (%)		
SC q8w 90 mg (n=100)	IV re-induction (n=100)	Power
40%	55%	59%
-	**60%**	**83%**
-	65%	95%

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Table 3: Populations for Analysis

Population	Description
Intent-to-treat population (ITT)	All participants randomized to 1 of the 2 intervention groups.
Treated population (safety, PK)	All participants in the ITT population who receive at least one dose of study intervention.

9.4. Statistical Analysis

9.4.1. Efficacy Analysis

Efficacy analyses will be based on an intent-to-treat principle; the efficacy data for each participant will be analyzed according to the assigned treatment regardless of the actual treatment received.

For the primary endpoint, the proportion of participants in clinical response at Week 16 will be compared between the IV group and the continuous SC q8w group using a 2-sided

Cochran-Mantel-Haenszel-chi-square test, stratified by baseline CDAI score (≤300 or >300) and prior biologic failure status at baseline (yes or no) at a significance level of 0.05.

Participants with missing data, defined as those who terminate the study before the designated visit or participants 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 participants with missing data.

Treatment failure rules will override the response status (eg, clinical response, clinical remission, and mucosal healing). Participants 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 Crohn's disease-related surgery due to lack of efficacy; OR
- Discontinued study intervention due to an adverse event of worsening Crohn's disease 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.

The study endpoints (as listed in Section 3) will be compared between the IV group and the continuous SC q8w group. Analyses suitable for categorical data (eg, chi-square test or Cochran-Mantel-Haenszel chi-square test, as appropriate) will be used to compare the proportion of participants achieving selected endpoints (eg, clinical remission) between the IV group and the continuous SC q8w group. In the case of rare events, Fisher's exact test will be used for treatment comparisons. Continuous variables will be compared between the IV group and the continuous SC q8w group using an analysis of variance/covariance.

9.4.2. Safety Analysis

Safety will be assessed through Week 24 by evaluating adverse events, clinical laboratory changes, physical examination, and vital signs. Adverse events will also be evaluated at a safety follow up performed at a site visit or by telephone approximately 20 weeks after the last study intervention administration (ie, Week 36 for participants who complete the final study intervention visit at Week 16). All participants who receive at least 1 administration of study intervention will be included in the safety analyses. Participants will be analyzed according to the actual treatment received.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Intervention-emergent adverse events are adverse events with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at

least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious adverse event.

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

- Adverse events.
- Serious adverse events.
- Reasonably related adverse events (very likely, probable, possible, as assessed by the investigator).
- Discontinuation of study intervention due to adverse event(s).
- Adverse events of clinical interest:
  - Injection site reactions.
  - Infusion-related adverse events (during or within 1 hour of the IV infusion).
  - Infections and serious infections.
  - Malignancies.

Clinical Laboratory Tests

The following clinical laboratory measures will be used to assess the safety of participants:

- 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.

9.4.3. Other Analyses

Pharmacokinetic Analyses

Descriptive statistics of serum ustekinumab concentrations will be calculated at each sampling time point. Serum ustekinumab concentrations over time will be summarized separately for the ustekinumab IV group and the continuous maintenance group.

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

Immunogenicity Analyses

The incidence of anti-ustekinumab antibodies will be summarized for all participants who have at least one sample obtained after their first dose of ustekinumab for detection of antibodies to ustekinumab.

Pharmacokinetic/Pharmacodynamic Analyses

Analyses of the PK, immunogenicity, and pharmacodynamics of study intervention will include:

- Characterization of the PK and immunogenicity of ustekinumab in participants.
- Assessment of the relationship between systemic ustekinumab exposure and:
  - clinical outcomes, including CDAI measures.
  - changes in CRP and fCal.
  - endoscopic outcomes.
- Correlation of the PK data in this study with the PK data of the UNITI trials.

9.5. Interim Analysis

An interim analysis will be performed in the study after 40 randomized participants have completed the efficacy assessment at Week 16. The purpose of this interim analysis will be to ensure the study is not futile and to assess sample size.

Details of the interim analyses and futility criteria will be presented in a separate statistical analysis plan. The sites and the study team will remain blinded, the only unblinded person will be an independent statistician who is not part of the study team.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definition of Terms

Abbreviations

ALT	Alanine aminotransferase
5-ASA	5-aminosalicylic acid
AST	Aspartate aminotransferase
AZA	Azathioprine
BCG	Bacille Calmette-Guérin
CDAI	Crohn's Disease Activity Index
C_{max}	Maximum serum concentration
CRF	Case report form
CRP	C-reactive protein
eDC	Electronic data capture
EU	European Union
fCal	Fecal calprotectin
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
β-hCG	β-human chorionic gonadotropin
HRT	Hormonal replacement therapy
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IgG1k	Human immunoglobulin G1 kappa
IL	Interleukin
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
LoR	Loss of response
MedDRA	Medical Dictionary for Regulatory Activities
6-MP	6-mercaptopurine
MTX	Methotrexate
PFS	Prefilled syringe(s)
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
PQC	Product quality complaint
PRO	Patient-reported outcome
qXw	Every X weeks (where X=4, 8 or 12)
SC	Subcutaneous
SES-CD	Simple endoscopic score for Crohn's disease
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TNF	Tumor necrosis factor
TU	Tuberculin units
US	United States
WBC	White blood cell

Definition of Terms

Study intervention	Ustekinumab administered as an ~6 mg/kg IV infusion or a 90 mg SC injection.

10.2. Appendix 2: Definition of Ustekinumab Initial Response and Current Therapy

Eligible participants must:

- Be on SC 90 mg ustekinumab q8w maintenance dose regimen and have received at least 2 doses of per label SC 90 mg ustekinumab treatment 8 weeks apart.

  AND

- Have demonstrated previous clinical remission **OR** previous clinical response within 20 weeks after receiving ustekinumab induction therapy given as a single IV dose of ~6 mg/kg followed by 90 mg SC injection at Week 8, based on either the clinical remission or clinical response criteria specified below.
- Note: Participants may have initially received SC 90 mg q12w maintenance and subsequently escalated to SC 90 mg ustekinumab q8w maintenance, but must have demonstrated previous clinical remission **OR** previous clinical response within 20 weeks after initiation of ustekinumab induction therapy, as above.

Evidence of previous ustekinumab doses and measures of initial response or remission should be documented by medical records, letter provided by a referring physician, patient diaries, reliable patient history with subsequent documentation or by other 'reason for referral' documents (eg, insurance authorization forms), if available, and recorded in the eCRF. If such documentation is not available, investigators can confirm the ustekinumab doses and initial response/remission in the eCRF according to their best knowledge and clinical judgement.

Evidence of Clinical Remission to Ustekinumab Treatment:

Any of the following available criteria should be documented and noted in the eCRF:

- Documented CDAI <150 (if score is available).
- Documented Harvey Bradshaw Index of <5 (if score is available).
- No more than mild abdominal pain with 3 or less soft or loose stools per day, on average, for at least a 1-week period.
- No abdominal pain, with an average of 5 or less soft or loose stools per day, for at least a 1-week period.

Evidence of Clinical Response to Ustekinumab Treatment:

Any of the following available criteria should be documented and noted in the eCRF:

PROs:

- Reduction of 3 points in total HBI score or reduction of at least 70 points in overall CDAI score, if documentation of these scores are available. Where documented in a patient's medical records, the scores for the individual components of these indexes should also be recorded.
- Meaningful reduction of stool frequency.
- Reduction of rectal bleeding.

- Meaningful reduction of daily abdominal pain/discomfort.
- Resolution of one or more extra-intestinal manifestations (eg arthralgia, pyoderma gangrenosum, etc).

Objective Measures of Disease Activity:

- Resolution of drainage from prior draining fistula(s).
- Improvement in ileocolonoscopy (resolution of all ulcerations in at least one ileocolonic segment).
- Normalization of CRP (<3 mg/L) or fCal (<250 mg/kg) in participants with elevated CRP/fCal at initiation of ustekinumab.
- Reduction in steroid dose (or elimination of corticosteroids) after initiation of ustekinumab.

Acceptable documentation

Evidence of previous ustekinumab doses and measures of initial response or remission should be documented by medical records, letter provided by a referring physician, patient diaries, reliable patient history with subsequent documentation or by other 'reason for referral' documents (eg, insurance authorization forms), if available. If such documentation is not available, investigators can confirm the ustekinumab doses and initial response/remission in the eCRF according to their best knowledge and clinical judgement.

10.3. Appendix 3: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised participants, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the participants may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines for immunocompromised participants should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised participants exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines for immunocompromised participants should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised participants exist, US guidelines must be followed.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). Tuberculosis, a comprehensive international approach. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.4. Appendix 4: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

Adverse Events Associated with the Study Population

- Adverse events related to symptoms of Crohn's disease.
- Adverse events related to worsening or progression of Crohn's disease.

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under 'All Adverse Events' in Section 8.3.1. Any anticipated event that meets the serious adverse event criteria will be reported to the sponsor as described under 'Serious Adverse Events' in Section 8.3.1. These anticipated events are exempt from expedited reporting as individual single cases to health authorities; however, if based on an aggregate review, it is determined that an anticipated event is possibly related to study intervention, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee

An Anticipated Event Review Committee will be established to perform reviews of pre-specified anticipated events at an aggregate level. The Anticipated Event Review Committee is a safety committee within the sponsor's organization that is independent of the sponsor's study team and will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

10.5. Appendix 5: Clinical Laboratory Tests

The following tests will be performed by a central laboratory, unless otherwise specified or approved by the medical monitor:

- Follicle stimulating hormone (for assessment of postmenopausal state, where applicable).[a]
- Stool sample tests for enteric pathogens.[a]
- Stool fecal calprotectin.
- Serum C-reactive protein.
- Serum pregnancy testing for women of childbearing potential.
- Serology for HIV antibody, HBsAg, anti-HBs, anti-HBc, hepatitis C virus antibody.[a]

[a] For some tests related to screening criteria, existing local or central laboratory results are acceptable to satisfy study requirements provided they were performed in the required time windows. Appropriateness of such tests may be discussed with the medical monitor.

- Hematology:
  - hemoglobin
  - hematocrit (to enable CDAI evaluations)
  - WBC count with differential
  - platelet count

- Serum Chemistry:
  - sodium
  - potassium
  - chloride
  - blood urea nitrogen/urea
  - creatinine
  - aspartate aminotransferase (AST)
  - alanine aminotransferase (ALT)
  - total and direct bilirubin
  - alkaline phosphatase
  - calcium
  - phosphate
  - albumin
  - total protein

Hematology and clinical chemistry tests should be repeated at Week 0 if the screening tests were done >2 weeks previously.

The following tests will be performed by a local laboratory, unless otherwise specified or approved by the medical monitor:

- Urine pregnancy testing for women of childbearing potential.
- If required, SARS-CoV-2 (COVID-19) test may be performed at a local lab (per Exclusion Criterion 27).

10.6. Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

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, 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 participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

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 participants, 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) involve 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 CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

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.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention 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, participant 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 participant:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

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 participants).
- Investigator's Brochure (or equivalent information) and amendments/addenda.
- Sponsor-approved participant recruiting materials.
- Information on compensation for study-related injuries or payment to participants 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 participants.
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct).
- Revision(s) to ICF and any other written materials to be provided to participants.
- If applicable, new or revised participant recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- New edition(s) of the Investigator's Brochure and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention.

- New information that may adversely affect the safety of the participants or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants.
- Report of deaths of participants 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 participants, 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)

FINANCIAL DISCLOSURE

Where appropriate, investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant 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 participant 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 participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants 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 participant will receive. Finally, they will be told that the investigator will

maintain a participant 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 participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The participant 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 participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF, will be assigned a new participant number, and then restart a new screening phase.

DATA PROTECTION

The collection and processing of personal data from participants 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 participants confidential.

The informed consent obtained from the participant 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 participant 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.

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

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ustekinumab, to understand Crohn's disease, to understand differential intervention responders, and to develop tests/assays related to ustekinumab and Crohn's disease. 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. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1).

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding ustekinumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence, to 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 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 for the study. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant 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 (ICMJE) 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. If 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 18 months after the study end date, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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.

DATA QUALITY ASSURANCE

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 from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

The sponsor will review 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.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. 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 the 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 participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements 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.

SOURCE DOCUMENTS

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: participant 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; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention 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 following data will be recorded directly into the CRF and will be considered source data:

- Investigator-completed scales and assessments.
- PROs.

The minimum source documentation requirements for the inclusion and exclusion criteria that specify a need for documented medical history (see Sections 5.1 and 5.2) are as follows:

- Referral letter from treating physician.
- 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 participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource 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 eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

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 as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). 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.

Central monitoring will take place for data identified by the sponsor as requiring central review.

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. Participant 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/she has been contacted by a regulatory agency concerning an upcoming inspection.

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 participant, 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.

STUDY AND SITE CLOSURE

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 participants by the investigator.
- Discontinuation of further study intervention development.

10.7. Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to 'All Adverse Events' under Section 8.3.1 for time of last adverse event recording).

Serious Adverse Event

A serious adverse event 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 (ie, participant was at risk of death at the time of the event - 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is at least possible (ie, possible, probable, or very likely) based on the definitions listed below.

ATTRIBUTION DEFINITIONS

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

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 participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention.
- Suspected abuse/misuse of a sponsor study intervention.
- Accidental or occupational exposure to a sponsor study intervention.
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention.
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention.
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product; eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors).
- Exposure to a sponsor study intervention from breastfeeding.

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

PROCEDURES

All Adverse Events

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

For all studies with an outpatient phase, including open-label studies, the participant must 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 participant is participating in a clinical study.
- Investigator's name and 24-hour contact telephone number.
- Local sponsor's name and 24-hour contact telephone number (for medical staff only).
- Site number.
- Participant number.
- Any other information that is required to do an emergency breaking of the blind.

Serious Adverse Events

The cause of death of a participant in a study within 90 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant'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 intervention or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant 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 a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (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 CRF) Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

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 in the Contact Information page(s), which will be provided as a separate document.

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 participants, 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.

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 ‘Serious Adverse Events’ under Section 8.3.1). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

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

10.8. Appendix 8: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.3.5.

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **Premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **Postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **Permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

NOTE: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Examples of Contraceptives

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Examples of highly effective contraceptives (ie, failure rate ≤1% per year when used consistently and correctly, which may differ from typical use failure rates) allowed during the study include:

USER INDEPENDENT:
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[a]
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Vasectomized partner *(considered a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT:
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[a] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[a] – oral – injectable
• Sexual abstinence *(considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

a. Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.

Examples of contraceptives that are not considered to be highly effective (ie, failure rate >1% per year) and that are not allowed during the study include:

• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[a]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[a]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a. Male condom and female condom should not be used together (due to risk of failure with friction)

Pregnancy During the Study

A female participant who becomes pregnant during the study must discontinue further study intervention. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Because the effect of the study intervention on sperm is unknown, pregnancies in partners of male participants included in the study will be reported. A male study participant is not required to discontinue study intervention if their partner becomes pregnant during the study.

Pregnancy Testing

A woman of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at all dosing visits prior to administration of study intervention. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

10.9. Appendix 9: Protocol Amendment History

This is the fourth global amendment. The summary of changes table for the current amendment is located directly before the Table of Contents (TOC). The summary of changes tables for the previous amendments are presented below:

Amendment 3, 19 May 2020

Overall Rationale for the Amendment: To allow subcutaneous injections of study intervention at Week 8 and Week 16 to be self-administered outside a study site, in cases where a site visit is not possible.

Section Number and Name	Description of Changes and Brief Rationale
1.1 Synopsis; 1,3 Schedule of Activities; 6.1 Study Intervention; 6.2.2 Drug Accountability; 6.4 Study Intervention Compliance;	**Description of Change:** Added text to allow subcutaneous injections of study intervention at Week 8 and Week 16 to be self-administered outside a study site in exceptional cases, where a study site visit is not possible, provided those participants have the appropriate experience or have received the required training to perform self-administration of SC injections and have received instructions for storage and handling of study materials.
	Rationale: To provide flexibility of dose administration in exceptional cases where a study site visit is not possible.
5.2. Exclusion Criteria	**Description of Change:** Added exclusion criterion 27, to document exclusion of patients with confirmed or suspected SARS-CoV-2 infection or who have had close contact with a person with confirmed or suspected SARS-CoV-2 infection within 6 weeks before baseline and to provide COVID-19-related guidance on study participation and exclusion.
	Rationale: To exclude patients with confirmed or potential SARS-CoV-2 infection.
8.2 Safety Assessments	**Description of Change:** Added instructions on adverse event reporting for participants who self-administer SC study intervention.
	Rationale: To provide safety reporting guidance outside the study site.
Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	**Description of Change:** Clarified the special reporting situation 'Medication error' to also include intercepted and potential medication errors for a Johnson & Johnson medicinal product.
	Rationale: To be consistent with safety reporting requirements.
Investigator Agreement Page	**Description of Change:** Changed the name of the Sponsor's Responsible Medical Officer.
	Rationale: To reflect the new assignment of the responsible physician for this study.

Amendment 2, 8 April 2020

Overall Rationale for the Amendment: To allow for self-administration of subcutaneous study intervention at Weeks 8 and 16 outside a study site (eg, at home), in cases where a study site visit is not possible under restrictions and limitations during the COVID-19 pandemic. Guidance on other aspects of study conduct during the COVID-19 pandemic is also included.

Section Number and Name	Description of Changes and Brief Rationale
Added 10.13. Appendix 13 - Guidance on Study Conduct During the COVID-19 Pandemic	**Description of Change:** Added appendix as guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.
	Rationale: To provide guidance on study conduct and assessments during the COVID-19 pandemic.

Amendment 1, 19 July 2019

Overall Rationale for the Amendment: To include information regarding the planned primary endpoint database lock at Week 16 and the final database lock. Other clarifications and changes were made to address investigator and site questions surrounding operational elements of the study.

Section Number and Name	Description of Changes and Brief Rationale
4.2 Scientific Rationale for Study Design	**Description of Change:** Added information regarding the planned primary endpoint database lock at Week 16 (when all participants have completed Week 16 or have terminated study participation prior to Week 16) and the final database lock (when all participants have completed Week 36 or have terminated study participation prior to Week 36).
	Rationale: Clarify the planned database locks, the first for periodic summarization of the primary endpoint and selected data at Week 16 and the second for the final analysis.
1.3 Schedule of Activities; 5.1 Inclusion Criteria	**Description of Change:** Increased the time window during which a prior radiograph taken within normal clinical practice may be used for tuberculosis and infection screening from 3 months to 6 months before Week 0.
	Rationale: Eligible patients would have been on ustekinumab therapy for at least 4 months at screening. The initial 3-month window before Week 0 within which a prior radiograph taken within normal clinical practice may be used for screening was not reflective of the study design; all patients eligible for the study will have received ustekinumab treatment for at least 16 weeks at study baseline and, as such, all eligible patients would require an additional study-specific radiograph prior to enrollment. To reflect local standard-of-care for tuberculosis screening of patients on ustekinumab therapy and potentially reduce radiation exposure, this window was increased to 6 months before Week 0.
5.1 Inclusion Criteria (Inclusion Criterion 6)	**Description of Change:** Changed the window for a negative TB test result before the first study intervention from 8 to 5 weeks and added computed tomography of the chest as an alternative to a chest radiograph.
	Rationale: To align with the 5-week screening period and allow an alternative method of TB screening, according to standard-of-care practices at study sites.
1.3 Schedule of Activities.	**Description of Change:** Addressed the following corrections in the Schedule of Activities for consistency with existing protocol text: • Stool sample for fecal calprotectin added at screening. • Preplanned surgery/procedures removed after baseline. • Clarified measurement of vital signs at time of SC injections. • Moved collection of height from baseline to screening. • Removed collection of weight from screening measures (collected at baseline) • Clarified collection of IBDQ at the early termination visit for patients who discontinued before Week 16.
	Rationale: To clarify the Schedule of Activities, to align with protocol text and address questions from investigators.
1.1 Synopsis; 3. Objectives and Endpoints	**Description of Change:** Removed vital signs from listed endpoints.
	Rationale: Vital signs will be collected and reported as safety evaluations or adverse events, but changes in vital signs will not be assessed as study endpoints.

Section Number and Name	Description of Changes and Brief Rationale
1.1 Synopsis; 1.2 Schema; 1.3 Schedule of Activities (footnote b); 4.1. Overall Design; 7.2 Participant Discontinuation/Withdrawal From the Study; 8. Study Assessments and Procedures;	**Description of Change:** Clarified timing of safety follow up as 20 weeks after a participant's last study intervention administration (ie, Week 36 for participants who complete the final study intervention visit at Week 16).
	Rationale: Allow early follow-up for participants who discontinue before Week 16.
1.3 Schedule of Activities; 8.5 Pharmacokinetic and Immunogenicity	**Description of Change:** Clarified collection of pharmacokinetic and immunogenicity blood samples in relation to study intervention.
	Rationale: Clarification of timing of blood sampling.
1.1 Synopsis; 4.1. Overall Design; 5.1 Inclusion Criteria	**Description of Change:** Clarified definition of secondary loss of response based on endoscopy as within 3 months before or at baseline and removed less specific wording that this is to be during the current disease flare.
	Rationale: To provide more specific definition of secondary loss of response.
1.1 Synopsis; 6.1. Study Interventions Administered	**Description of Change:** Added clarification that either the IV infusion or SC injection may be administered first at Week 0 and provided guidance on minimum time windows between study interventions at Week 0.
	Rationale: Clarification of initial study intervention.
4.4 End of Study Definition	**Description of Change:** Corrected the definition for completion of the primary efficacy period (from Week 24 to Week 16).
	Rationale: Correction of primary efficacy period.
1.3 Schedule of Activities; 8.1.5 Inflammatory Bowel Disease Questionnaire	**Description of Change:** Indicated that participants who do not remain in the study until Week 16 or do not perform the IBDQ at Week 16 should complete the IBDQ at the early termination visit.
	Rationale: Clarification of early termination assessment of IBDQ.
8.8 Biomarkers	**Description of Change:** Added information on serum/whole-blood-based biomarkers.
	Rationale: Additional details and clarification of biomarker assessments.
10.11 Appendix 11: CDAI Standard Weight Table	**Description of Change:** Added a standard weight table for CDAI.
	Rationale: Provided additional information for CDAI determination.
Throughout the protocol	**Description of Change:** Minor grammatical/spelling changes and clarifications made.
	Rationale: Minor changes only, therefore are not summarized.

10.10. Appendix 10: Sample 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 =	_____ * (add or subtract by sign, round to 3 decimal places)	x 1 =	_____

* 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)

10.11. Appendix 11: CDAI Standard Weight Table

Actual Height (cm)	Standard Weight (kg)	
	Men	Women
137.2 to 138.3	54.4	48.5
138.4 to 139.6	54.9	49.0
139.7 to 140.9	55.3	49.4
141.0 to 142.1	55.8	49.9
142.2 to 143.4	56.2	50.3
143.5 to 144.7	56.7	50.8
144.8 to 146.0	57.1	51.2
146.1 to 147.2	57.6	51.7
147.3 to 148.5	58.0	52.2
148.6 to 149.8	58.5	52.6
149.9 to 151.0	59.0	53.1
151.1 to 152.3	59.4	53.6
152.4 to 153.6	59.9	54.2
153.7 to 154.8	60.3	54.8
154.9 to 156.1	60.8	55.3
156.2 to 157.4	61.2	56.0
157.5 to 158.7	61.7	56.7
158.8 to 159.9	62.1	57.4
160.0 to 161.2	62.6	58.0
161.3 to 162.5	63.0	58.7
162.6 to 163.7	63.5	59.4
163.8 to 165.0	64.1	60.1
165.1 to 166.3	64.6	60.8
166.4 to 167.5	65.2	61.4
167.6 to 168.8	65.8	62.1
168.9 to 170.1	66.4	62.8
170.2 to 171.4	67.1	63.5
171.5 to 172.6	67.8	64.2
172.7 to 173.9	68.5	64.9
174.0 to 175.2	69.2	65.5
175.3 to 176.4	69.8	66.2
176.5 to 177.7	70.5	66.9
177.8 to 179.0	71.2	67.6
179.1 to 180.2	71.9	68.3
180.3 to 181.5	72.6	68.9
181.6 to 182.8	73.4	69.9
182.9 to 184.1	74.1	70.3
184.2 to 185.3	75.0	71.0
185.4 to 186.6	75.7	71.7
186.7 to 187.9	76.6	72.3
188.0 to 189.1	77.5	73.0
189.2 to 190.4	78.4	73.7
190.5 to 191.7	79.1	74.4
191.8 to 192.9	80.2	75.1
193.0 to 194.2	81.2	75.7
194.3 to 195.5	82.1	76.4

Actual Height (cm)	Standard Weight (kg)	
	Men	Women
195.6 to 196.8	83.0	77.1
196.9 to 198.0	83.9	77.8
198.1 to 199.3	84.8	78.5
199.4 to 200.6	85.7	79.1
200.7 to 201.8	86.6	79.8
201.9 to 203.1	87.5	Not applicable
203.2 to 204.4	88.5	Not applicable
204.5 to 205.6	89.4	Not applicable
205.7 to 206.9	90.3	Not applicable
207.0 to 208.2	91.2	Not applicable
208.3 to 209.5	92.1	Not applicable
209.6 to 210.7	93.0	Not applicable
210.8	93.9	Not applicable

10.12. Appendix 12: Sample Inflammatory Bowel Disease Questionnaire

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 2 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 2 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

10.13. Appendix 13: Guidance on Study Conduct during the COVID-19 Pandemic

BACKGROUND

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

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely, virtually, or will be delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study and any changes will be communicated to the sites and health authorities according to local guidance.

If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer or designee to discuss plans for study intervention and follow-up.

GUIDANCE SPECIFIC TO THIS PROTOCOL

Study Population

Exclusion Criteria (Protocol Section 5.2)

A potential participant with the following features will be excluded from participating in the study.

27. Criterion added per Amendment 2:
    During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection.

    - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test
        - obtained at least 2 weeks after conditions (a), (b), or (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

          AND
        - with absence of ALL conditions (a), (b) and (c) above during the period between the negative test result and the baseline study visit.

Notes on COVID-related Exclusion

- If a patient is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form (CRF) under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.
- The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations, guidance from authorities, or standards of care.

Precautions

For those patients who may carry a higher risk for severe COVID-19 illness (eg, patients aged over 65 years), follow the guidance from local health authorities when considering the potential benefits and risks of enrolling patients into the study and during study participation.

Study Interventions and Assessments

Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak; therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures.

Administration of Study Intervention

In cases where a site visit is not possible under restrictions and limitations due to the COVID-19 pandemic, participants may self-administer subcutaneous (SC) injections of study intervention outside a study site (eg, at home) at Weeks 8 and 16. Those participants will receive instructions on compliance, storage, disposal of used syringes, handling of unused study material, and adverse event reporting. The specific protocol changes are documented below:

Study Interventions Administered (Protocol Section 6.1)

Subcutaneous injections at Week 0 will be administered by qualified staff at the study site. At Weeks 8 and 16, SC injections should be administered by qualified study site staff during the study visit, if possible. However, in cases where a site visit is not possible, participants who have adequate experience or have been trained how to self-inject may self-administer SC study intervention (in compliance with the SmPC or local label) at the times instructed by the investigator.

Study-site personnel will instruct participants on how to store study intervention for at-home use. For each administration of study intervention, the time and date of injection, whether study intervention was self-administered, and if so, whether SC administration was complete (based on the returned syringe[s]) will be recorded in the CRF.

Drug Accountability and Compliance (Protocol Sections 6.2.2 and 6.4)

Study intervention at Week 0 will be administered with the assistance of a staff member at the study site who will be supervising study intervention administration at this visit. Study intervention at Week 8 and Week 16 will be administered at the study visit, whenever possible, with the assistance of a staff member. For any study intervention administration performed by the participant outside of a study site, participants will receive a sharps container to dispose of used syringes and will be instructed to return the sharps container and cartons to the study site with the diary at their next visit.

Participants will record the time and date of study intervention administrations in the diary. Study site personnel will utilize participant's diaries to ensure compliance and record at-home study intervention administrations in the eCRF.

Any participant who will be self-administering study intervention at home at Weeks 8 and 16 will receive detailed instructions on storage of study intervention, disposal of used syringes, and handling of unused study material.

Notes on Shipment of Study Intervention to Participants

If it is necessary to ship the study intervention directly to study participants, shipment by the study site itself is preferred under this exception due to the COVID-19 pandemic. Shipment should be made in a manner that allows tracking of both transport and delivery. The participant should acknowledge receipt of the shipment to the site (eg, by returning a dated and signed receipt form).

In case adequate shipment by the study site is not possible (for example, owing to capacity limitations, logistics, or special transport conditions for the study intervention), direct transport by the sponsor may be accepted in justified exceptional cases, provided that the sponsor appoints a suitably qualified service provider as trustee. The sponsor must contractually oblige this service provider to maintain the pseudonymization and, if necessary, blinding of study participants to the sponsor using appropriate measures. Both the transport and handover conditions for study intervention should be part of the contractual arrangements, so that pharmaceutical drug safety of study intervention as well as protection of the privacy and personal data of participants are adequately safeguarded. The study intervention must be delivered directly to the participant or a person authorized by the participant, and must not be given to neighbors or deposited at a storage location. Written confirmation of dose and dose regimens by the investigator should also be obtained prior to shipment.

The personnel of the service provider in charge of the transport should be trained and instructed accordingly. As personal data are transferred to the service provider, this requires a contract of assignment with the sponsor or legal representative.

For direct shipment of study intervention to participants, written instructions on storage and return of used and unused study intervention should be provided to participants. When shipped by study sites, the receipt, consumption and return of study intervention must be documented in a form that allows the study site to meet its documentation requirements (ie, drug accountability), as defined in ICH GCP 4.6.3.

Study Assessments and Analyses

Safety Assessments (Protocol Section 8.2)

In cases of self-administration of SC study intervention at home, participants are requested to contact their treating physician as soon as possible to consider reporting of an adverse event.

Clinical laboratory safety monitoring may be performed at a certified local laboratory identified by the study site rather than at the central laboratory; for selected measures (eg, urine pregnancy), home testing may be employed.

Missed Assessments

Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix “COVID-19-related” in the CRF.

Other relevant study data elements impacted by the COVID-19 pandemic should also be documented/labeled as "COVID-19-related" in CRFs and/or other study systems, as directed by sponsor guidance; these may include missed/delayed/modified study visits/assessments/dosing, and instances where temporary measures such as those above are implemented.

Where applicable, other study procedures may be conducted at an appropriate facility identified by the study site.

Study Analyses

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 the statistical analysis plan(s).

11. REFERENCES

1. Adalimumab SmPC.

2. Adedokun OJ, Zhenhua X, Gasink C, Jacobstein D, Szapary P, Johanns J, Gao L-L, Davis H, Hanuauer S, Fegan BG, Ghosh S Sandborn WJ. Pharmacokinetics and Exposure-Response Relationships of Ustekinumab in Patients with Crohn's Disease. Gastroenterology. 2018; https://doi.org/10.1053/j.gastro.2018.01.043.

3. Amiot A, Serrero M, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, Buisson A, Stefanescu C, Trang-Poisson C, Altwegg R, Marteau P, Vaysse T, Bourrier A, Nancey S, Laharie D, Allez M, Savoye G, Moreau J, Vuitton L, Viennot S, Aubourg A, Pelletier A-L, Bouguen G, Abitbol V, Gagniere C, Bouhnik Y. Alimentary Pharmacology and Therapeutics. 2017; 46:310-321.

4. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70(3):439-444.

5. Certolizumab US PI.

6. Claire, P, Severine, B, Nicolas, D, Nicolas D, Maria N, Pierre D, Julien B, Romain G, Medina B, Myriam L, Benjamin P. Trough levels and antibodies to ustekinumab are not correlated to response to ustekinumab treatment in Crohn's disease patients. ECCO 2017 #P360.

7. Costa F, Mumolo MG, Ceccarelli L, et al. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. Gut. 2005; 54:364-368.

8. D'Haens GR, Panaccione R, Higgins P, Vermeire S, Gassull M, Chowers Y, Hanauer S, Herfarth H, Hommes D, Kamm M, Lofberg, R, Quary A, Sands B, Sood A, Watermayer G, Lashner B, Lemann M, Plevy S, Reinisch W, Schreiber S, Siegel C, Targan S, Watanabe M, Feagan B, Sandborn WJ, Colombel J-F, Travis S. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: When to Start, When to Stop, Which Drug to Choose and How to Predict Respsnse. American Journal of Gastroenterology. 2011;106, 199-212.

9. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao L-L, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel J-F, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus Jr EF, Dieleman LA, Katz S, Rutgeerts P. Ustekinumab as Induction and Maintenance. Therapy for Crohn's Disease. NEJM. 2016;375:1946-60. Online Supplement.

10. Feagan BG, Sandborn WJ, Gasink C, Group U-I-US, et al. Ustekinumab as induction and maintenance therapy for Crohn's Disease. N Engl J Med. 2016;375:1946–1960.

11. Gomollón F, Dignass A, Annese V et al. Journal of Crohn's and Colitis. 3rd European Evidence-based Consensus on the GTiagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. 2017;3-25.

12. Heron V, Restellini S, Bessissow T, Lemieux C, Lakatos P, Wild G, Seidman E, Bitton A, Afif W. Re-induction with ustekinumab in Crohn's disease patients with a loss of response to treatment. ECCO 2018 Abstract 438.

13. Infliximab SmPC.

14. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology. 1994;106(2):287-296.

15. Khorrami S, Ginard D, Marín-Jiménez I, Chaparro M, Sierra Monica, Aguas M, Sicilia B, Garcia-Sanchez V, Suarez C, Villoria A, Taxonera C, Velasco-Guardado An, Martinez-Gonzalez J, Gisbert JP. Ustekinumab for the Treatment of Refractory Crohn's Disease: The Spanish Experience in a Large Multicentre Open-label Cohort. Inflamm Bowel Dis. 2016 Jul;22(7):1662-9.

16. Kopylov U, Afif W, Cohen A, Bitton A, Wild G, Bessissow T, Wyse J, Al-Taweel T, Szilagyi A, Seidman E. Subcutaneous ustekinumab for the treatment of anti-TNF resistant Crohn's disease--the McGill experience. J Crohn's Colitis. 2014 Nov;8(11):1516-22.

17. Lichtenstein GR et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018 Mar;113(4):481-517.

18. Ma, C, Fedoera RN, Kaplan G, Dieleman LA, Devlin SM, Stern N, Kroeker KI, Seow CH, Leung Y, Novak KL, Halloran BP, Huang VW, Wong K, Blustein PK, Ghosh S, Panaccione R. Long-term Maintenance of Clinical, Endoscopic and Radiographic Response to Ustekinimab in moderate-to-Server Crohn's Diease: Real-world Experience from a Multicenter Cohort Study. Inflammatory Bowel Disease. 2017. DOI 10.1097/MIB.0000000000001074.

19. Park S, Evans E, Sandborn WJ, Boland B. Ustekinumab IV 6 mg/kg Loading Dose Re-induction Improves Clinical and Endoscopic Response in Crohn's disease: A Case Series. American Journal of Gastroenterology. 2018; 113:627-629.

20. Qiu Y, Chen B-L, Mao R, Zhang S-H, He Y, Zeng Z-R, Ben-Horin S, Chen M-H. Journal of Gastroenterology. 2017;52:535-554.

21. Sandborn W, Rutgeerts P, Gasink C, Jacobstein D, Gao L.-L, Johanns J, Sands B, Hanauer SB, Targan S, Ghosh S, de Villiers WJS, Colombe J-F, Feagan BG. ECCO 2017, Abstract OP010.

22. Sandborn WJ et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N. Engl. J. Med. 2014;369(8):711-721.

23. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgerrts PJ. Long-term Outcome of Treatment with Infliximab in 614 Crohn's Disease Patients: Results from a Single Centre Cohort. Gut. 2008; doi:10.1136/gut.2008.155812.

24. Solem CA, Loftus EV, Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(8):707-712.

25. Srinavasan A, VasudevanA, McFarlane A, Sparrow M, Gibson P, Van Langenberg DR. Anti-TNF-Re-induction is as Effective, Simpler and Cheaper Compared with Dose Interval Shortening for Secondary Loss of Response in Crohn's Diseaes. Journal of Crohn's and Colitis. 2017: doi:10.1093/ecco-jcc/jjx144.

26. Stallmach A, Langbein C, Atreya T, Dignass A, Ende K, Hampe J, Hartmann F, Neurath MF, Maul J, Preiss JC, Schmelz R, Siegmund B, Schulze H, Teich N, van Arnim U, Baumgart CD, Schmidt C. Alimentary Pharmacology and Therapeutics. 2016; 44:1199-1212.

27. STELARA [EU SmPC]. Beerse, Belgium: Janssen-Cilag International NV; 2016.

28. Summary of Clinical Pharmacology Studies, ustekinumab. Treatment of Adults with Moderately to Severely Active Crohn's Disease. EDMS-ERI-92904905, 1.0. 2015.

29. Vedolizumab SmPC.

30. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker of inflammatory bowel disease. Inflamm Bowel Dis. 2004;10(5):661-665.

31. Wils P, Bouhnik Y, Michetti P, Flourie B, Brixi H, Bourrier A, Allez M, Duclos B, Grimaud J-C, Buisson A, Amiot A, Fumery M, Roblin X, Peryin-Biroulet L, Filippi J, Bougeuen G, Abitbol V. Subcutaneous Ustekinumab Provides Clinical Benefit for Two-Thirds of Patients With Crohn's Disease Refractory to Anti-Tumor Necrosis Factor Agents. Clin Gastroenterol Hepatol. 2016 Feb;14(2):242-50.e1-2.

32. Wils P, Bouhnik Y, Michetti P, Flourie B, Brixi H, Bourrier A, Allez M, Duclos B, Serrero M, Buisson A, Amiot A, Fumery M, Roblin X, Peryin-Biroulet L, Filippi J, Bouguen G, Abitbol V, Coffin B, Simon M, Laharie D, Pariente G. Long-term efficacy and safety of ustekinumab in 122 refractory Crohn's disease patients: a multicentre experience. Aliment Pharmacol Ther. 2018 Jan 8. [Epub ahead of print].

INVESTIGATOR AGREEMENT

STELARA (ustekinumab)
Clinical Protocol CNTO1275CRD3008 Amendment 4

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 intervention, 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): PPD _____

Institution: Janssen-Cilag Polska

Signature: PPD PPD Date: _____

Reason: I attest to the accuracy and integrity of this document.
Date: 2020.08.05 21:15:16 +02'00'
Adobe Reader version: 11.0.20

(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.

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Approved, Date: 5 August 2020