

Janssen Research & Development *

Statistical Analysis Plan

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

Protocol CNTO1275CRD3007; Phase 3b

**Stelara® (ustekinumab), Humira® (adalimumab)
Version: Final**

Status: Approved
Date: 16 December 2020
Prepared by: Janssen Scientific Affairs, LLC.
Document No.: EDMS-ERI-159815779, 1.0

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-thioguanine
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
WPAI	Work Productivity and Activity Index

DEFINITIONS OF TERMS

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

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods to compare the efficacy and safety of ustekinumab to that of Adalimumab in the Treatment of Biologic Naïve Subjects with Moderately-to-Severely Active Crohn's Disease.

1.1. Trial Objectives

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

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

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

1.2. Trial Design

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

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

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

At Week 0, after all study-related procedures have been completed, subjects will be randomized to one of two groups to receive the following:

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

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

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

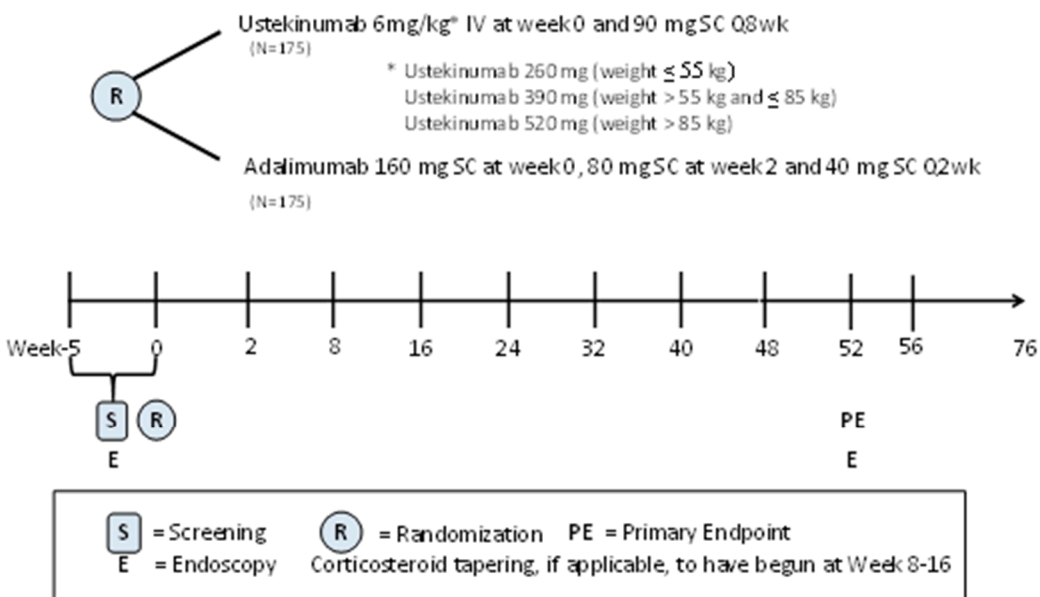
All SC study agent administrations at Weeks 0 and 2 will be performed (or supervised) by an unblinded study site staff member. At these visits, subjects will be trained to self-administer SC study agent by the unblinded study site staff member for subsequent study agent administrations. The blinded,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

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

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

Study assessments include CDAI, video ileocolonoscopy; CD-related healthcare utilization (eg, CD-related hospitalizations, surgeries, ER visits, radiology examinations, initiation of biologic treatment outside of that provided by protocol); PROs (IBDQ, PROMIS-29, and WPAI); laboratory evaluations (including hematology, chemistry, CRP, pregnancy tests, and fecal calprotectin); biomarkers; physical examinations; vital signs; weight; review of concomitant medications and adverse events (AEs); and evaluation of serum concentrations of study agent as well as development of antibodies to study agent.

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

Figure 1 Schematic Overview of the Study

1.3. Statistical Hypotheses for Trial Objectives

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

1.4. Sample Size Justification

The assumptions that form the basis for sample size and power calculations incorporated into this protocol to support this primary endpoint were based on available Phase 3 registrational studies. For ustekinumab, induction data from the UNITI-2 study and maintenance results from IM-UNITI were utilized, focusing on the anti-TNF-naïve subset of subjects.¹⁰ For adalimumab assumptions, data from the open-label induction and then maintenance phase of the CHARM⁴ study were utilized, again focusing on the anti-TNF naïve subset of subjects.

In the UNITI-2 trial, 58% of subjects who were anti-TNF naïve responded to induction with ~6 mg/kg IV ustekinumab.¹⁰ Among ustekinumab induction responders, 65% were in remission at Week 44 on 90 mg SC q8w (ie, 38% of the original treated subjects [58% x 65%]). In order to model a treat-through study-design, the subjects who were initial non-responders to ustekinumab induction were also incorporated into the estimates. Among the remaining 32% of initial anti-TNF naïve UNITI-2 recipients of IV ustekinumab, 42% of these ustekinumab induction non-responders were in remission at Week 44 (ie, 18% of the original treated patients [32% x 42%]). Thus, the overall estimate for remission after one year of treatment in the proposed study is 38% + 18%, or **56%** of all treated subjects for the ustekinumab group.

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

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

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

Table 1 Power to detect a treatment effect based on different proportions of subjects achieving clinical remission at Week 52 (n=175 each group)

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

1.5. Randomization and Blinding

Treatment Allocation

Allocation to treatment group will be performed using a central randomization center by means of an Interactive Web Response System (IWRS). Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared under the supervision of the sponsor. Permuted block randomization with stratification variables including the use of steroids at baseline (Yes, No), CDAI score at baseline (≤ 300 or > 300), and ulcerations >5 mm (Yes, No) will be used.

Blinding

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

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

The ustekinumab and adalimumab placebo syringes will be packaged in containers identical outward appearance; however, the adalimumab and ustekinumab syringes themselves are not exactly identical. For that reason, the investigator site personnel will not be allowed to see the syringes out of the study agent containers and subjects will be instructed to not discuss the syringes with them. To maintain the blind, at Weeks 0 and 2, study agent will be administered at the study site under the supervision of a site staff member who is not otherwise a part of the study team and is unblinded to study agent, also serving as a means to train subjects as to how to properly administer subsequent injections to themselves, eg at home. After Week 2, subjects will self-administer study agent out of sight of the investigator staff. At no time should the site personnel see the syringes themselves, either full or empty. The unblinded site personnel and subjects will track the use of study agent by affixing the (blinded) tear-off labels from the study agent container to the subject's source documents or diary; after Week 2, this will be monitored by study site personnel to assess compliance and perform study agent reconciliation.

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

administration at Week 56). In these cases, this information will not be shared with the sponsor study team.

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, 2, 8, 16, 24, 32, 40, 48, 52 (primary endpoint), and 56, with a final follow-up telephone call (or on-site, if preferred) visit at Week 76.

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

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 2]	[10 to 18]	[14]
		[1]	[4]	[Week 8]	[48 to 64]	[56]
		[1]	[5]	[Week 16]	[104 to 120]	[112]
		[1]	[6]	[Week 24]	[160 to 176]	[168]
		[1]	[7]	[Week 32]	[216 to 232]	[224]
		[1]	[8]	[Week 40]	[272 to 288]	[280]
		[1]	[9]	[Week 48]	[328 to 344]	[336]
		[1]	[10]	[Week 52]	[345 to 383]	[364]
		[1]	[11]	[Week 56]	[384 to 400]	[392]
telephone call or on-site		[1]	[12]	[Week 76]	[524 to 540]	[532]

*Relative to week0. At Week 52, the window could be extended to \pm 19 days for analysis purpose only.

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

Baseline disease characteristics:

- Crohn's disease duration (years) (<2 years, ≥ 2 to <5 years, or ≥ 5 years)
- Involved gastrointestinal areas (ileum only, colon only, ileum & colon)
- CDAI score (≤ 300 or > 300)
- 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)
- Narcotic pain medications (receiving, not receiving)

Prior history of CD medication:

- Received conventional immunomodulators (Yes, No)
- Failed/intolerant to conventional immunomodulators only
- Failed/dependent/intolerant to corticosteroids only
- Failed/intolerant to conventional immunomodulators and Failed/dependent/intolerant to corticosteroids

Surgery history:

- Prior intra-abdominal surgeries
 - 0 (i.e. NO prior intra-abdominal surgeries)
 - ≥ 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
 - Mild (3-6)
 - Moderate (7-16)
 - Severe (>16)
- Ulceration location
 - Ileum only
 - Colon only
 - Ileum and colon
- Maximum ulceration size
 - ≤ 5 mm
 - > 5 mm

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 \geq 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

No formal interim analysis is planned. 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)	
Height (cm)	
Categorical Variables:	
Age (\leq median age, $>$ median age)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Weight (\leq 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)	

^aIf multiple race categories are indicated, then Race is recorded as “Multiple.”

In addition, the histogram plots for the distributions of age at baseline will be provided.

4.1.2. Baseline Characteristics

Crohn’s disease baseline disease characteristics (i.e., Crohn’s disease duration [years], surgery history, baseline endoscopy information, age at diagnosis [years], baseline CDAI scores, baseline SES-CD score [0-56], baseline CRP and Fecal Calprotectin, baseline IBDQ [32-224], baseline PROMIS-29 and baseline WPAI-CD) will be summarized for the full analysis set.

4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized overall.

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 completing the final follow-up

- 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 52 and through week 76 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

4.3. Treatment Compliance

Study agent compliance with the dose missing numbers (1, 2, 3, more than 3) will be summarized descriptively through Week 56 for the full analysis set.

4.4. Extent of Exposure

The exposure data will be summarized through Week 56. The number 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

4.5. 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 database lock and the subjects with major protocol deviations will be summarized by category through Week 52 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.

4.6. 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 IV/oral corticosteroids or other non-biologic systemic therapies will be summarized by treatment groups. In addition, reasons for which subjects discontinued previous therapies (contraindication, inadequate response, intolerance [ie, AEs], or other) will be summarized.

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 (ustekinumab treatment and adalimumab treatment). 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.

Analyses suitable for categorical data (e.g. Cochran-Mantel-Haenszel chi-square tests, or logistic regression, as appropriate) will be used to compare the proportions of subjects achieving selected endpoints (e.g., clinical remission). In cases of rare events, Fisher's exact test will be used for treatment comparisons. Continuous response parameters will be compared using 2-sided analysis of variance on the van der waerden normal scores.

5.2. Analysis Specifications

5.2.1. Level of Significance

Unless otherwise specified, a 2-sided significance level of 5% will be used. A testing procedure is specified to control the overall Type 1 error rate for the primary and major secondary endpoints.

In order to control the overall Type 1 error rate, the primary endpoint and major secondary endpoints will be tested in a hierarchical fashion. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive, and the subsequent endpoint(s) will be tested only if the preceding endpoint in the hierarchy is positive (the order of major secondary endpoints is specified in Section 5.4). In particular, the proportion of subjects achieving corticosteroid-free remission at Week 52 in Ustekinumab group will first be compared with that in the Adalimumab group at the 2-sided 0.05 level of significance. If the proportion of subjects with corticosteroid-free remission is significantly different between the Ustekinumab group and the Adalimumab group, then clinical response at week 52 will be compared at the 2-sided 0.05 level of significance. If significant, PRO-2 symptom remission at Week 52 will be compared at the 2-sided 0.05 level of significance. If significant, clinical remission at week 16 will be compared at the 2-sided 0.05 level of significance. If significant, endoscopic remission at week 52 will be compared at the 2-sided 0.05 level of significance as well.

For other endpoints, the testing will be performed 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.

5.3. Primary Endpoint Analysis

5.3.1. Definition of Endpoint

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

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. Note that at each visit, the most recent hematocrit value (central laboratory) before the current visit will be used for the calculation of CDAI. 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.

The CDAI score will only be calculated for a visit if ≥ 4 of the 8 components are available at that visit. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last non-missing component, with the exception of missing value of hematocrit. For hematocrit, for missing values 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. The weight component of the CDAI will be based on the standard weight table ([Attachment 5](#)).

If the CDAI score cannot be calculated (ie, < 4 components available) at a visit, the CDAI score will be considered missing.

5.3.2. Primary Estimand (Estimand 1)

The primary estimand, i.e. a precise definition of the primary targeted treatment effect, is defined by the following 5 attributes:

Treatments by Week 52:

- Ustekinumab group
- Adalimumab group

Population: biologic naïve subjects with moderately-to-severely active CD who have previously failed or were intolerant to conventional therapy (corticosteroids and/or oral immunomodulators).

Variable (Endpoint): the proportion of subjects with clinical remission (defined as a CDAI score < 150) at Week 52.

Intercurrent Events and Corresponding Strategies:

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. A concomitant change in immunomodulator agents ([Attachment 6](#))
4. A change in concomitant medications except immunomodulator agents ([Attachment 7](#))
5. Discontinuation of study agent due to COVID-19.
6. Discontinuation of study agent due to reasons other than lack of efficacy or an AE of worsening Crohn's disease or COVID-19

Intercurrent events (ICEs) in categories 1-4 will be handled by the composite strategy, and ICE category 5 and 6 will be handled by the treatment policy strategy. The estimand for the primary endpoint acknowledge that having an intercurrent event in categories 1-4 is an unfavorable outcome. If a subject had any of the ICE categories 1-4 prior to Week 52, the subject will be considered not to be in **clinical remission** at Week 52. For subjects experiencing ICE 5 and 6, observed values of the variable will be used to determine remission/non-remission status.

Population-level summary: Difference in percentage of subjects who achieved clinical remission at Week 52 between Ustekinumab group and Adalimumab group

5.3.3. Analysis Methods for the Primary Estimand

5.3.3.1. Estimator (Analysis) for the Primary Estimand

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 analysis, the number and proportion of subjects achieving a clinical remission (defined as a CDAI score < 150) at Week 52 will be summarized. The clinical remission 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 collects after experiencing ICE1-4, subject will be considered not having clinical remission regardless of their CDAI score. A subject experiencing ICE 5 and 6 will use their observed data on CDAI scores through Week 52 (if available), If the CDAI score cannot be calculated (ie, <4 components available) at Week 52, the CDAI score will be considered missing for Week 52. Subjects who have a missing CDAI score at Week 52 (after accounting for the intercurrent events) will be considered not to be in clinical remission as measured by the CDAI score (ie, Nonresponder Imputation (NRI)). The endpoint will be compared between the ustekinumab treatment group and the adalimumab treatment group using 2-sided Cochran-Mantel Haenszel-chi-square test, stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No) at a significance level of 0.05. 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.

5.3.4. Supplementary Estimands for the Primary Endpoint

5.3.4.1. Estimand 2

The attributes of this supplementary estimand are the same as those for the primary estimand with the exception of the ICE strategy, which are described as follows:

ICE strategy: ICEs 1,2, and 4 are addressed by the composite strategy. ICEs 3,5, and 6 are handled by treatment policy strategy.

5.3.4.2. Estimand 3

The attributes of this supplementary estimand are the same as those for the primary estimand with the exception of the ICE strategy, which are described as follows:

ICE strategy: ICEs 1-4 are addressed by the composite strategy. Intercurrent event 5 is addressed by the hypothetical strategy: as if subjects would have not experienced this intercurrent event. This supplementary estimand defines the treatment effect as if the treatment was taken as directed and no intercurrent event would have occurred; therefore, CDAI data at all visits after a intercurrent event will be set to missing and subject will be considered as not having clinical remission after

intercurrent event(discontinuation of study agent due to COVID-19). ICE 6 is handled by treatment policy strategy.

5.3.4.3. Estimand 4 and 5

Supplementary estimand 4 will be assessed using the full analysis set but excluding randomized, never treated subjects. Supplementary estimand 5 will be analyzed using the full analysis but excluding subjects if they have a missing CDAI score at Week 52 (ie, < 4 components of the CDAI score are available at Week 52). The attributes of supplementary estimands 4 and 5 are the same as those for the primary estimand.

5.3.4.4. Estimator (Analysis) for the Supplementary Estimands of the Primary Endpoint

The same analysis methods for the primary Estimand (Estimand 1) described in section 5.3.3.1 will be used for Estimands 2-5. But ICE strategies in section 5.3.4.2 and 5.3.4.3 will be applied on estimands 2 and 3.

5.3.5. Sensitivity Analysis for the Primary Estimand

To assess the robustness of the primary estimand analysis, A sensitivity analysis for primary estimand will use the same attributes as those for primary defined in Section 5.3.2. However, missing CDAI will be imputed by having their last observed value carried forward and same ICE strategies as those for primary estimand will be used on imputed CDAI score for primary estimand.

5.3.6. 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 using the primary estimand in section 5.3.2 when the number of subjects in the subgroups permits. The same ICE strategies will be applied as were used for the primary estimand. The odds ratios of ustekinumab group vs. adalimumab and corresponding 95% confidence intervals will be provided for each of the subgroups in Section 2.4.

5.3.7. Summary of Analyses Related to the Primary Endpoint

Table 4 Summary of Analyses Related to the Primary Endpoint Table 2: Summary of Analyses Related to the Primary Endpoint of Clinical Remission at Week 52

Analysis (Analysis Set)	Missing data	Analysis method/Summary statistics
Analyses based on Primary Estimand , where ICEs 1-4(CD related surgery, discontinuation of study agent due to an AE of worsening CD or due to lack of efficacy, concomitant immunomodulator change and change in concomitant medications except immunomodulator) are handled by the composite strategy. ICEs 5-6(, discontinuation of study agent due to COVID-19 and discontinuation of study agent due to reasons other than lack of efficacy or an AE of worsening Crohn’s disease or COVID-19) are handled by treatment policy strategy.		
Primary Analysis(Full Analysis Set-FAS)	Missing data due to missed visits or missed data collection (< 4 components of the CDAI score), or due to discontinuation of study intervention related to ICE category 5-6 in the absence of observed data. Subjects with missing data are considered not to be clinical remission	<ul style="list-style-type: none"> Summaries of the proportion of subjects who achieved the endpoint strata adjusted proportion difference (ustekinumab group-adalimumab group) and 95% CI P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No))
Subgroup Analyses (Individual subgroup levels defined in Section 2.4, FAS)	Missing data due to missed visits or missed data collection (< 4 components of the CDAI score), or due to discontinuation of study intervention related to ICE category 5-6 in the absence of observed data. Subjects with missing data are considered not to be clinical remission	<ul style="list-style-type: none"> Summaries of the proportion of subjects who achieved the endpoint Odds ratios and 95% CIs P-value from the logistic regression (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No))
Sensitivity Analysis for Primary Estimand(FAS) Last observation carried forward: subjects who have a missing CDAI score at Week 52 will have their last CDAI score carried forward	For missing CDAI score due to missed visits or missed data collection(< 4 components of the CDAI score), or due to discontinuation of study intervention related to ICE category 5-6 in the absence of observed data, CDAI score will have their last non-missing value carried forward. If any of ICE 1-4 occurs prior to week 52, then subject is considered as not to be clinical remission at week 52. Otherwise, clinical remission status will be determined by observed or carried forward CDAI score.	<ul style="list-style-type: none"> Summaries of the proportion of subjects who achieved the endpoint strata adjusted proportion difference (ustekinumab group-adalimumab group) and 95% CI P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No))
Analyses based on Supplementary Estimand 2 , where ICEs 1,2, and 4 are addressed by the composite strategy. ICEs 3,5, and 6 are handled by treatment policy strategy.		

Analysis (Analysis Set)	Missing data	Analysis method/Summary statistics
Supplementary Analysis 1 (FAS)	Missing data due to missed visits or missed data collection (< 4 components of the CDAI score), or due to discontinuation of study intervention related to ICE category 5-6 in the absence of observed data. Subjects with missing data are considered not to be clinical remission	<ul style="list-style-type: none"> Summaries of the proportion of subjects who achieved the endpoint strata adjusted proportion difference (ustekinumab group-adalimumab group) and 95% CI P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No))
Analyses based on Supplementary Estimand 3 , where ICEs 1-4 are addressed by the composite strategy. ICE 5 is addressed by the hypothetical strategy. ICE 6 is handled by treatment policy strategy.		
Supplementary Analysis 2 (FAS)	Missing data due to missed visits or missed data collection (< 4 components of the CDAI score), or due to discontinuation of study intervention related to ICE category 6 in the absence of observed data. , CDAI data after discontinuation of study agent due to COVID-19 will be set to missing. Subjects with missing data are considered not to be clinical remission	<ul style="list-style-type: none"> Summaries of the proportion of subjects who achieved the endpoint strata adjusted proportion difference (ustekinumab group-adalimumab group) and 95% CI P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No))
Analyses based on Supplementary Estimand 4-5 , ICEs 1-4 are addressed by the composite strategy. ICEs 5 and 6 are handled by treatment policy strategy.		
Supplementary Analysis 3 Full Analysis Set excluding Randomized, never treated subjects	Missing data due to missed visits or missed data collection (< 4 components of the CDAI score), or due to discontinuation of study intervention related to ICE category 5-6 in the absence of observed data. Subjects with missing data are considered not to be clinical remission.	<ul style="list-style-type: none"> Summaries of the proportion of subjects who achieved the endpoint strata adjusted proportion difference (ustekinumab group-adalimumab group) and 95% CI P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No))
Supplementary Analysis 4 Observed case: Full Analysis Set- Exclude subjects from the analysis if they have a missing CDAI score at week 52(ie. < 4 components of the CDAI score are available at Week 52)	No missing data on CDAI at Week 52	<ul style="list-style-type: none"> Summaries of the proportion of subjects who achieved the endpoint strata adjusted proportion difference (ustekinumab group-adalimumab group) and 95% CI P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No))

5.4. Major Secondary Endpoints Analyses

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

1. Corticosteroid-free remission at Week 52
2. Clinical response at Week 52
3. PRO-2 symptom remission at Week 52
4. Clinical remission at Week 16
5. Endoscopic remission at Week 52

5.4.1. Definitions of Major Secondary Endpoints

The proportion of subjects with:

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

Video Ileocolonoscopy

During the screening period, prior to randomization, all subjects will have an ileocolonoscopy performed, including attempts at intubation of the terminal ileum, which will be video-recorded for subsequent central reading and scoring. Investigators will determine enrollment eligibility at the screening colonoscopy, based upon presence of ulcerations in at least one segment and also note whether or not any of the ulcers present exceed 0.5 cm in diameter. At Week 52, within a window of 50 to 54 weeks, all subjects remaining in the study will undergo a second ileocolonoscopy (due to Covid-19, we extended the window up to 12 weeks after Week 52 visit for second ileocolonoscopy). Subjects who do not remain in the study at Week 52 (due to discontinuation of study agent and/or termination of study participation) will instead have their follow-up ileocolonoscopy at the early termination visit. All of these procedures will be video-recorded, following the more detailed directions provided in the separate study reference (or ileocolonoscopy) manual.

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

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 5. The total SES-CD score ranges from 0 to 56.

Table 5 Sample score sheet and scoring definitions for the Simple Endoscopic Score for Crohn's Disease (SES-CD)

	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 (\varnothing 0.1 – 0.5 cm)	Large ulcers (\varnothing 0.5 – 2.0 cm)	Very large ulcers (\varnothing > 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.

\varnothing =Diameter.

Calculation of the SES-CD score:

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 segment is scored) at a visit, the total SES-CD score will be considered missing.

5.4.2. Estimands for the Major Secondary Endpoints

The following describes the attributes of the estimands for the major secondary endpoints (corresponding to Estimands 6-10):

Treatments (for Estimands 6-10) Same as Estimand 1:

- Ustekinumab group
- Adalimumab group

Population (for Estimands 6-10): Biologic naïve subjects with moderately-to-severely active CD who have previously failed or were intolerant to conventional therapy (corticosteroids and/or oral immunomodulators).

Variables and Population-level Summary (for Estimands 6-10)

Table 6 Variables and Population-level Summary for the estimand for each Major Secondary Endpoint

Estimand	Variable (Endpoint)	Population-level summary
6	Corticosteroid-free remission at Week 52 (CDAI score <150 and not taking any corticosteroids for at least 30 days prior to Week 52).	Difference in percentage of subjects who achieved Corticosteroid-free remission at Week 52 between Ustekinumab group and Adalimumab group
7	Clinical response at Week 52 (≥ 100 -point reduction from baseline in CDAI score or CDAI score <150).	Difference in percentage of subjects who achieved clinical response at Week 52 between Ustekinumab group and Adalimumab group
8	PRO-2 symptom remission at Week 52 (an abdominal pain [AP] mean daily score at or below 1 and stool frequency [SF] mean daily score at or below 3, ie, $AP \leq 1$ and $SF \leq 3$)	Difference in percentage of subjects who achieved PRO-2 symptom remission at Week 52 between Ustekinumab group and Adalimumab group
9	Clinical remission at Week 16 (CDAI score <150).	Difference in percentage of subjects who achieved clinical remission at Week 16 between Ustekinumab group and Adalimumab group
10	Endoscopic remission at Week 52 (SES-CD score ≤ 3 , or SES-CD =0 for subjects who enter the study with an SES-CD =3).	Difference in percentage of subjects who achieved endoscopic remission at Week 52 between Ustekinumab group and Adalimumab group

Intercurrent Events and Corresponding Strategies:

The intercurrent events and ICEs strategy for all major secondary endpoints are the same as those used in the primary estimand. The estimand for the major secondary endpoints

acknowledge that having an intercurrent event in categories 1-4 is an unfavorable outcome. If a subject had any of the ICE categories 1-4 prior to Week 52, the subject will be considered not to be in **Corticosteroid-free remission, clinical response, PRO-2 symptom remission or endoscopic remission at week 52**. If a subject had any of the ICE categories 1-4 prior to Week 16, the subject will be considered not to be in **clinical remission at week 16**. For subjects experiencing ICE 5 and 6, observed values of the variable will be used for all major secondary endpoints, if available.

5.4.3. Analysis Methods for the Estimands for the Major Secondary Endpoints

5.4.3.1. Main Estimators (Analyses) for the Estimands 6-10

The major secondary endpoints, defined in Section 5.4.1, will be compared between Ustekinumab and Adalimumab and will use the full analysis set and the estimands defined in Section 5.4.2. The estimands will be estimated by differences between Ustekinumab and Adalimumab in the percentages of subjects who meet each endpoint and their associated 95% CIs. In addition, each endpoint will be compared between Ustekinumab and Adalimumab using the CMH chi-square test (2-sided) stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No), at a significance level of 0.05. The 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. Abdominal pain and stool frequency are 2 components of CDAI score. 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 16/52, the CDAI score will be considered missing for Week 16/52. Subjects who have a missing CDAI score at Week 16/52 will be considered not to be in clinical remission or clinical response as measured by the CDAI score (ie, Nonresponder Imputation (NRI)).

The SES-CD score will be calculated based on the approach specified in Section 5.4.1. If SES-CD score is missing at Week 52, the subject will be considered not to have achieved endoscopic remission at Week 52.

5.4.4. Supplementary Estimands for the Endoscopic Remission at Week 52

5.4.4.1. Supplementary Estimands 11-14

Supplementary estimands 11-14 for the Endoscopic Remission will be used to complement Estimand 10 (Endoscopic Remission). The attributes of the supplementary estimands are the same as those for the main estimands for endoscopic remission. However, supplementary estimands 11-14 use different analysis set with main estimand for endoscopic remission.

Supplementary estimand 11 will be assessed using the full analysis but excluding subjects whose endoscopic records were out of Week 52 visit window. Supplementary estimand 12 will be analyzed using the full analysis set but excluding subjects if they have a missing SES-CD score

at Week 52. Supplementary estimand 13 will be assessed using the full analysis but excluding subjects who are missing SES-CD score due to COVID-19 at Week 52. Supplementary estimand 14 will be analyzed using the full analysis set but excluding subjects who have Week 52 visit but missing SES-CD score at Week 52.

5.4.4.2. Estimators for Endoscopic remission (Supplementary Estimand 11-14) at Week 52

The same analysis methods for the main estimand 10 (endoscopic remission) described in sections 5.4.3.1 will be used for the supplementary estimands 11-14. Endoscopic remission at Week 52 will be compared between Ustekinumab group and Adalimumab group and will use three different analysis data set specified in section 5.4.4.1. The estimands will be estimated by difference in the strata adjusted percentage of subjects who achieve endoscopic remission at Week 52 between Ustekinumab and Adalimumab and the associated 95% CI. Endoscopic remission at Week 52 will be compared between Ustekinumab and Adalimumab using the CMH chi-square test (2-sided) stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No), at a significance level of 0.05.

5.4.5. Summary of Analyses Related to Major Secondary Endpoints

Table 7 below provides an overview of all the analyses related to the major secondary endpoints, the estimands, the analysis sets, the data handling rules to be used, and the analysis methods and summary statistics.

Table 7: Summary of Analyses Related to Major Secondary Endpoints

Endpoints (Analysis Set)	Missing data	Analysis method/Summary statistics
<u>Analyses based on Main Estimands 6-10</u> where ICEs 1-4 are handled by the composite strategy and ICEs 5-6 are handled by treatment policy strategy.		
<ul style="list-style-type: none"> Corticosteroid-free Remission at Week 52 (FAS) Clinical Response at Week 52 PRO-2 symptom remission at Week 52 Clinical Remission at Week 16 (Full Analysis Set for all endpoints above) Endoscopic Remission at Week 52 (Subjects with SES-CD Score ≥ 3 at Baseline in Full Analysis Set) 	Missing data due to missed visits or missed data collection, or due to discontinuation of study intervention related to ICE category 5 and 6 in the absence of observed data. Subjects with missing data are considered to be non-responders (NRI)	<ul style="list-style-type: none"> Summaries of the proportion of subjects who achieved the endpoint Treatment difference (Ustekinumab group and Adalimumab group) and 95% CI P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No)).
<u>Analyses based on Supplementary Estimands 11-14</u> where ICEs 1-4 are handled by the composite strategy and ICEs 5-6 are handled by treatment policy strategy.		

Table 7: Summary of Analyses Related to Major Secondary Endpoints

Endpoints (Analysis Set)	Missing data	Analysis method/Summary statistics
Supplementary Estimand 11 Endoscopic Remission at Week 52 (Subjects with SES-CD Score ≥ 3 at Baseline in Full Analysis Set excluding subjects whose endoscopic records were out of Week 52 visit window)	Missing data due to missed visits or missed data collection, or due to discontinuation of study intervention related to ICE category 5 and 6 in the absence of observed data. Subjects with missing data are considered to be non-responders (NRI)	<ul style="list-style-type: none"> • Summaries of the proportion of subjects who achieved the endpoint • Treatment difference (Ustekinumab group and Adalimumab group) and 95% CI • P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No)).
Supplementary Estimand 12 Endoscopic Remission at Week 52 (Subjects with SES-CD Score ≥ 3 at Baseline in Full Analysis Set excluding subjects with missing SES-CD score at Week 52)	No missing data on SES-CD	<ul style="list-style-type: none"> • Summaries of the proportion of subjects who achieved the endpoint • Treatment difference (Ustekinumab group and Adalimumab group) and 95% CI • P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No)).
Supplementary Estimand 13 Endoscopic Remission at Week 52 (Subjects with SES-CD Score ≥ 3 at Baseline in Full Analysis Set excluding subjects who are missing SES-CD score due to COVID-19 at Week 52)	Missing data due to missed visits or missed data collection, or due to discontinuation of study intervention related to ICE category 5 and 6 in the absence of observed data. Subjects with missing data are considered to be non-responders (NRI)	<ul style="list-style-type: none"> • Summaries of the proportion of subjects who achieved the endpoint • Treatment difference (Ustekinumab group and Adalimumab group) and 95% CI • P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No)).
Supplementary Estimand 14 Endoscopic Remission at Week 52 (Subjects with SES-CD Score ≥ 3 at Baseline in Full Analysis Set excluding subjects who have Week 52 visit but missing SES-CD score at Week 52)	Missing data due to missed visits or missed data collection, or due to discontinuation of study intervention related to ICE category 5 and 6 in the absence of observed data. Subjects with missing data are considered to be non-responders (NRI)	<ul style="list-style-type: none"> • Summaries of the proportion of subjects who achieved the endpoint • Treatment difference (Ustekinumab group and Adalimumab group) and 95% CI • P-value from the CMH test (stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No)).

5.5. Secondary Endpoints

The secondary endpoints in the following list will be analyzed.

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

5.6. Other Endpoints

Other efficacy endpoint at (or through) Week 52

- The change in CDAI score from baseline at all postbaseline visits through Week 52
- Maintenance of clinical remission, defined as CDAI < 150 at Week 52, among subjects in remission at Week 16
- Maintenance of clinical response, defined as CDAI decreased at least 100 from baseline or CDAI < 150 at Week 52 among subjects in response [CDAI decrease at least 100 points from baseline] at Week 16
- The time to first flare (a flare is defined as an increase in CDAI score of > 100 points at any subsequent visits through Week 52 [based upon loss of clinical response]) among subjects in clinical response at Week 16
- The change from baseline in the sum of the number of stools and the abdominal pain scores in the prior 7 days, compared individually and combined, without weighting, at all postbaseline visits through Week 52 (sum PRO-2)

-
- The change in the weighted (as per the CDAI) sum of the abdominal pain and stool frequency subscores of the CDAI from baseline at all postbaseline visits through Week 52 (PRO-2 weighted)
 - PRO-2 symptom improvement/response, defined as at least a 1 point improvement (or a mean score of zero) in mean daily CDAI AP score from baseline, and also a reduction in stool frequency [SF] mean daily score of 3 or more (or a mean score of zero) from baseline, compared at each visit through Week 52
 - PRO-2 symptom remission, defined as an abdominal pain [AP] mean daily score at or below 1 and a stool frequency [SF] mean daily score at or below 3, ie, $AP \leq 1$ and $SF \leq 3$, compared at each visit through Week 52
 - Abdominal Pain [AP] improvement, defined as a 1 point or greater improvement in mean daily CDAI AP score from baseline, or a mean score of zero, among subjects with mean $AP > 0$ at baseline, compared at each visit through Week 52
 - Reduction in frequency of diarrhea, defined as a reduction of at least 3 (or a mean number < 1) in stool frequency [SF] (i.e. mean daily number of liquid or very soft stools from CDAI in the week prior to the visit) from baseline, among subjects with mean $SF > 1$ at baseline, compared at each visit through Week 52
 - The proportion of subjects with corticosteroid-free response at Week 52 (defined as a CDAI score decrease ≥ 100 from baseline and not taking any corticosteroids for at least 30 days prior to Week 52)
 - The proportion of subjects with corticosteroid-free remission at Week 52 (defined as a CDAI score < 150 and not taking any corticosteroids for at least 30 days prior to Week 52) among subjects who were on corticosteroids at baseline
 - The proportion of subjects with corticosteroid-free response at Week 52 (defined as a CDAI score decrease ≥ 100 from baseline or $CDAI < 150$ and not taking any corticosteroids for at least 30 days prior to Week 52) among subjects who were on corticosteroids at baseline
 - The total number of visits subjects are in steroid-free remission through Week 52
 - The proportion of subjects with endoscopic response (defined as a reduction in SES-CD score by 50% from baseline or $SES-CD \leq 3$ or $SES-CD = 0$ for subjects who enter the study with an $SES-CD = 3$) at Week 52
 - The change from baseline in SES-CD at Week 52
 - The proportion of subjects with endoscopic improvement (change in SES-CD score of at least 3 points) at Week 52
 - The proportion of subjects with a minimum of 25% improvement from baseline in SES-CD score at Week 52
 - The proportion of subjects with fistula resolution (closure of all open/draining perianal/perirectal fistulas) compared at each postbaseline visit through Week 52 among subjects with one or more open/draining perianal or perirectal fistulas at baseline
 - The proportion of subjects with fistula response (defined as closure of 50% of open/draining perianal/perirectal fistulas) compared at each postbaseline visit through Week 52 among subjects with one or more open/draining perianal or perirectal fistulas at baseline

- The change from baseline in CRP concentration at all postbaseline visits through Week 52
- The proportion of subjects with normalization of CRP (defined as ≤ 3 mg/L) compared at each postbaseline visit through Week 52 among subjects with abnormal CRP (> 3 mg/L) at baseline
- The change from baseline in fecal calprotectin concentration, compared at Week 8, 16, and 52
- The proportion of subjects with fecal calprotectin ≤ 250 $\mu\text{g/g}$, compared at Week 8, 16, and 52 among subjects with baseline fecal calprotectin at >250 $\mu\text{g/g}$ at baseline
- The proportion of subjects with fecal calprotectin ≤ 100 $\mu\text{g/g}$ at Week 8, 16 and 52 among subjects with fecal calprotectin >250 $\mu\text{g/g}$ at baseline
- The proportion of subjects with clinical remission and a $\geq 50\%$ reduction from baseline in CRP or fecal calprotectin, compared at Week 8, 16, and 52
- The proportion of subjects with clinical remission and a $\geq 50\%$ reduction from baseline in CRP or fecal calprotectin, compared at Week 8, 16, and 52, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 $\mu\text{g/g}$ at baseline
- The proportion of subjects with clinical and biomarker remission, defined as CDAI < 150 , CRP <3 mg/L, and also fecal calprotectin ≤ 250 $\mu\text{g/g}$, compared at Week 8, 16, and 52, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 $\mu\text{g/g}$ at baseline
- The proportion of subjects with clinical and biomarker response (clinical response and $\geq 50\%$ reduction from baseline in CRP or fecal calprotectin), compared at Week 8, 16, and 52
- The proportion of subjects with clinical and biomarker response (clinical response and $\geq 50\%$ reduction from baseline in CRP or fecal calprotectin) compared at Week 8, 16, and 52, among participants with elevated CRP (>3 mg/L) or fecal calprotectin (>250 $\mu\text{g/g}$) at baseline
- The proportion of subjects with clinical response, CRP <3 mg/L, and fecal calprotectin ≤ 250 $\mu\text{g/g}$ at Week 8, 16 and 52
- The proportion of subjects with clinical response, CRP <3 mg/L, and fecal calprotectin ≤ 250 $\mu\text{g/g}$ at Week 8, 16, and 52, among participants with elevated CRP (>3 mg/L) or fecal calprotectin >250 $\mu\text{g/g}$ at baseline
- The proportion of subjects who are on concomitant narcotic pain medications for CD
- The proportion of subjects able to eliminate concomitant narcotic pain medication use for CD
- The total number of days subjects are off narcotic pain medications for CD through Week 52 among subjects who are on narcotic pain medication for CD at baseline

PRO Endpoints:

- The change from baseline in the IBDQ score (including IBDQ domains), compared at Week 8, 16, and 52
- The proportion of subjects with IBDQ response (≥ 16 -point improvement from baseline), compared at Week 8, 16, and 52
- The proportion of subjects with IBDQ remission (IBDQ score >170), compared at Week 8, 16, and 52

- The change from baseline in the PROMIS-29 domains of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score, Ability to Participate in Social Roles and Activities Score, Physical Function Score, and Pain Intensity Score compared at Week 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a T-score decrease of ≥ 5 in each individual domain of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score at Weeks 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a T-score increase of ≥ 5 in each individual domains of Ability to Participate in Social Roles and Activities Score, and Physical Function Score at Weeks 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a T-score decrease of ≥ 3 in each individual domain of Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score at Weeks 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a T-score increase of ≥ 3 in each individual domain of Ability to Participate in Social Roles and Activities Score, and Physical Function Score at Weeks 8, 16, and 52 (results reported separately for each domain)
- The proportion of subjects with a score decrease of $\geq \frac{1}{2}$ baseline standard deviation in Pain Intensity Score at Weeks 8, 16, and 52
- The proportion of subjects with a T-score decrease of ≥ 5 in Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score and increase of ≥ 5 in Ability to Participate in Social Roles and Activities Score, and Physical Function Score at Weeks 8, 16, and 52 (Results reported as proportion of patients achieving improvement across all domains)
- The proportion of subjects with a T-score decrease of ≥ 3 in Anxiety Score, Depression Score, Fatigue Score, Pain Interference Score, Sleep Disturbance Score and increase of ≥ 3 in Ability to Participate in Social Roles and Activities Score, and Physical Function Score at Weeks 8, 16, and 52 (Results reported as proportion of patients achieving improvement across all domains)
- Change from baseline in combined pain score from PROMIS-29 and number of liquid or soft stools from CDAI, compared at Week 8, 16, and 52
- The change from baseline in the WPAI questionnaire, compared at Week 8, 16, and 52

Healthcare resource utilization endpoints:

- The proportion of subjects with CD-related hospitalization, surgeries, or initiation of non-study alternate biologic for CD through Week 52
- The proportion of subjects with CD-related hospitalization or surgeries through Week 52
- The proportion of subjects initiating a non-study alternate biologic for CD through Week 52
- The proportion of subjects with CD-related hospitalization through Week 52
- The proportion of subjects with CD-related surgeries through Week 52
- The proportion of subjects with a CD-related ER visit through Week 52

- The total number of days a subject has a CD-related hospitalization through Week 52
- The proportion of subjects with an endoscopic procedure related to CD (not protocol-directed) through Week 52

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

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

5.6.1. Definitions**5.6.1.1. Crohn's Disease-related Healthcare Utilization**

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

5.6.1.2. C-reactive Protein and Fecal Calprotectin

C-reactive protein and fecal calprotectin will be evaluated during the study to monitor efficacy.

5.6.1.3. PROs

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

5.6.1.3.1. IBDQ

The IBDQ is a validated disease-specific instrument composed of 32 Likert-scaled items (see [Attachment 1](#)).¹⁶ The total score ranges from 32 to 224 using the 7-point response options, with

higher scores indicating better health-related quality of life. A total IBDQ score > 170 is associated with clinical remission. A change of 16 or more points in the total score is considered clinically meaningful. The IBDQ scale contains 4 component subscales: bowel symptoms, systemic symptoms, emotional function, and social function. Each subscale can be computed with total scores ranging from 10 to 70, 5 to 35, 12 to 84, and 5 to 35, respectively.

5.6.1.3.2. PROMIS-29

The PROMIS-29 Questionnaire will be utilized for this study (see [Attachment 2](#)). PROMIS-29 questionnaires are highly reliable, precise measures of subject-reported health status.¹¹ The PROMIS-29 questionnaire measures physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference. The PROMIS-29 also measures pain intensity on a 10-point scale from no pain (0) to worst pain imaginable (10).¹³

5.6.1.3.3. WPAI-CD

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

The WPAI-CD consists of the following 6 questions:

Q1: currently employed (working for pay)? (yes, no) *If No, skip to Q6.*

Q2: hours missed from work in the past 7 days due to CD? (hours)

Q3: hours missed from work in the past 7 days due to other reasons? (hours)

Q4: hours actually worked in the past 7 days? (hours)

Q5: degree to which CD affected work productivity while at work in the past 7 days? [0 (no effect) to 10 (completely prevented from working)]

Q6: degree to which CD affected regular activities outside of work in the past 7 days? [0 (no effect) to 10 (completely prevented from daily activities)]

Based on the answers to the above 6 questions, 4 types of scores (in percentage) are calculated, with higher scores indicating greater impairment and less productivity, i.e., worse outcomes, as follows. **Note** that for subjects with answer='No' to Q1, only the 4th score (i.e., percent activity impairment outside work due to CD) can be calculated.

1. **Percent work time missed** due to CD (absenteeism): $100 * Q2 / (Q2 + Q4)$
2. **Percent impairment while working** due to CD (presenteeism): $100 * Q5 / 10$
3. **Percent overall work impairment** due to CD (combining absenteeism and presenteeism): $100 * \{ Q2 / (Q2 + Q4) + [(1 - Q2 / (Q2 + Q4)) * (Q5 / 10)] \}$
4. **Percent activity impairment outside work** due to CD: $100 * Q6 / 10$

Change from baseline in WPAI scores measures the change in work productivity and/or activity impairment, where a positive change indicates a worsening and a negative change indicates an improvement.

5.6.2. Analysis Methods

Other endpoints listed and defined in Sections 5.5. and 5.6 above will be analyzed based on the FAS according to randomized treatment group regardless of the treatment actually received.

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. Graphical data displays (e.g., K-M plots) may also be used to summarize the data.

The estimand approach as defined above for the major secondary endpoints (Section 5.4.3) will also be used for these endpoints.

Binary Endpoints

- Subjects who have an intercurrent event in categories 1-4 (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 treatment group and the adalimumab treatment group using 2-sided Cochran-Mantel Haenszel-chi-square test, stratified by corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, No) unless otherwise specified. In case of rare events, Fisher's exact test will be used for treatment comparisons. 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.

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 an intercurrent event in categories 1-4 (as specified in Section 5.3.2). For subjects experiencing an intercurrent event category 5 and 6, their observed values will be used, if available. Missing data for scores will be carried forward from last non-missing observed value prior to missing visits except WPAI endpoints. Observed value will be used in analysis of WPAI endpoints.

The continuous variables (such as changes from baseline and total number of visits) will be compared between the ustekinumab treatment group and the adalimumab treatment group using an analysis of covariance on van der Waerden normal scores with baseline value, corticosteroid status at Week 0 (yes or no), baseline CDAI score (≤ 300 or > 300), and any ulceration > 5 mm (Yes, 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). A survival analysis could be used to analyze the time to first flare. Poisson regression model will be applied to analyze total number of steroid-free remission visits.

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 the safety analysis, 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 52 for the primary endpoint and through Week 76 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)
- Malignancies.

In addition to the summary tables, 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 and direct bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, blood urea nitrogen (BUN)/urea, and creatinine).
- Stool fecal calprotectin
- 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 56 of the study. Markedly abnormal post baseline laboratory values will also be presented in listings.

Markedly abnormal changes from baseline are defined in [Table 8](#). 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 $<100 \times 10^9/L$ 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 8 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
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

6.3. Vital Signs and Physical Examination Findings

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

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1.1. Pharmacokinetics and Immunogenicity

Blood samples for measuring serum concentrations of ustekinumab and adalimumab, and antibodies to ustekinumab and to adalimumab will be collected (before study drug administration) from all subjects 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, 32, 48, 52, and early termination if applicable
 - Adalimumab Weeks 0, 16, 52, and early termination if applicable
- Antibodies to study agent:
 - Ustekinumab Weeks 0, 8, 16, 52, and early termination if applicable
 - Adalimumab Weeks 0, 16, 52, and early termination if applicable

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

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 at least one administration of assigned study agent and have appropriate samples for detection of antibodies to ustekinumab or to adalimumab.

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 adalimumab or ustekinumab treatment and/or CD. Assessment will be performed including:

1. To understand the molecular effects of adalimumab and ustekinumab.
2. To understand CD pathogenesis.
3. To understand why an individual may respond differently to adalimumab or ustekinumab.

7.2.1. Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all subjects. Assays to be performed may include proteins associated with proinflammatory and anti-inflammatory effects, the recruitment and proliferation of cells associated with inflammation and repair, and markers associated with tissue injury or repair. These analyses will include but not be limited to IL-17A and IL-22.

7.2.2. Whole Blood-based Biomarkers

Whole blood samples will be collected from all subjects 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.

8. HEALTH ECONOMICS

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

For each CD related healthcare resource utilization (hospitalizations, surgeries, emergency room [ER] visits or initiation of biologic treatment outside of that provided by protocol), the number and percentage of subjects who experience at least 1 occurrence of the given utilization from baseline through Week 52 or Week 76 will be summarized. In addition, comparisons between assigned treatment groups will be provided if appropriate.

The time to the first Crohn's disease-related utilization through Week 52 will be compared using the Kaplan-Meier method. The time to the first Crohn's disease-related utilization is defined as the number of days elapsed from the date of randomization to the date of the first utilization prior to or at Week 52. Subjects who didn't have CD related healthcare resource utilization prior to Week 52 will be censored at the date of Week 52 visit, date of death, the date of study agent discontinuation prior to Week 52, or the date of last visit prior to Week 52 for those who terminated study participation prior to Week 52, whichever happens first.

No imputation will be performed for missing health economics values, the missing values will remain as missing.

9. REFERENCES

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ATTACHMENTS

ATTACHMENT 1: SAMPLE INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

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Updated from: IBDQ - United Kingdom-English - Version of 09 May 08 - Mapi Research Institute.

ID4529/IBDQ_AU2.0_eng-GB.doc

IBDQ (enGB) 03JUN2016 FINAL – ICON Language Services

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

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

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

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

EXAMPLE

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

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

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

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

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

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

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

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

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

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

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

-
4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
6. How much energy have you had during the last 2 weeks? Please choose an option from
- 1 NO ENERGY AT ALL
 - 2 VERY LITTLE ENERGY
 - 3 A LITTLE ENERGY
 - 4 SOME ENERGY
 - 5 A MODERATE AMOUNT OF ENERGY
 - 6 A LOT OF ENERGY
 - 7 FULL OF ENERGY
7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME

-
8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
11. How often during the last 2 weeks have you been troubled because of fear of not finding a toilet? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME

-
12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from
- 1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
 - 2 A LOT OF DIFFICULTY
 - 3 A FAIR BIT OF DIFFICULTY
 - 4 SOME DIFFICULTY
 - 5 A LITTLE DIFFICULTY
 - 6 HARDLY ANY DIFFICULTY
 - 7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES
13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
14. How often during the last 2 weeks have you had problems getting a good night's sleep or been troubled by waking up during the night? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME

-
16. How often during the last 2 weeks have you had to avoid attending events where there was no toilet close at hand? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of wind? Please choose an option from
- 1 A MAJOR PROBLEM
 - 2 A BIG PROBLEM
 - 3 A SIGNIFICANT PROBLEM
 - 4 SOME TROUBLE
 - 5 A LITTLE TROUBLE
 - 6 HARDLY ANY TROUBLE
 - 7 NO TROUBLE
18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be at? Please choose an option from
- 1 A MAJOR PROBLEM
 - 2 A BIG PROBLEM
 - 3 A SIGNIFICANT PROBLEM
 - 4 SOME TROUBLE
 - 5 A LITTLE TROUBLE
 - 6 HARDLY ANY TROUBLE
 - 7 NO TROUBLE
19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME

-
20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from
- 1 NONE OF THE TIME
 - 2 A LITTLE OF THE TIME
 - 3 SOME OF THE TIME
 - 4 A GOOD BIT OF THE TIME
 - 5 MOST OF THE TIME
 - 6 ALMOST ALL OF THE TIME
 - 7 ALL OF THE TIME
22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME

-
24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the toilet even though your bowels were empty? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME

-
28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from
- 1 NO SEX AS A RESULT OF BOWEL DISEASE
 - 2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
 - 3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
 - 4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
 - 5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
 - 6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
 - 7 NO LIMITATION AS A RESULT OF BOWEL DISEASE
29. How much of the time during the last 2 weeks have you been troubled by nausea or an upset stomach? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME
31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from
- 1 ALL OF THE TIME
 - 2 MOST OF THE TIME
 - 3 A GOOD BIT OF THE TIME
 - 4 SOME OF THE TIME
 - 5 A LITTLE OF THE TIME
 - 6 HARDLY ANY OF THE TIME
 - 7 NONE OF THE TIME

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

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

ATTACHMENT 2: SAMPLE PROMIS-29 QUESTIONNAIRE

PROMIS–29 Profile v2.0

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

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

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PROMIS–29 Profile v2.0

<u>Fatigue</u>						
In the past 7 days...		Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41	How run-down did you feel on average? ...	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
FATEXP40	How fatigued were you on average?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
<u>Sleep Disturbance</u>						
In the past 7 days...		Very poor	Poor	Fair	Good	Very good
Sleep109	My sleep quality was	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
In the past 7 days...		Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116	My sleep was refreshing	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Sleep20	I had a problem with my sleep	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Sleep44	I had difficulty falling asleep	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
<u>Ability to Participate in Social Roles and Activities</u>						
In the past 7 days...		Never	Rarely	Sometimes	Usually	Always
SRPPER11 _CaPS	I have trouble doing all of my regular leisure activities with others	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
SRPPER18 _CaPS	I have trouble doing all of the family activities that I want to do	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
SRPPER23 _CaPS	I have trouble doing all of my usual work (include work at home)	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
SRPPER46 _CaPS	I have trouble doing all of the activities with friends that I want to do	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
<u>Pain Interference</u>						
In the past 7 days...		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PAININ22	How much did pain interfere with work around the home?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PAININ31	How much did pain interfere with your ability to participate in social activities? ..	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
PAININ34	How much did pain interfere with your household chores?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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PROMIS-29 Profile v2.0

Pain Intensity

In the past 7 days...

Global07	How would you rate your pain on average?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		0	1	2	3	4	5	6	7	8	9	10
		No pain										Worst pain imaginable

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ATTACHMENT 3: SAMPLE WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: CROHN'S DISEASE (WPAI-CD)**Work Productivity and Activity Impairment Questionnaire:
CROHN'S DISEASE (WPAI-CD)**

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

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

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

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

_____HOURS

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

_____HOURS

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

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

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

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

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

CIRCLE A NUMBER

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

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

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

CIRCLE A NUMBER

ATTACHMENT 4: CROHN'S DISEASE ACTIVITY INDEX

<u>DISEASE ACTIVITY INDEX</u>	<u>SUM</u>	<u>X FACTOR</u>	<u>SUBTOTAL</u>
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			
<input type="checkbox"/> = arthritis/arthralgia	_____	x 20	= _____
<input type="checkbox"/> = iritis/uveitis	_____	x 20	= _____
<input type="checkbox"/> = erythema nodosum/pyoderma gangrenosum/aphthous stomatitis	_____	x 20	= _____
<input type="checkbox"/> = anal fissure, fistula or abscess	_____	x 20	= _____
<input type="checkbox"/> = other fistula	_____	x 20	= _____
<input type="checkbox"/> = 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	_____	x 30	= _____
During the previous 7 days has Subject received opiate therapy on each of the 7 days: 0 = no 1 = yes	_____		
Abdominal mass: 0 = none 2 = questionable 5 = definite	_____	x 10	= _____
Hematocrit: Males: (47-Hct) = SUM Females: (42-Hct) = SUM	_____	x 6	= _____ (add or subtract by sign)
(Standard Weight - Actual Body Weight) x 100 = _____ Standard Weight	_____	x 1	= _____ (add or subtract by sign, round to 3 decimal places)
* If this value is less than -10 then enter -10 here. Standard weight and actual weight must be in same units (kg or lb)			
TOTAL = _____			(round total to integer)

ATTACHMENT 5: STANDARD WEIGHT TABLE

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

ATTACHMENT 6: CONCOMITANT IMMUNOMODULATOR AGENTS CHANGE

Detailed concomitant 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 52 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 52 are more than 14 days.

ATTACHMENT 7: CONCOMITANT MEDICATIONS CHANGE EXCEPT IMMUNOMODULATOR AGENTS

Detailed concomitant medications change except immunomodulator agents are:

1). Corticosteroids:

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 52 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 52 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 52 due to reasons other than worsening Crohn's disease. This includes initiation of oral corticosteroids for subjects who were not receiving oral corticosteroids at.

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 52 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 52 due to worsening Crohn's disease.

2). Protocol-prohibited medications:

An initiation of any of the following post baseline of this study due to worsening Crohn's disease:

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

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

c. Experimental or investigational Crohn's disease medications