Janssen Research & Development *

Statistical Analysis Plan

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

POWER

Protocol CNTO1275CRD3008; Phase 3b

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

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AMENDMENT HISTORY

N/A

ABBREVIATIONS

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

DEFINITIONS OF TERMS

Term	Definition
Clinical remission	CDAI score < 150
Clinical response	Decrease in CDAI score of ≥ 100 from baseline or CDAI score <150
IBDQ remission	Score of >= 170
Normalization of C-reactive protein or Fecal Calprotectin	C-reactive protein (CRP) ≤ 3 ug/L or Fecal Calprotectin (<250 mg/kg) (among subjects with abnormal CRP or Fecal Calprotectin at baseline)
Endoscopic improvement	Change in SES-CD score of at least 3 points
Endoscopic remission	SES-CD score ≤3, or SES-CD =0 for subjects who enter the study with an SES-CD =3
Endoscopic response	Reduction in SES-CD score by 50% from baseline or SES-CD score ≤3, or SES-CD =0 for subjects who enter the study with an SES-CD =3

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods to compare the efficacy and safety of Intravenous Re-induction Therapy with Ustekinumab in Patients with Moderately to Severely Active Crohn's Disease

1.1. Trial 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.

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 [FeCa] levels), after IV Ustekinumab re-induction.
- Assess the overall safety of IV Ustekinumab re-induction.

The exploratory objectives are to explore 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.

1.2. Trial Design

This is a randomized, double-blind, placebo-controlled, multicenter, 24-week, Phase 3b study in adult patients with active moderate to severe 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.

1.3. Statistical Hypotheses for Trial Objectives

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/g (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.

1.4. Sample Size Justification

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 re-induction 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 re-induction group and 40% in the continuous SC q8w 90mg group, 100 participants per treatment group will yield an overall power above 80%, at a significance level of 0.05 (2-sided, Mantel-Haenszel test).

Table 1 provides the power for detecting a treatment difference between the IV Ustekinumab re-induction group and the continuous SC q8w 90mg Ustekinumab group (for 100 participants per group) under varying assumptions for the clinical response rates.

Table 1: 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%

1.5. Randomization and Blinding

Treatment Allocation

Following clinical assessments at baseline, all enrolled participants will be randomized in a 1:1 ratio to one of two re-induction 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 one of two re-induction 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 administration of study intervention (Ustekinumab ~6 mg/kg or placebo) plus a single SC administration of study intervention (Ustekinumab 90 mg or placebo) in a double-blinded manner. During study visits at Weeks 8 and 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) 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.

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.

2. GENERAL ANALYSIS DEFINITIONS

This analysis plan provides the general analysis definitions and describes the planned subject information, efficacy, safety, pharmacokinetics, and antibody analyses for the two treatment groups.

2.1. Visit Windows

Study visits are to occur at Screening (within 1- 5 weeks prior to Week 0), and Weeks 0, 8, 16 (primary endpoint) and visit at Week 24.

Study visits should occur at the week indicated ± 4days for each visit up to and including Week 16 and ±7 days for Week 24 (Table 2). Note that while out of window visits should be recorded as protocol deviations, it is preferable to perform visits and procedures out of window than not perform them at all. One exception may be if sufficient time has passed that it is now in-window

for the next, subsequent visit, in which case it is advised to contact the medical monitor for assistance in how to best manage the situation.

Table 2: Visit Windows

Parameter	Analysis Period	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
	[1]	[1]	[Screening]	[<1]	[-35 to -7]
	[1]	[2]	[Week 0]	[<=1]	[1]
	[1]	[3]	[Week 8]	[52 to 60]	[56]
	[1]	[4]	[Week 16]	[108 to 116]	[112]
telephone call or on-site	[1]	[5]	[Week 24]	[161 to 175]	[168]

2.2. Pooling Algorithm for Analysis Centers

There is no pooling algorithm for analysis centers.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set(s)

In this study, the efficacy analyses will be based on intent-to-treat principle. That means efficacy analyses will be performed on the full analysis set, which is defined as all randomized subjects. The full analysis set will be used for all primary and secondary efficacy analyses.

2.3.2. Safety Analysis Set

All subjects in the ITT population who receive at least 1 administration of study agent will be included in the safety analyses. Subjects will be analyzed according to the actual treatment received.

2.3.3. Pharmacokinetics Analysis Set

The PK analysis set is defined as all subjects who have received at least 1 administration of study agent and have at least one valid blood sample drawn for PK analysis. Subjects will be analyzed according to the actual treatment received.

2.3.4. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all subjects who have received at least 1 administration of study agent and have at least one valid blood sample drawn for detection of antibodies to study agent. Subjects will be analyzed according to the actual treatment received.

2.4. Definition of Subgroups

To evaluate the consistency of efficacy in the primary endpoint over demographic, baseline disease characteristics, and CD medication history, subgroup analyses will be performed when the number of subjects in the subgroups permits.

Baseline demographics:

- Baseline age (≤ median age, >median age)
- Sex (male, female)
- Race (White, non-White)
- Baseline weight (≤ median, > median)
- Baseline smoking status (smoking, non-smoking)

Baseline disease characteristics:

- Baseline CDAI score (≤300 or >300)
- Crohn's disease duration (years) (<2 years, >=2 to <5 years, or >=5 years)
- Involved gastrointestinal areas (ileum only, colon only, ileum & colon)
- CRP (≤ 3 mg/L, > 3 mg/L)
- Fecal Calprotectin (≤250 mg/kg, > 250 mg/kg)

Concomitant medication using at baseline:

- Oral corticosteroids (including budesonide) (receiving, not receiving)
- 6-MP/AZA/MTX (receiving, not receiving)
- Oral corticosteroids (including budesonide) and (6-MP/AZA/MTX) (receiving, not receiving)
- Oral corticosteroids (including budesonide) or (6-MP/AZA/MTX) (receiving, not receiving)

Surgery history:

- Prior intra-abdominal surgeries
  - 0 (i.e. NO prior intra-abdominal surgeries)
  - 1
  - ≥1
  - ≥2
- Prior total or subtotal colectomy (independent of CD-related surgeries)
- Prior other CD related partial bowel resection
- Current or prior fistula
  - Current draining fistula
  - Previous fistula history
- Prior perianal CD related Surgery

Baseline endoscopy information

- Endoscopic disease severity per SES-CD score
  - No ulcers (0-2)
  - Mild (3-6)
  - Moderate (7-16)
  - Severe (>16)
- Ulceration location
  - None
  - Ileum only
  - Colon only
  - Ileum and colon

Pre-Study Ustekinumab trough concentration

- By level
  - Undetectable
  - >0 – 0.8
  - 0.8 – 1.3
  - >1.3
- By quartiles

Antibodies to Ustekinumab

- Yes/no

Number of Biologics Failed Prior to Ustekinumab

- None
- 1 Biologic
- 2 Biologics
- 3 Biologics
- 4 Biologics

Prior response to Ustekinumab

- Remission
  - Yes/no

- Response (Subjects with normalization of)
  - CRP (≤3 mg/L)
  - FeCa (≤250 mg/kg)

Total length of time using Ustekinumab for CD

- ≤ 24 weeks
- > 24 weeks to ≤ 52 weeks
- > 52 weeks to ≤ 104 weeks
- > 104 weeks

Other

- CDAI > 300 and receiving corticosteroids and/or 6-MP/AZA/MTX at baseline (Yes, No)

2.5. Study Day and Relative Day

Study Day 1 refers to the first study agent administration. The study day for an event is defined as:

- Event date - (date of Study Day 1) +1, if event date is ≥ date of Day 1
- Event date - date of Day 1, if event date < date of Day 1

2.6. Baseline

In general, the baseline measurement is defined as the closest measurement taken prior to or at the time of the first study agent administration date unless otherwise specified.

2.7. Imputation Rules for Missing AE Date

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is the earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date

  - Month and day of the study agent start date, if this date is in the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the date of AE, if the AE occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of AE, if the AE occurred in that year.

Completely missing resolution dates will not be imputed.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Interim analysis is planned at Week 16 database lock. There is no Data Monitoring Committee (DMC) for this study.

4. SUBJECT INFORMATION

The full analysis set will be used for the subject information analyses as specified below unless otherwise noted.

Descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data. In addition, subject listings will also be used to present the data.

4.1. Demographics and Baseline Characteristics

4.1.1. Demographics

Table 3 presents a list of the demographic variables that will be summarized for the full analysis set.

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Categorical Variables:	
Age (≤ median age, >median age)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Weight (≤ median, > median)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple, Unknown, Not reported)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)	

a If multiple race categories are indicated, then Race is recorded as "Multiple."

4.1.2. Baseline Characteristics

Crohn's disease baseline disease characteristics (i.e., Crohn's disease duration [years], surgery history, age at diagnosis [years], baseline CDAI scores, baseline SES-CD score [0-56], baseline CRP and Fecal Calprotectin, baseline IBDQ [32-224] will be summarized for the full analysis set.

4.2. Disposition Information

The number of subjects in the following disposition categories will be summarized throughout the study by treatment group and overall:

- Subjects randomized
- Subjects receiving study agent
- Subjects completing the study
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent
- Subjects who terminated study prematurely
- Reasons for termination of study

The above categories will include summaries over the period of Week 16 and through Week 36 if appropriate. The reasons for discontinuation of study agent and termination of study due to COVID-19 will be included in the summary tables.

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study agent
- Subjects who terminated study prematurely
- Subjects who were unblinded during the study period
- Subjects who were randomized yet did not receive study agent
- Subjects who discontinued study agent due to COVID-19
- Subjects who terminated study prematurely due to COVID-19
- Treatment Compliance
- Study agent compliance with the number of missing SC injections (1, 2, 3, more than 3) will be summarized descriptively through Week 16 for the full analysis set.

4.3. Extent of Exposure

The exposure data will be summarized through week 8/16 for week 16/end of study database lock separately. The number, cumulative dose and percentage of subjects who receive study agents will be summarized by treatment group for the safety analysis set. Descriptive statistics will be presented for the following parameters:

- Number of study agent injections or Infusions

4.4. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to week 16/end of study database lock and the subjects with major protocol deviations will be summarized by category through Week 36 for the full analysis set.

- Entered but did not satisfy criteria
- Developed withdrawal criteria but not withdrawn
- Received a disallowed concomitant treatment
- Received a wrong treatment or an incorrect dose
- Other

Subjects with major protocol deviations will also be listed. A listing will also be provided for subjects who had any COVID-19 related protocol deviations.

4.5. Prior and Concomitant Medications

Prior medications are defined as any therapy used before the day of first dose of study agent. Subjects' prior CD medication history with immunomodulators (MTX, AZA, and 6-MP) or oral corticosteroids or other non-biologic systemic therapies or CD-related biologic medication history will be summarized by treatment groups.

Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue on after the first dose of study agent. The number of subjects who received oral corticosteroid treatment at baseline and the doses over time of these subjects will be summarized.

Subjects who received concomitant corticosteroids for indications other than CD will be listed.

5. EFFICACY

In general, efficacy data summaries will be provided for the full analysis set. All efficacy analyses will be based on intent-to-treat principle.

5.1. General Method of Analysis

Descriptive statistics (eg, mean, median, standard deviation, interquartile range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphical data displays (eg, line plots) may also be used to summarize the data whenever appropriate. Listings may also be utilized to present data at a subject level.

All endpoints will be based on a superiority comparison between the 2 randomized groups (~6 mg/kg IV re-induction of Ustekinumab and SC q8w 90 mg Ustekinumab). All efficacy analyses will be based on intent-to-treat principle. Therefore, the efficacy data for each subject randomly assigned to treatment group will be analyzed according to the assigned treatment regardless of the actual treatment received. All randomized subjects will be included in the efficacy analyses.

5.1.1. Data Handling Rules

5.1.1.1. Missing Data Imputation

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

5.1.2. Estimand

Composite Strategy

The Composite Strategy assesses the treatment effects not only based on the variable measurements, but also based on intercurrent events (ICE(1-4)) defined in Section 5.1.2.1. If a participant met any of the ICE criteria the subject will be a non-responder for response variables and will have a score of no improvement for continuous variables for signs and symptoms. This estimand acknowledges that meeting the ICE (TF) criteria is an unfavorable outcome.

5.1.2.1. Composite Estimand

The Composite Estimand is defined by the 5 components:

- **Population**: Subjects with moderately-to-severely active CD who have previously responded to Ustekinumab induction therapy, followed by a secondary LoR to SC q8w 90 mg Ustekinumab maintenance treatment
- **Treatment**:
  - Ustekinumab IV re-induction
  - Ustekinumab SC q8w
- **Variable**:
  - Binary: The endpoint (e.g. Clinical Response) is defined as responders who had not met any TF criteria prior to the specific visit at which the endpoint was assessed.
  - Continuous: The endpoint is defined as change from baseline score prior to meeting TF criteria and 0 (no improvement) after meeting TF criteria.
- Intercurrent Events (ICEs):

The following are the intercurrent events considered for this trial:

1. A Crohn's disease-related surgery due to lack of efficacy
2. Discontinuation of study agent due to an AE of worsening CD or due to lack of efficacy
3. Protocol-prohibited medications (Attachment 4)
4. A change in corticosterioids and immunomodulator (Attachment 5)

- Population **level summary**:
  - Binary: difference in proportion of responders between Ustekinumab IV re-induction group and Ustekinumab SC group
  - Continuous: difference in mean changes between Ustekinumab IV re-induction group and Ustekinumab SC group

This estimand examines the difference through 24 weeks without increasing/initiating select background CD medications or discontinuing study intervention prior to that point, between Ustekinumab IV re-induction and Ustekinumab SC group.

5.2. Analysis Specifications

5.2.1. Level of Significance

Unless otherwise specified, a 2-sided significance level of 5% will be used.

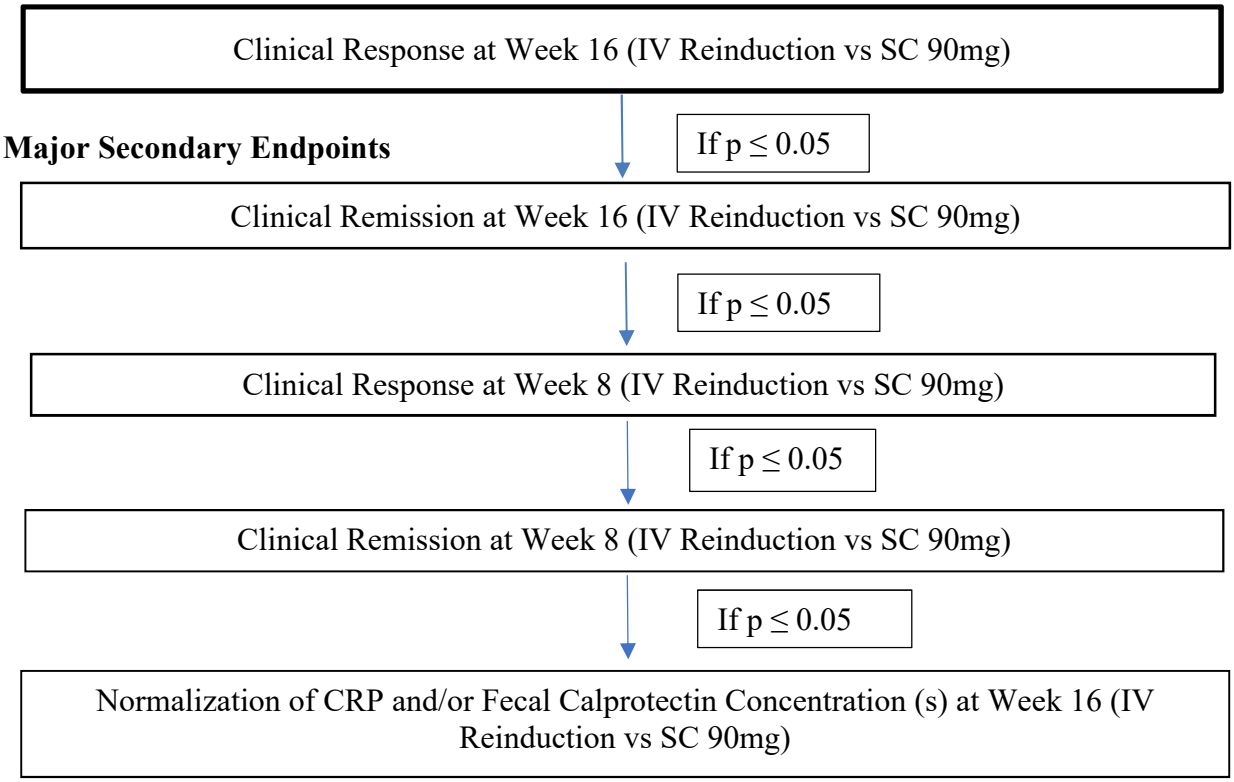
5.2.2. Multiplicity Adjustment for Testing Procedures

This study has 1 primary endpoint (proportion of participants who achieved a clinical response at Week 16) and 4 major secondary endpoints. With 5 endpoints and 2 treatment comparisons for each of these endpoints, there are a total of 5 hypotheses to be tested. The 5 hypotheses for the endpoints are explicitly listed in attachment 6.

The overall Type I error of the 5 hypotheses in attachment 6 will be controlled at a significance level of ≤ 0.05. The testing procedure tests the primary and 4 major secondary endpoints for the two regimens of Ustekinumab IV re-induction vs Ustekinumab SC, in a fixed sequence and each endpoint is tested at the two-sided 0.05 level of significance. The fixed sequence testing method tests an endpoint only if the null hypotheses of no difference between the Ustekinumab IV re-induction and Ustekinumab SC was rejected at the 0.05 level for all the endpoints above it in the sequence. This is shown visually in Figure 1 below.

Figure 1: Multiplicity Control

Primary Endpoint



5.3. Primary Endpoint Analysis

5.3.1. Definition of the Endpoints

The primary endpoint of the study is the proportion of subjects with clinical response (defined as a ≥100-point reduction from the baseline CDAI score, or a CDAI score <150) at Week 16.

5.3.1.1. CDAI

The CDAI will be assessed by collecting information for 8 different CD-related variables: extra-intestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid stools, abdominal pain/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being.[4,9] The last 4 variables are scored over 7 days by the subject on a diary card. For the total number of liquid or very soft stools, abdominal pain/cramps, and general wellbeing, if only 5 days or 6 days of data are available for the calculation, the weights of 7/5 and 7/6 will be used for the calculation respectively; if the values are recorded for less than 5 days, the subscore will not be calculated.

When at least 4 of the 8 components are available, missing components will be imputed. For missing hematocrit at baseline, the hematocrit value obtained closest and prior to the date of the Week 0 administration will be used. For all other visits, the hematocrit value obtained closest to the date of the visit will be used provided it was obtained within ± 10 days of the visit. If the laboratory value is obtained outside the ± 10-day window, then the closest previous hematocrit value will be carried forward.

5.3.2. Analysis Methods

The primary efficacy analysis of the primary endpoint will be analyzed at the Week16 database lock based on the Composite Estimand (Table 4)**.**

Intercurrent Events and Corresponding Strategies:

Intercurrent events (ICEs) in categories 1-4 in 5.1.2 will be handled by the composite strategy. The estimand for the primary endpoint acknowledge that having any intercurrent event is an unfavorable outcome. If a subject had any of the ICE categories 1-4 at or prior to Week 16, the subject will be considered not to be in **clinical response** at Week 16**.**

In the primary efficacy analysis (i.e. the main estimator for the primary estimand), data from all subjects in the FAS (Section 2.3.1) will be analyzed according to the randomized study intervention regardless of the study intervention they actually received.

In the primary efficacy analysis, the number and proportion of subjects achieving a clinical response (defined as a ≥100-point reduction from the baseline CDAI score, or a CDAI score <150) at Week 16 will be summarized. The clinical response endpoints as measured by the CDAI score will be determined based on these CDAI scores. The CDAI score will be calculated as described in Section 5.3.1.1. If any CDAI score is collected after experiencing ICE1-4, subject will be considered not having clinical response regardless of their CDAI score. If the CDAI score cannot be calculated (ie, <4 components available) at Week 16, the CDAI score will be considered missing for Week 16. Subjects who have a missing CDAI score at Week 16 will be considered not to be in

clinical response as measured by the CDAI score (ie, Nonresponder Imputation (NRI)). The endpoint will be compared between the Ustekinumab IV re-induction treatment group and continuous SC q8w treatment group using 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. Strata adjusted proportion difference from CMH method will be calculated. 95% asymptotic confidence interval for strata-adjusted proportion difference based on Wald-type statistic will be calculated as well.

5.3.3. Sensitivity Analyses for Primary Endpoint

To assess the robustness of the primary endpoint analysis, the following three sensitivity analyses will be conducted.

(1) Per protocol: exclude randomized, never treated subjects

(2) Observed case: exclude subjects from the analysis if they have a missing CDAI score at Week 16 (ie, the CDAI score is missing at Week 16)

(3) Last observation carried forward: subjects who have a missing CDAI score at Week 16 (ie, the CDAI score is missing at Week 16) will have their last CDAI score carried forward.

The same ICE strategies as those used for the primary endpoint analysis in 5.3.2 will be applied on the above three sensitivity analyses.

5.3.4. Subgroup analyses

To evaluate the consistency of the efficacy of the primary endpoint over demographic, baseline disease characteristics, Crohn's disease medication use at baseline, surgery history and baseline endoscopy information, subgroup analyses are planned when the number of subjects in the subgroups permits. The same data handling rules and ICE strategies will be applied as were used for the primary endpoint analysis in 5.3.2. The odds ratios of Ustekinumab IV re-induction group vs. continuous SC q8w and corresponding 95% confidence intervals will be provided for each of the subgroups in Section 2.4.

5.3.5. Summary of Analyses Related to the Primary Endpoint

Table 4: Summary of Analyses Related to the Primary Endpoint of Clinical Response at Week 16

Analysis (Analysis Set)	**Missing data**	**Analysis method/Summary statistics**
All analyses in this table are based on Composite Estimand.		
Primary Analysis (Full Analysis Set-FAS)	Missing data due to missed visits or missed data collection (missing CDAI score). Subjects with missing data are considered not to be in clinical response	· Summaries of the proportion of subjects who achieved the endpoint · Strata adjusted proportion difference (Ustekinumab IV re-induction group-Ustekinumab SC q8w group) and 95% CI · P-value from the CMH test (stratified by baseline CDAI score (≤ 300 or > 300),

Table 4: Summary of Analyses Related to the Primary Endpoint of Clinical Response at Week 16

		and prior biologic failure status at baseline (yes or no))
Subgroup Analyses (Individual subgroup levels defined in Section 2.4, FAS)	Missing data due to missed visits or missed data collection (missing CDAI score). Subjects with missing data are considered not to be in clinical response	· Summaries of the proportion of subjects who achieved the endpoint · Odds ratios and 95% CIs · P-value from the logistic regression (stratified by baseline CDAI score (≤ 300 or > 300), and prior biologic failure status at baseline (yes or no)
Sensitivity Analysis 1 Full Analysis Set excluding Randomized, never treated subjects	Same as Primary Analysis	Same as Primary Analysis
Sensitivity Analysis 2 Observed case: Full Analysis Set-Exclude subjects from the analysis if they have a missing CDAI score at week 16 (ie. < 4 components of the CDAI score are available at Week 16)	No missing data on CDAI at Week 16	Same as Primary Analysis
Sensitivity Analysis 3 (FAS) Last observation carried forward: subjects who have a missing CDAI score at Week 16 will have their last CDAI score	For missing CDAI score due to missed visits or missed data collection (< 4 components of the CDAI score), CDAI score will have the last non-missing value carried forward. If any of ICE 1-4 occurs prior to Week 16, then subject is considered as not to be in	Same as Primary Analysis

Table 4: Summary of Analyses Related to the Primary Endpoint of Clinical Response at Week 16

carried forward	clinical response at Week 16. Otherwise, clinical response status will be determined by observed or carried forward CDAI score.	

5.4. Major Secondary Endpoints Analyses

The 4 major secondary endpoints are:

- Clinical remission at Week 16
- Clinical response at Week 8
- Clinical remission at Week 8
- Normalization of CRP and/or FeCal calprotectin concentration(s) at Week 16, among participants with an elevated CRP and/or FeCa at baseline

5.4.1. Definitions of Major Secondary Endpoints (in corresponding order)

The proportion of subjects with:

- Clinical remission is defined as a CDAI score < 150
- Clinical response is defined as a CDAI score decrease ≥100 from baseline or CDAI score <150
- Normalization of CRP is defined as CRP ≤3 mg/L and normalization of FeCal calprotectin concentration is defined as fecal calprotectin ≤250 mg/kg

5.4.1.1. C-reactive Protein

C-reactive protein has been demonstrated to be useful as a marker of inflammation in patients with irritable 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 [7, 15].

Blood samples for the measurement of CRP will be collected from all participants at visits indicated in the Schedule of Activities. CRP 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.

5.4.1.2. Calprotectin

Fecal calprotectin has been demonstrated to be a sensitive and specific marker in identifying intestinal inflammation and response to treatment in patients with irritable bowel disease [6].

Stool samples for determination of FeCa 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 FeCa 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 postbaseline FeCa tests will not be released to the investigators.

5.4.2. Analyses method for the Major Secondary Endpoints

The major secondary endpoints, defined in Section 5.4.1 will be compared between Ustekinumab IV re-induction group and continuous Ustekinumab SC q8w group and will use the full analysis set. The same data handling rule and ICE strategies as primary analysis in Section 5.4.2 will be used in analyses for major secondary endpoints related to CDAI score. The endpoints will be estimated by differences between the Ustekinumab IV re-induction group and the Ustekinumab SC q8w group in the percentages of subjects who meet each endpoint and their associated 95% CIs. In addition, each endpoint will be compared between Ustekinumab IV re-induction group and Ustekinumab SC q8w group using the CMH chi-square test (2-sided) 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. The tests of superiority will be based on the p-values from the CMH test.

The CDAI score will be calculated as described in Section 5.3.1.1. The clinical response or remission endpoints as measured by the CDAI score will be determined based on these CDAI scores. If the CDAI score cannot be calculated (ie, <4 components available) at Week 8/16, the CDAI score will be considered missing for Week 8/16. Subjects who have a missing CDAI score at Week 8/16 will be considered not to be in clinical remission or clinical response as measured by the CDAI score (ie, Nonresponder Imputation (NRI)).

If CRP or fecal concentration is missing at Week 16, CRP or fecal concentration will have their last non-missing value carried forward at Week 16. If any of ICE 1-4 occurs at or prior to week 16, then the subject is considered as not to be normalization at week 16. Otherwise, normalization status will be determined by observed or carried forward CRP or Fecal value.

5.4.3. Summary of Analyses Related to Major Secondary Endpoints

Table 5 below provides an overview of all the analyses related to the major secondary endpoints, the analysis sets, the data handling rules to be used, and the analysis methods and summary statistics.

Table 5: Summary of Analyses Related to Major Secondary Endpoints

Analysis **(Analysis Set)**	**Missing data**	**Analysis method/Summary statistics**
All analyses for major secondary endpoints are handled by the composite strategy		

Table 5: Summary of Analyses Related to Major Secondary Endpoints

Clinical Remission at Week 16 (FAS)	Missing data due to missed visits or missed data collection (missing CDAI score). Subjects with missing data are considered not to be in clinical remission	• Summaries of the proportion of subjects who achieved the endpoint • Strata adjusted proportion difference (Ustekinumab IV re-induction group-Ustekinumab SC q8w group) and 95% CI • P-value from the CMH test (stratified by baseline CDAI score (≤ 300 or > 300), and prior biologic failure status at baseline (yes or no))
Clinical Response at Week 8 (FAS)	Missing data due to missed visits or missed data collection (missing CDAI score). Subjects with missing data are considered not to be in clinical response	• Summaries of the proportion of subjects who achieved the endpoint • Strata adjusted proportion difference (Ustekinumab IV re-induction group-Ustekinumab SC q8w group) and 95% CI • P-value from the CMH test (stratified by baseline CDAI score (≤ 300 or > 300), and prior biologic failure status at baseline (yes or no))
Clinical Remission at Week 8 (FAS)	Missing data due to missed visits or missed data collection (missing CDAI score). Subjects with missing data are considered not to be in clinical remission	• Summaries of the proportion of subjects who achieved the endpoint • Strata adjusted proportion difference (Ustekinumab IV re-induction group-Ustekinumab SC q8w group) and 95% CI • P-value from the CMH test (stratified by baseline CDAI score (≤ 300 or > 300), and prior biologic failure status at baseline (yes or no))
Normalization of CRP and/or FeCal concentration(s) at Week 16 (Randomized Subjects with an elevated CRP and/or FeCa at baseline)	For missing CRP or Fecal, CRP or Fecal will have their last non-missing value carried forward. If any of ICE 1-4 occurs prior to week 16, then the subject is considered as not to be normalized at Week 16. Otherwise, normalization status will be determined by observed or carried forward CRP or Fecal value.	• Summaries of the proportion of subjects who achieved the endpoint • strata adjusted proportion difference (Ustekinumab IV re-induction group-Ustekinumab SC q8w group) and 95% CI • P-value from the CMH test (stratified by baseline CDAI score (≤ 300 or > 300), and prior biologic failure status at baseline (yes or no))

5.5. Other Endpoints

The testing of the other endpoints will occur regardless of the significance of the major secondary endpoints. The testing of these endpoints will not be adjusted for multiplicity, and statements of significance for these endpoints will be based on nominal p-values. A 2-sided significance level of 0.05 will be used.

5.5.1. Secondary Efficacy Endpoints at Week 24

The secondary endpoints in the following list will be analyzed.

- The proportion of subjects with clinical response (defined as a CDAI score decrease ≥100 from baseline or a CDAI score < 150) at Week 24
- The proportion of subjects with clinical remission (defined as CDAI < 150) at Week 24
- Normalization of CRP at Week 16, among participants with an elevated CRP
- Normalization of FeCal concentration(s) at Week 16, among participants with an elevated FeCal at baseline
- Normalization of CRP and/or FeCal concentration(s) at Week 24, among participants with an elevated CRP and/or FeCal at baseline
- Normalization of CRP at Week 24, among participants with an elevated CRP
- Normalization of FeCal concentration(s) at Week 24, among participants with an elevated FeCal 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.

5.5.2. Other Efficacy Endpoints:

- The proportion of subjects with endoscopic response (defined as a reduction in SES-CD score by 50% from baseline or SES-CD score ≤3 or SES-CD =0 for subjects who enter the study. with an SES-CD =3) at Week 16
- The proportion of subjects with endoscopic improvement (reduction of ≥3 points from baseline in SES-CD) at Week16.
- The proportion of subjects with endoscopic remission (SES-CD score ≤3 or SES-CD =0 for subjects who enter the study with an SES-CD =3) at Week 16.
- Complete absence of mucosal ulcerations in any ileocolonic segment (score=0 for all segments for the "Presence and size of ulcers" component) at Week 16
- Change from baseline in SES-CD score at Week 16.
- The proportion of subjects with a minimum of 25% improvement from baseline in SES-CD score at Week 16
- The 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

- The change in the weighted sum of the abdominal pain and stool frequency scores of the CDAI (PRO-2 weighted) from baseline at Week 16
- The change from baseline in the IBDQ score (including IBDQ domains) at Week 16
- The proportion of subjects with IBDQ remission (IBDQ score ≥170) at Week 16
- The proportion of subjects with corticosteroid-free response at Week 24 (defined as a CDAI score decrease ≥ 100 from baseline or a CDAI score < 150 and not taking any corticosteroids for at least 30 days prior to Week 24)
- The proportion of subjects with corticosteroid-free response at Week 24 (defined as a CDAI score decrease ≥ 100 from baseline or a CDAI score < 150 and not taking any corticosteroids for at least 30 days prior to Week 24) among subjects who were on corticosteroids at baseline
- The proportion of subjects with corticosteroid-free remission at Week 24 (defined as a CDAI score < 150 and not taking any corticosteroids for at least 30 days prior to Week 24) among subjects who were on corticosteroids at baseline
- The proportion of subjects with clinical remission and ≥50% reduction from baseline in CRP or fecal calprotectin at Week 16
- The proportion of subjects with clinical remission and ≥50% reduction from baseline in CRP or fecal calprotectin at Week 16 where fecal calprotectin assessed, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 mg/kg at baseline
- The proportion of subjects with clinical remission and CRP ≤3 mg/L and fecal calprotectin ≤250 mg/kg at 16 where fecal calprotectin assessed at baseline
- The proportion of subjects with clinical remission and CRP ≤3 mg/L and fecal calprotectin ≤250 mg/kg at 16 where fecal calprotectin assessed, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 mg/kg at baseline
- The proportion of subjects with clinical biomarker response (clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin) at Week 16
- The proportion of subjects with clinical biomarker response (clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin) at Week 16 where fecal calprotectin assessed, among participants with elevated CRP (>3) or fecal calprotectin (>250 mg/kg) at baseline
- The proportion of subjects with clinical response and CRP ≤3 mg/L and fecal calprotectin ≤250 mg/kg at Week 16
- The proportion of subjects with clinical response and CRP ≤3 mg/L and fecal calprotectin ≤250 mg/kg at Week 16 where fecal calprotectin assessed, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 mg/kg at baseline
- The proportion of subjects with fistula resolution (closure of all perianal/perirectal fistulas) at Week 8 and Week 16 among subjects with one or more open/draining perianal or perirectal fistulas at baseline

5.5.3. Definitions

5.5.3.1. Inflammatory Bowel Disease Questionnaire

The IBDQ is a validated, 32-item self-report questionnaire for participants with irritable bowel disease to evaluate patient-reported outcomes 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.

5.5.3.2. 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).

5.5.3.3. Video Ileocolonoscopy

An ileocolonoscopy will be used to assess SES-CD at baseline (Week 0) and at the Week 16 visit to determine the presence or absence of mucosal inflammation and ulceration. An ileocolonoscopy was done as an optional procedure and is not available for all patients. 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 28 days before or after the Week 16 visit.

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.

The ileocolonoscopy procedures will 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 the treatment group.

Simplified endoscopic activity score for Crohn's disease (SES-CD)

The Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) is a scoring system developed to provide a more granular evaluation of endoscopic disease severity in patients with Crohn's disease. It is constructed based on the evaluation of 4 endoscopic components across 5 predefined ileocolonic segments. The 4 endoscopic components within each segment are: the presence/size of ulcers, the proportion of mucosal surface covered by ulcers, the proportion of mucosal surface affected by any other lesions, and the presence/ type of narrowing (also commonly referred to as strictures/ stenosis clinically). Each endoscopic component is scored from 0 to 3 for each segment, and a total score is calculated as a sum of all the component scores across all the segments, as outlined in Table 6. The total SES-CD score ranges from 0 to 56.

Table 6 Sample score sheet and scoring definitions for the Simple Endoscopic Score for Crohn's Disease (SES-CD)

The total SES-CD score at a visit will be calculated based on all segments scored at the visit. If the total SES-CD score cannot be calculated (i.e., no segments are scored) at a visit, the total SES-CD score will be considered missing.

	Ileum	Right Colon	Transverse Colon	Left Colon	Rectum	Total
1. Presence and size of ulcers (0-3)						15 max
2. Extent of ulcerated surface (0-3)						15 max
3. Extent of affected surface (0-3)						15 max
4. Presence and type of narrowings (0-3)						11 max*
Total 1 + 2 + 3 + 4 =						SES-CD (56 max)

	Score = 0	Score = 1	Score = 2	Score = 3
Size of ulcers	None	Aphthous ulcers (ø 0.1 – 0.5 cm)	Large ulcers (ø 0.5 – 2.0 cm)	Very large ulcers (ø > 2.0 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

* The maximum sub-score for narrowings (i.e. stricturing) is 11 points. The presence of a narrowing that cannot be passed can be only observed once.

ø =Diameter.

5.5.4. Analysis Methods

Other efficacy endpoints except endoscopy endpoints related to SES-CD score listed and defined in Sections 5.5.1 and 5.5.2 will be analyzed based on the FAS according to randomized treatment group regardless of the treatment actually received.

Endoscopy endpoints related to SES-CD score will be analyzed on subjects with total SES-CD score ≥3 at baseline.

Descriptive statistics (i.e., mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables.

The data handling rule and ICE strategies as defined above for the major secondary endpoints (Section 5.4.3) will also be used for these endpoints.

Binary Endpoints

Subjects who have any intercurrent event (as specified in section 5.3.2) will be considered to not have achieved the binary endpoints. Subjects with missing data for an endpoint will be considered to have not achieved the associated binary endpoint.

The proportions will be compared between the Ustekinumab IV re-induction group and continuous Ustekinumab SC q8w group using 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) unless otherwise specified. In case of rare events, Fisher's exact test will be used for treatment comparisons.

Continuous Endpoints

Baseline values (at Week 0) will be assigned from the point of an intercurrent event categories 1-4 onward, regardless of the observed data if a subject has any intercurrent event (as specified in Section 5.3.2). Missing data for scores will be carried forward from last non-missing observed value prior to missing visits.

The continuous variables (such as changes from baseline) will be compared between the Ustekinumab IV re-induction group and Ustekinumab SC q8w group using an analysis of covariance on van der Waerden normal scores with baseline value, baseline CDAI score (≤ 300 or > 300), and prior biologic failure status at baseline (yes or no) as stratification factors unless otherwise specified. For the change from baseline in CDAI score, the baseline CDAI (continuous)will be used as a covariate instead of baseline CDAI score (<=300 or >300).

6. SAFETY

Safety will be assessed by summarizing the incidence and type of AEs, and examining changes in laboratory parameters (hematology and chemistry).

In all safety analyses, subjects who received at least 1 (partial or complete) dose of study agent will be included. No formal hypothesis testing is planned.

Depending on the safety data categories, the cumulative safety data will be analyzed through different study periods which include through Week 16 for the primary endpoint and through Week 36 for the final follow-up of the study as appropriate.

6.1. 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). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. Any AE occurring at or after the initial administration of study agent through the end of the trial is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it

is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events (including COVID-19 related AEs) will be included in the analysis. For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summary tables will be provided for:

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

In addition to the summary tables above, listings will be provided for subjects who:

- Had SAEs
- Discontinuation of study agent due to AEs
- Had serious infections
- Had Malignancies

Since safety should be assessed relative to exposure and follow-up, most AE summary tables will include average weeks of follow-up and average number of study agent administrations for each treatment group.

Additional summaries, listings, or narratives will be provided for any deaths.

6.2. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the safety analysis set. The clinical laboratory parameters to be evaluated by the central laboratory include but are not limited to:

- Hematology assessments will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential WBC count.
- Blood chemistry assessments will include but are not limited to the following: chemistry panel (total bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, blood urea nitrogen (BUN)/urea, and creatinine).
- Stool fecal calprotectin
- C-reactive protein

Descriptive statistics will be presented for all chemistry, hematology, and other laboratory tests at scheduled time points.

Box plots of laboratory measurements and change from baseline will be provided for selected laboratory analytes.

The proportion of subjects with any markedly abnormal post baseline laboratory values (hematology and chemistry) in selected laboratory measurements will be summarized. Markedly abnormal clinical laboratory will be summarized through Week 24 of the study. Markedly abnormal post baseline laboratory values will also be presented in listings.

Markedly abnormal changes from baseline are defined in Table 7. For a laboratory value to be considered markedly abnormal, the corresponding laboratory criteria below must be met. For example, for a platelet value to be markedly abnormal, the platelet value must be <100 $x10^9$/L and must be at least 50% decrease from the baseline platelet value. If the baseline value is missing for a parameter, the determination of whether the laboratory value is markedly abnormal will be based solely on the actual value (ie, the criterion for a specific increase or decrease from baseline will not be utilized).

Table 7: Markedly Abnormal Criteria for Laboratory Parameters

Hematology Test	**Criteria for Markedly Abnormal Status**
Hemoglobin (g/L)	Decrease from baseline > 20 g/L & absolute value < 100 g/L
Hematocrit, fraction	absolute value < 0.3 fraction
WBC ($x10^9$/L)	Decrease absolute value < 3 x 10^9/L Increase absolute value > 20 x 10^9/L
Neutrophils ($x10^9$/L)	Percent decrease from baseline ≥ 33% & absolute value < 1.5 x 10^9/L
Lymphocytes ($x10^9$/L)	Percent decrease from baseline ≥ 33% & absolute value < 1.5 x 10^9/L
Eosinphils ($x10^9$/L)	Percent increase from baseline ≥ 100 % & absolute value > 1.0 x 10^9/L
Platelets ($x10^9$/L)	Percent decrease from baseline ≥ 50% & absolute value < 100 x 10^9/L
Chemistry Test	
ALT/SGPT (U/L)	Percent increase ≥ 100 & Value > 100
AST/SGOT (U/L)	Percent increase ≥ 100 & Value > 100
Total Bilirubin (umol/L)	Percent increase ≥ 100 & Value > 41.0

Table 7: Markedly Abnormal Criteria for Laboratory Parameters

Non-fasting glucose (mmol/L)	Percent decrease from baseline ≥ 33 & absolute value < 3.05 mmol/L Percent increase from baseline ≥ 50 & value > 8.88 mmol/L
Creatinine (umol/L)	Percent increase from baseline >= 66 & absolute value > 99 umol/L
Albumin (g/L)	Decrease ≥ 10 & Value < 25
BUN/Urea (mmol/L)	Percent increase ≥ 66 & Value > 14.28
Alkaline phosphatase (U/L)	Percent increase ≥ 100 & Value >250
Sodium (mmol/L)	(Increase ≥ 10 & Value >150) OR (Decrease ≥ 10 & Value < 120)
Potassium (mmol/L)	(Increase ≥ 0.8 & Value > 5.5) OR (Decrease ≥ 0.8 & Value < 3.0)
Chloride (mmol/L)	Value < 85 OR Value > 120
Calcium (mmol/L)	(Increase ≥ 0.37 & Value > 2.62) OR (Decrease ≥ 0.37 & Value < 1.87)
Phosphorus (mmol/L)	(Increase ≥ 0.81 & Value >1.94) OR (Decrease ≥ 0.32 & Value < 0.65)
Total protein (g/L)	Value < 45 OR Value > 100

6.3. Vital Signs and Physical Examination Findings

Weight and weight changes from baseline will be summarized at each visit time point through Week 24.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1.1. Pharmacokinetics and Immunogenicity

At baseline, blood samples for measuring serum concentrations of Ustekinumab, and antibodies to Ustekinumab will be drawn before the IV infusion (for PK and antibodies) and approximately60 minutes after completion of the IV infusion (for PK only). All other blood samples will be collected before administration of the study intervention at scheduled visits as indicated in the Time and Events Schedule in the protocol.

Serum concentrations and antibodies to study agent will be assessed at the following timepoints:

- Serum concentrations:
  - Ustekinumab — Weeks 0, 8, 16, 24, and early termination if applicable

- Antibodies to study agent:
  - Ustekinumab — Weeks 0, 8, 16, 24, and early termination if applicable

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

7.1.2. Pharmacokinetic and Immunogenicity Analyses

The PK analysis will be based on subjects who received at least 1 administration of study agent and had at least one valid blood sample drawn for serum concentrations. No imputation of missing concentration data will be performed; that is, data summaries will be based on the observed data.

If there were multiple samples collected prior to an injection, the closest sample before the injection will be used. If a sampling time or an injection time was missing, the date will be used. If sampling date was the same as the injection date, the sample will be included in the statistical summary.

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

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

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

7.2. Biomarker

The goal of the biomarker analyses is to examine the biologic response to treatment and to identify biomarkers that are relevant to Ustekinumab treatment and/or CD. Assessment will be performed including:

1. To understand the molecular effects of Ustekinumab.
2. To understand CD pathogenesis.
3. To understand why an individual may respond differently to Ustekinumab.

7.2.1. 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.

7.2.2. Whole Blood-based Biomarkers

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

The biomarker results will be reported in a separate report.

REFERENCES

1. Ali T, Madhoun MF, Orr WC, et al. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. Inflamm Bowel Dis 2013;19:2440-2443.

2. American Red Cross. Blood donation information website. http://www.redcrossblood.org/learn-about blood/blood-facts-and-statistics. Accessed 20 November 2017.

3. Anathakrishnan AN, Long MD, Martin CF, et al. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. Clin Gastroenterol Hepatol 2013;11:965-971.

4. Cella D, Riley W, Stone A, et al, on behalf of the PROMIS Cooperative Group. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks. J Clin Epidemiol 2010;63:1179-1194.

5. Cosnes J, Cattan S, Blain A et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis 2002;8:244-250.

6. Feagan BG, Sandborn WJ, Gasink C, et al, for the UNITI–IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med 2016; 375:1946-1960.

7. Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. Gastroenterology 2013;145:996–1006.

8. http://www.shelbypsych.com/Forms/Pre-treatment%20symptom%20profile.pdf ; last accessed 10/17/2017.

9.https://view.officeapps.live.com/op/view.aspx?src=http%3A%2F%2Fwww.reillyassociates.net%2FEnglish-UK-WPAI-CD-eDiary-.doc; last accessed 7/26/2017.

10. 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.

11. Panaccione R, Ghosh S. O ptimal use of biologics in the management of Crohn's disease. Ther Adv Gastroenterol 2010;3:179-189.

12. Stelara® (Ustekinumab) package insert. Horsham, PA: Janssen Research and Development; 2017.

13. van Langenberg DR, Papandony MC, Gibson PR. Sleep and physical activity measured by accelerometry in Crohn's disease. Aliment Pharmacol Ther 2015;41:991-1004.

14. Vergara-Gomez M, Montserrat A, Casellas F. Clinical outcomes assessment: A new validation of the Spanish Work Productivity and Activity Impairment Questionnaire—Crohn's Disease Version. Value in Health. 2011:859 – 861. Published by Elsevier Inc. doi:10.1016/j.jval.2011.02.1179

15. Yanai H, Hanauer S. Assessing response and loss of response to biological therapies in IBD. Am J Gastroenterol 2011;106:685-698

ATTACHMENTS

ATTACHMENT 1: SAMPLE INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

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

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

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

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

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

EXAMPLE

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

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

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel

problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ATTACHMENT 2: 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)

ATTACHMENT 3: STANDARD WEIGHT TABLE

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

ATTACHMENT 4: PROTOCOL-PROHIBITED MEDICATIONS

a. Immunomodulatory agents other than 6-MP, AZA or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil).

b. Immunomodulatory biologic agents (including but not limited to TNF antagonists, vedolizumab, natalizumab, abatacept).

c. Experimental or investigational Crohn's disease medications (including but not limited to thalidomide, briakinumab, traficet, AMG 827).

ATTACHMENT 5: CONCOMITANT CORTICOSTEROIDS AND IMMUNOMODULATOR CHANGE

Corticosteroid agents:

a. Receiving oral corticosteroids (excluding budesonide) at a dose of > 5 mg/day (prednisone equivalent) above the baseline dose for more than 3 consecutive days within 30 days prior to Week 16 due to worsening Crohn's disease. This includes initiation of oral corticosteroids for subjects who were not receiving oral corticosteroids at baseline of this study.

b. Receiving oral budesonide at dose of >= 3 mg/day above the baseline dose for more than 3 consecutive days within 30 days prior to Week 16 due to worsening Crohn's disease. This includes initiation of oral budesonide for subjects who were not receiving oral budesonide at baseline.

c. Receiving oral corticosteroids (excluding budesonide) at a dose of > 5 mg/day (prednisone equivalent) above the baseline dose for more than any 7 days in total within 30 days prior to Week 16 due to reasons other than worsening Crohn's disease. This includes initiation of oral corticosteroids for subjects who were not receiving oral corticosteroids at baseline.

d. Receiving oral budesonide at dose of >= 3 mg/day above the baseline dose for more than any 7 days in total within 30 days prior to Week 16 due to reasons other than worsening Crohn's disease. This includes initiation of oral budesonide for subjects who were not receiving oral budesonide at baseline.

e. Initiation IV corticosteroids within 30 days prior to Week 16 due to worsening Crohn's disease.

Immunomodulator agents:

a. Initiation of oral 6-MP/AZA due to worsening Crohn's disease during study and the total receiving days within 90 days prior to Week 16 are more than 14 days.

b. Initiation of oral, subcutaneous, or intramuscular MTX due to worsening Crohn's disease during study and the total receiving days within 90 days prior to Week 16 are more than 14 days.

ATTACHMENT 6: Statistical Hypothesis

Hypothesis	Control
Primary Endpoints	
H1. Ustekinumab IV re-induction is superior to the continuous SC q8w as assessed by the proportion of subjects achieving a clinical response at Week 16 ***(primary hypothesis)***	Controlled as in figure 1
Major Secondary Endpoints	
H2. Ustekinumab IV re-induction is superior to the continuous SC q8w as assessed by proportion of subjects who achieved a clinical remission at Week16	Controlled as in figure 1
H3. Ustekinumab IV re-induction is superior to the continuous SC q8w as assessed by proportion of subjects who achieved a clinical response at Week 8	Controlled as in figure 1
H4. Ustekinumab IV re-induction is superior to the continuous SC q8w as assessed by proportion of subjects who achieved a clinical remission at Week8	Controlled as in figure 1
H5. Ustekinumab IV re-induction is superior to the continuous SC q8w as assessed by proportion of subjects who achieved Normalization of CRP and/or FeCa concentration at Week 16	Controlled as in figure 1