Janssen Research & Development

Statistical Analysis Plan (Part II)

A Phase 2b, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of JNJ-64304500 in Subjects with Moderately to Severely Active Crohn's Disease

Protocol 64304500CRD2001; Phase 2b

JNJ-64304500 (TRIDENT)

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

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ABBREVIATIONS

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	analysis of covariance
AST	Aspartate aminotransferase
AZA	Azathioprine
BDS	Biologics Development Sciences
Bio-IR	biologic intolerant or refractory
Bio-NF	biologic nonfailure, i.e., inadequate response to or failed to tolerate corticosteroids or immunomodulators, but not a biologic
BSFS	Bristol Stool Form Scale
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CRF	case report form
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPS	Data presentation specifications
ECG	electrocardiogram
GHAS	Global Histology Activity Score
GMS	Global Medical Safety
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
LLN	lower limit of normal
LOCF	last observation carried forward
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
MTX	Methotrexate
NAbs	neutralizing antibodies
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NKG2D	natural killer group 2 member D
NRS	numerical rating scale
PCS	Physical Component Summary
PD	pharmacodynamic
PK	pharmacokinetic(s)
PRO	patient-reported outcome(s)
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	36-item Short Form Health Survey
SNP	Single Nucleotide Polymorphism
SSG	Statistical Support Group
SUSAR	suspected unexpected serious adverse reaction

TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal

1. INTRODUCTION

The protocol 64304500CRD2001 is comprised of 2 parts, Part I and Part II. Except for trial objectives and trial design sections, all other sections in this SAP will be focused on Part II. The planned analyses for Part I were specified in a separate SAP. This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for Part II.

1.1. Trial Objectives

The objectives are the same in Part I and Part II.

Primary Objectives

- To evaluate the efficacy of JNJ-64304500 to reduce the Crohn's Disease Activity Index (CDAI) score from baseline.
- To evaluate the safety of JNJ-64304500.

Secondary Objectives

- To evaluate the efficacy of JNJ-64304500 to induce clinical remission, clinical response, and endoscopic healing of the mucosa, and to maintain remission.
- To evaluate the relationship between efficacy and the presence of the natural killer group 2 member D (NKG2D) and/or major histocompatibility class I chain-related protein B (MICB) single-nucleotide polymorphism (SNP) biomarkers.
- To evaluate the efficacy of JNJ-64304500 to improve general and disease-specific health-related quality of life and to reduce Crohn's disease-related hospitalizations and surgeries.
- To evaluate the pharmacokinetics (PK), immunogenicity, pharmacodynamics (PD), and biomarkers (i.e., reductions in CRP, fecal calprotectin, and fecal lactoferrin) of JNJ-64304500 therapy.

1.2. Trial Design

This protocol is comprised of 2 parts (Part I and Part II) that are designed to evaluate the efficacy and safety of JNJ-64304500 in subjects with moderately to severely active Crohn's disease. Both parts of the protocol will enroll Bio-IR and Bio-NF subjects, as defined below.

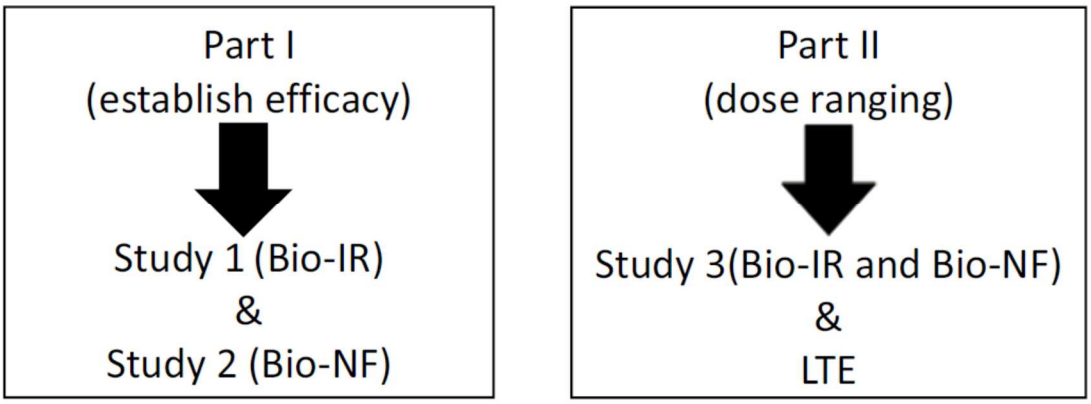
In Part I, the following 2 studies were conducted:

- Study 1: A study in subjects who are biologic intolerant or refractory (Bio-IR);
- Study 2: A study in subjects who have not previously failed a biologic therapy (Biologic nonfailure [Bio-NF]).

In Part II, the following study will be conducted:

- Study 3: A dose-ranging study in subjects who are Bio-IR or Bio-NF.

Figure 1: Schematic representation of 64304500CRD2001



The target population for each part of the protocol consists of men or women ≥18 years of age with moderately to severely active Crohn's disease (of at least 3 months' duration), defined as a CDAI score ≥220 but ≤450 at Week 0, with elevated CRP (>3.0 mg/L) and/or fecal calprotectin (>250 mg/kg) at screening. Subjects must have colitis, ileitis, or ileocolitis previously confirmed at any time in the past by radiography, histology, and/or endoscopy.

Additionally, subjects must have previously failed or been intolerant to 1 or more approved biologic agents (ie, TNFα-antagonists or vedolizumab, hereafter referred to as biologic intolerant or refractory subjects) **or** have demonstrated an inadequate response to or failed to tolerate corticosteroids or immunomodulators (ie, 6-mercaptopurine [6-MP], azathioprine [AZA], or methotrexate [MTX]) but not a biologic agent (hereafter referred to as biologic nonfailure subjects). These 2 populations are described below:

Biologic intolerant or refractory (Bio-IR) subjects are defined as those who have received an advanced therapy, including infliximab (or a biosimilar for infliximab), adalimumab (or a biosimilar for adalimumab), certolizumab pegol, or vedolizumab at a dose approved for the treatment of Crohn's disease, and either did not respond initially, responded initially but then lost response, or were intolerant to the medication. Bio-IR subjects must allow a ≥8-week washout for prior TNFα antagonist use and a 16-week washout period for prior vedolizumab use.

Biologic nonfailure (Bio-NF) subjects are defined as those who have demonstrated an inadequate response to or have failed to tolerate corticosteroids or the immunomodulators 6-MP, AZA, or MTX. Subjects who have demonstrated corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease) are also eligible. Bio-NF subjects may also have received biologic therapy but only if it was discontinued for reasons other than lack of efficacy or intolerance (eg, drug holiday).

Part I studied the safety and efficacy of a high dose regimen of JNJ-64304500 (400 mg SC at Week 0 then 200 mg SC q2w through Week 22) compared with placebo. All planned analyses for Part I were defined in the SAP for Part I.

Part II will study the efficacy and safety of multiple dose regimens of JNJ-64304500 compared with placebo, and with ustekinumab (STELARA®) as a reference arm. In Part II, approximately 250 Bio-IR or Bio-NF subjects will be randomly assigned to receive placebo or ustekinumab or 1 of 3 dose levels of JNJ-64304500 in a ratio of 1:1:1:1:1 using permuted block randomization, stratified by baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), and Bio-IR status (yes or no). The maximum proportion of either Bio-NF or Bio-IR subjects will be 60%.

The treatment groups in Part II will be as follows:

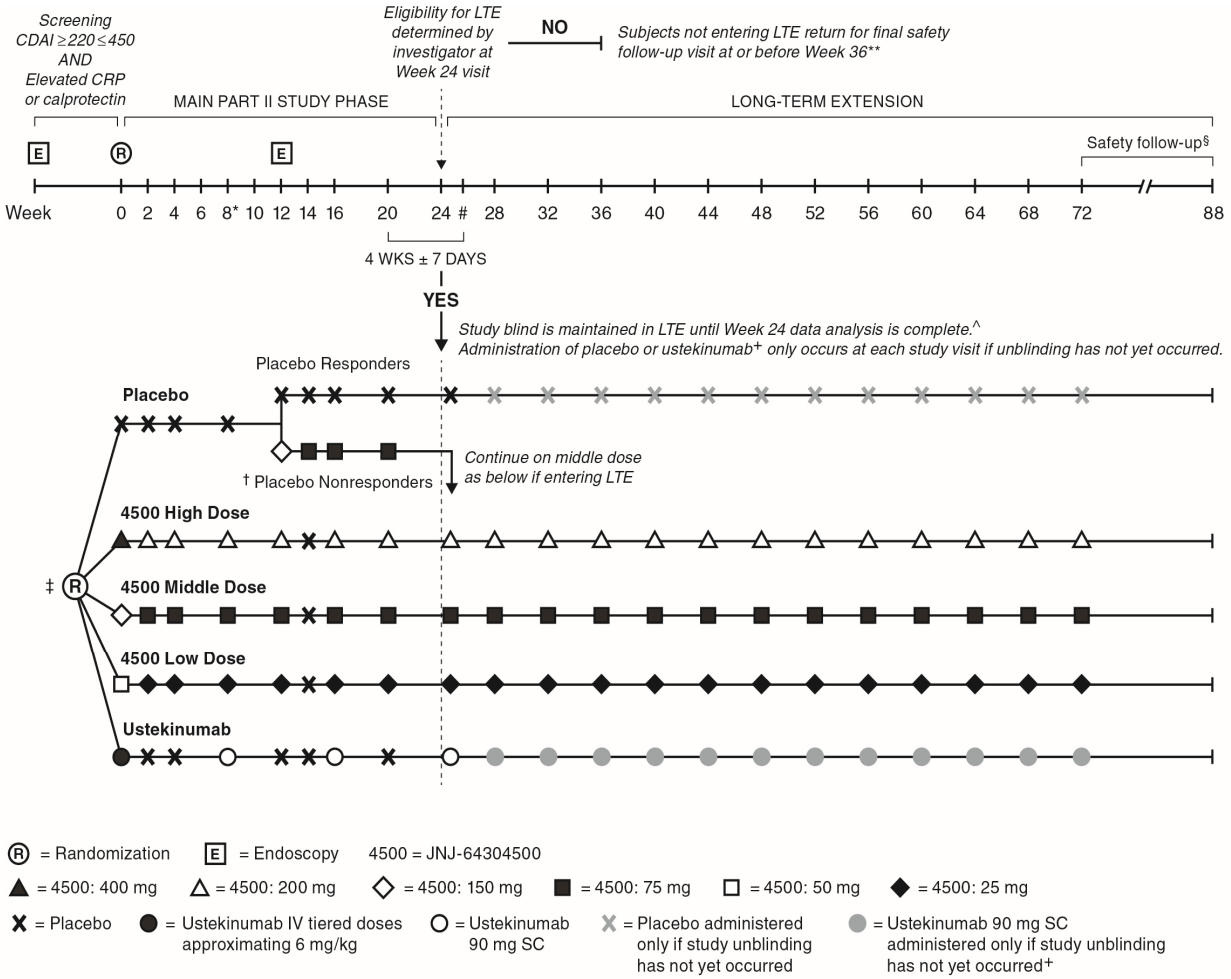
- Placebo SC at Weeks 0, 2, 4, and 8; from Week 12, these subjects will receive additional doses as follows:
  - Placebo-treated subjects who are in clinical response at Week 12 (≥100-point reduction from baseline in CDAI or CDAI <150) will continue to receive placebo at Weeks 12, 14, 16, and 20.
  - Placebo-treated subjects who are not in clinical response at Week 12 will receive JNJ-64304500 150 mg SC at Week 12 and then JNJ-64304500 75 mg SC at Weeks 14, 16, and 20.
- High dose: JNJ-64304500 400 mg SC at Week 0 and 200 mg SC at Weeks 2 and 4, then 200 mg SC every 4 weeks (q4w) through Week 20.
- Middle dose: JNJ-64304500 150 mg SC at Week 0 and 75 mg SC at Weeks 2 and 4, then 75 mg SC q4w through Week 20.
- Low dose: JNJ-64304500 50 mg SC at Week 0 and 25 mg SC at Weeks 2 and 4, then 25 mg SC q4w through Week 20.
- Ustekinumab (tiered doses approximating 6 mg/kg intravenously [IV]) at Week 0 (as indicated in the bullets below), followed by 90 mg SC at Weeks 8 and 16.
  - Ustekinumab 260 mg (weight ≤55 kg).
  - Ustekinumab 390 mg (weight >55 kg and ≤85 kg).
  - Ustekinumab 520 mg (weight >85 kg);

Subjects who are receiving oral 5-ASA compounds, conventional immunomodulators (ie, AZA, 6-MP, or MTX), enteral therapy, and/or antibiotics for the treatment of Crohn's disease at baseline should maintain a stable dose through the final safety visit. Subjects who are receiving corticosteroids at baseline should maintain a stable dose through Week 12. Subjects who are receiving corticosteroids at Week 0 and who are in clinical response at Week 12 will be encouraged to initiate corticosteroid tapering at the Week 12 visit.

The primary endpoint for Part II is the change from baseline in the CDAI score at Week 12.

The main part of Part II of this protocol is through Week 24. Initially, Part II of the protocol did not have a long-term extension (LTE), but it was subsequently added in Protocol Amendment 5. After Protocol Amendment 5 was implemented, subjects who complete Part II Week 24 assessments, and who may benefit from continued treatment in the opinion of the investigator, are eligible to enter the Part II LTE. In the Part II LTE, each subject will be eligible to receive up to 52 weeks of additional study drug (for a total of up to 72 weeks of study drug in Part II). A schematic representation of the Part II (including the LTE) is shown in Figure 2.

Figure 2: Schematic Overview of the 64304500CRD2001 Part II (including the Long-term Extension)



* Timepoint for primary endpoint.

** The final follow-up and safety visit for subjects who complete the main study phase through Week 24 and do not enter the LTE is 16 weeks after the last dose of study drug. Final follow-up and safety visit for subjects in the LTE occurs 16 weeks after the last dose of study drug. For subjects receiving placebo in the LTE, the final safety visit will occur at the visit during which treatment allocation is disclosed to subject.

† Placebo nonresponders receive middle dose (150 mg at Week 12, 75 mg at Weeks 14, 16 and 20).

‡ Bio-IR (intolerant/refractory) and Bio-NF (nonfailure) will be randomized 1:1:1:1:1 ratio.

\# First dose of study drug in long-term extension.

§ Final safety follow-up visit occurs 16 weeks after last dose of active study drug (4500 and ustekinumab).

^ Because the timing of the Week 24 database analysis is dependent upon the timing and completion of Part II enrollment, whether an individual subject will receive his/her treatment allocation during the LTE will depend upon his/her Part II enrollment date. Therefore, a proportion of subjects will complete the entire LTE in a blinded fashion before study unblinding, while others could be unblinded to treatment allocation during their participation in the LTE.

\+ In countries where commercial ustekinumab is available and approved for adult Crohn's disease, subjects will no longer receive study drug after unblinding. A final safety follow-up visit will be performed 16 weeks after the final dose of study drug, regardless of whether or not the subject decides to continue on commercial ustekinumab. In countries where commercial ustekinumab is not available or approved for adult Crohn's disease, ustekinumab will continue to be provided to subjects through Week 72, followed by a final safety follow-up visit 16 weeks after the last dose of study drug.

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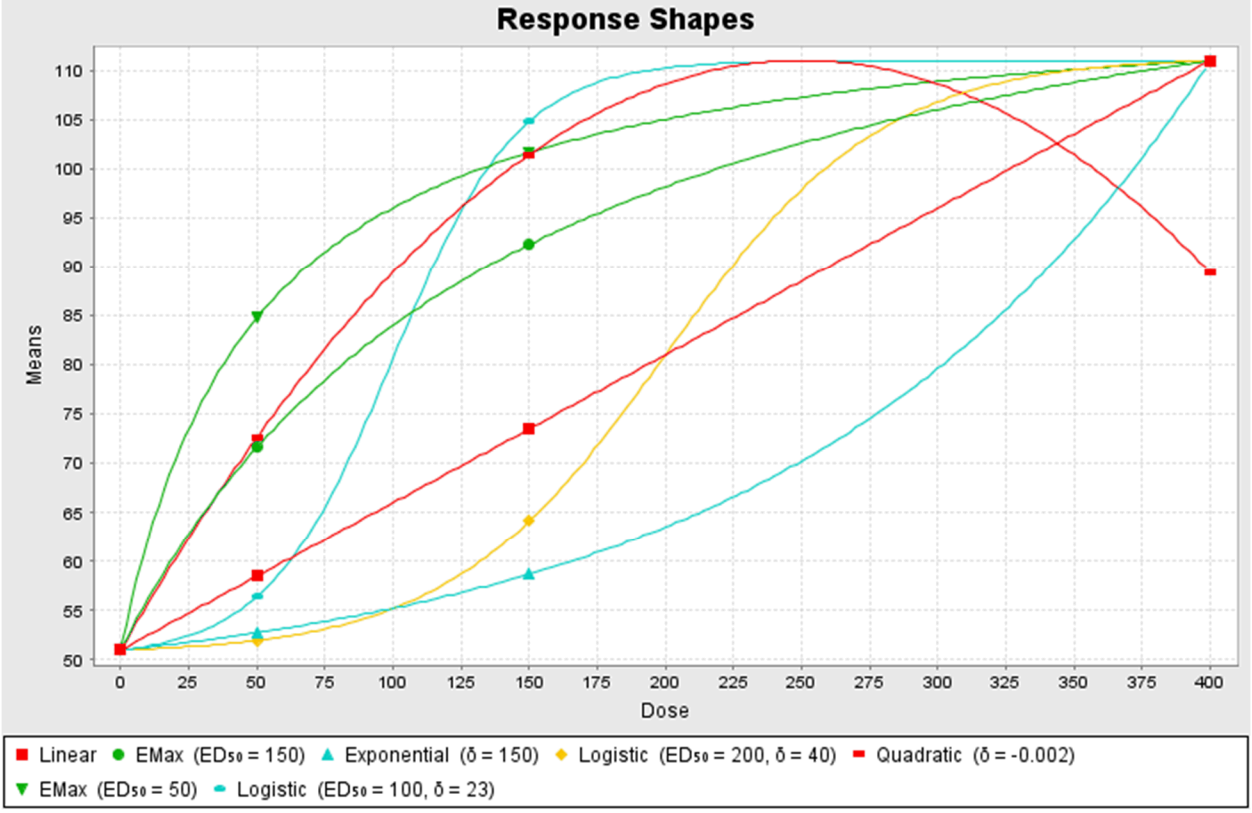
1.3. Statistical Hypotheses for Trial Objectives

The hypothesis for Part II is that there is dose-response for the JNJ-64304500 doses and placebo in inducing a reduction from baseline in CDAI at Week 12 in subjects with moderately to severely active Crohn's disease. The null hypothesis to be tested is that there is no dose-response for the JNJ-64304500 doses and placebo in inducing a reduction from baseline in CDAI at Week 12 in subjects with moderately to severely active Crohn's disease.

1.4. Sample Size Justification

Sample size and power to detect a dose response signal were evaluated using the Multiple Comparison Procedures with modeling techniques (MCP mod) method, assuming the true underlying dose-response curve is one of the shapes shown in Figure 3. Response is defined as the difference in the CDAI score between Week 0 and Week 12. For the sample size calculation, doses under consideration are placebo, JNJ-64304500 high dose, JNJ-64304500 middle dose, and JNJ-64304500 low dose. The ustekinumab dose is not used for sample size calculation since it is included in Part II as a reference arm.

Figure 3: Dose-response shapes included in power calculation



The assumptions for the sample size calculations in Part II were based on the Part I Week 12 analysis results. For Bio-IR subjects in Part I, the mean CDAI change from baseline at Week 12 was -30.9 (SD=85.15) and -77.4 (SD=103.68) for the placebo and JNJ-64304500 groups (this corresponds to the high dose in Part II), respectively. For Bio-NF subjects in Part I, the mean CDAI change from baseline at Week 12 was -70.9 (SD=93.59) and -144.7 (SD=92.50) for the placebo and JNJ-64304500 groups, respectively.

For Part II, assuming the mean CDAI change from baseline at Week 12 is -111 in the JNJ-64304500 high dose group and -51 in the placebo group (these values are derived assuming a 1:1 ratio of Bio-IR and Bio-NF subjects) with a common SD of 102, 50 subjects per treatment group will provide a mean power of 85% to detect a dose-response signal for change from baseline in CDAI at Week 12 based on 7 candidate dose-response models (Figure 3, Table 1 and Table 2) at an overall Type 1 error rate of 0.05 (2-sided). For ease of interpretation, the reverse of the change from baseline in the CDAI at Week 12 (Week 0 – Week 12) will be used as the response variable in the dose response analysis so that larger values in response will indicate a better outcome in Figure 3. Table 1 gives the model specifications for the candidate models that have been selected for this study based on potential outcomes. Table 2 shows the power for detecting a dose response signal under the different shapes at an overall Type 1 error rate of 0.05 (2 sided).

Table 1: Candidate Dose-response[a] Models

Model Type	Model specification[b]
E_{max} 1	dose/(50+dose)
E_{max} 2	dose/(150+dose)
Exponential	exp(dose/150)-1
Linear	dose
Logistic 1	1/{1+exp[(200 –dose)/40]}
Logistic 2	1/{1+exp[(100 –dose)/23]}
Quadratic	dose-0.002*(dose**2)

[a] Response is the difference in the CDAI score between Week 0 and Week 12 (Week 0 – Week 12).
[b] A standardized version of the dose response model

Table 2: Power for Detecting a Dose Response Signal Under Different Shape at an Overall Type 1 Error of 0.05 (2 sided)

Sample size Per Group	Emax 1	Emax2	Exponential	Linear	Logistic 1	Logistic 2	Quadratic	Mean Power
50	85%	85%	89%	86%	89%	95%	68%	85%

Fifty subjects per treatment group will also provide 83% power to detect a treatment difference between the JNJ-64304500 treatment group with the highest dose and the placebo treatment group for change from baseline in CDAI at Week 12 based on a 2-sample t-test at a Type 1 error rate of 0.05 (2-sided; Table 3). This will result in a total sample size of 250 subjects in Part II (incorporating an additional 50 subjects for the ustekinumab treatment group).

Table 3: Power to detect a treatment difference and sample size combinations at an overall Type 1 error of 0.05 (2-sided) for Part II				
Sample size per group	**Placebo**	**JNJ-64304500 high dose**	**Difference**	**Power***
Mean change from baseline in CDAI score at Week 12				
Based on data from Part I (assuming 1: 1 of Bio-IR and Bio-NF subjects)				
45	-51	-91	40	45%
45	-51	-101	50	63%
45	-51	-111	60	79%
45	-51	-121	70	90%
45	-51	-131	80	96%
50	-51	-91	40	49%
50	-51	-101	50	68%
50	-51	-111	60	83%
50	-51	-121	70	92%
50	-51	-131	80	97%
*Assuming a standard deviation of 102 (based on JNJ-64304500 group at Week 12) for each group.				

1.5. Randomization and Blinding

1.5.1. Randomization and Treatment Allocation

Central randomization will be implemented in Part II. Subjects will be randomly assigned to 1 of 5 treatment groups (1:1:1:1:1 ratio), based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), and Bio-IR status (yes or no). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject.

1.5.2. Blinding

To maintain the study blind, the study agent container will have a label containing the study name and medication number or syringe number. The label will not identify the study agent in the container. The medication number or syringe number will be entered in the case report form (CRF) when the drug is dispensed. The study agents will be identical in appearance and packaging.

Planned efficacy and safety evaluations for Part II will be performed after the following planned database locks (DBLs) (additional database locks may be added as needed):

- **Week 12 DBL for Part II:** Occurs when all Part II subjects have completed their Week 12 visit or have terminated their study participation before Week 12.
- **Week 24 DBL for Part II:** Occurs when all Part II subjects have completed their Week 24 visit or have terminated their study participation before Week 24.
- **Final DBL for Part II:** Occurs when all Part II subjects who entered the Part II LTE have completed their final safety visit in the Part II LTE or have terminated their study participation before the final safety visit in the Part II LTE. For Part II subjects who did not enter the LTE, all their data (included data collected after Week 24) will be included in this lock.

At the time of the Week 12 DBL for Part II, the sponsor, except for site monitors (who have interactions with the investigative sites), will become unblinded to treatment assignment. The study blind will be maintained for investigators, site personnel, subjects, and site monitors until the Week 24 analyses have been completed for Part II.

Data that may potentially unblind the treatment assignment (i.e., study drug serum concentrations, anti-drug antibodies, treatment allocation, and study drug preparation/accountability data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. In particular, before unblinding, this information will be available only to a limited number of data management staff for purposes of data cleaning, and if applicable, to quality assurance representatives for the purposes of conducting independent drug audits.

The SNP status and postbaseline results for CRP, fecal lactoferrin, and fecal calprotectin tests will be blinded to the investigative site. If an investigative site requests these data, it will be provided to them after the final analyses based on final DBL for Part II have been completed.

The designated pharmacists, or other appropriately licensed and authorized personnel, and independent drug monitors will be unblinded to study agent. Placebo infusions/injections will have the same appearance as the ustekinumab infusions/JNJ-64304500 injections. Under no circumstances should unblinded personnel reveal the treatment assignment for a subject.

For bioanalytical purposes, before the PK, anti-drug antibody, and PD bioanalyses are initiated, the unblinded data management team will provide the sponsor bioanalysts with the information about which treatment (JNJ-64304500 or placebo) the subjects received. For the purpose of performing PK, immunogenicity, and PD bioanalyses, bioanalysts in Biologics Clinical Pharmacology at Janssen will be unblinded to treatment-level data (JNJ-64304500 or placebo) at the time of analyzing serum samples for the determination of drug concentrations, detection of antibodies to study agents, or PD assessments. Samples will be separated based on treatment administered; subject identification and dose given will not be disclosed.

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

Additionally, a given subject's treatment assignment may be unblinded to the sponsor, Institutional Review Board/Independent Ethics Committee (IRB/IEC), and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions (SUSARs).

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

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Actual scheduled visits will be used for all by-visit analyses in the study. Early termination visit and final efficacy and safety visit will be mapped to scheduled visits according to slotting rules that will be prespecified prior to the database lock. The study visits scheduled should occur at the times delineated in the Time and Events Schedule of the protocol.

2.2. Analysis Sets

2.2.1. Randomized Analysis Set

The randomized analysis set includes all subjects who are randomized in the study. Subjects in the randomized analysis set will be analyzed according to the treatment group to which they were assigned regardless of the treatment they actually received.

2.2.2. Efficacy Analysis Set

The efficacy analyses will be based on the full analysis set (FAS) and includes all randomized subjects in Part II who received at least one dose of study agent (Placebo or JNJ-64304500 or ustekinumab, including a partial dose). The efficacy data will be analyzed according to the treatment group to which they were assigned regardless of the treatment they actually received.

2.2.3. Safety Analysis Set

The safety analysis set includes all randomized subjects in Part II who received at least one dose of study agent (Placebo or JNJ-64304500 or ustekinumab, including a partial dose). The safety data will be analyzed according to the treatment they actually received.

2.2.4. Pharmacokinetics Analysis Set

The pharmacokinetics (PK) analysis set includes all randomized subjects in Part II who received at least one complete dose of JNJ-64304500 or ustekinumab and has at least 1 PK sample obtained after their first dose of JNJ-64304500 or ustekinumab.

In the PK analyses, subjects will be analyzed according to the treatment they actually received.

2.2.5. Immunogenicity Analysis Set

The immunogenicity analysis set includes all subjects in Part II who received at least 1 (partial or complete) dose of JNJ-64304500 or ustekinumab and who have appropriate samples for detection of antibodies to JNJ-64304500 or ustekinumab (i.e., subjects with at least 1 sample obtained after their first dose of JNJ-64304500 or ustekinumab).

In the immunogenicity analyses, subjects will be analyzed according to the treatment they actually received.

2.3. Definition of Subgroups

Subgroups of interest in this study include but are not limited to:

1. Demographics at baseline:
   a. Age (≤ median age, >median age)
   b. Sex (male, female)
   c. Race (White, non-White)
   d. Weight at baseline (≤ median, > median; ≤ 1st quartile, >1st quartile and ≤ 2nd quartile, >2nd quartile and ≤ 3rd quartile, >3rd quartile)
   e. Center location (Asia, Eastern Europe, Western Europe, North America)

2. Disease characteristics at baseline:
   a. Crohn's disease duration (≤ 5 years, > 5 years to ≤ 15 years, or > 15 years)
   b. Involved gastrointestinal areas (ileum only, colon only, ileum & colon)
   c. CDAI score (≤ 300, > 300)
   d. CRP (≤ 3 mg/L, > 3 mg/L)
   e. Fecal Calprotectin (≤250 mg/kg, > 250 mg/kg)

3. Concomitant Crohn's-disease medication at baseline:
   a. Oral corticosteroids (including budesonide and beclomethasone dipropionate) (receiving, not receiving)
   b. Oral 5-ASA compounds (receiving, not receiving)
   c. Immunomodulators (6-MP/AZA/MTX) (receiving, not receiving)
   d. Oral corticosteroids (including budesonide and beclomethasone dipropionate) and Immunomodulators (receiving, not receiving)
   e. Oral corticosteroids (including budesonide and beclomethasone dipropionate) or Immunomodulators (receiving, not receiving)

4. CD-related medication history:
   a. Refractory or intolerant to 6-MP/AZA/MTX (yes, no)
   b. Refractory, dependent on or intolerant to oral or IV corticosteroids (yes, no)
   c. Refractory, dependent on, or intolerant to oral or IV corticosteroids, but not refractory or intolerant to 6-MP/AZA/MTX (yes, no)
   d. Refractory, dependent on or intolerant to oral or IV corticosteroids, and refractory or intolerant to 6-MP/AZA/MTX (yes, no)
   e. Bio-IR status (yes, no)
   f. Subjects with biologic failure (ie, Primary nonresponse, secondary nonresponse, or intolerance) to:
      – One anti-TNF only without vedolizumab (yes, no)

  - Two or more anti-TNFs without vedolizumab (yes, no)
  - Vedolizumab only (yes, no)
  - Vedolizumab and one anti-TNF (yes, no)
  - Vedolizumab and two or more anti-TNFs (yes, no)
  - Two or more anti-TNFs regardless of vedolizumab (yes, no)
- For subjects with biologic failure to at least one anti-TNF
  - Primary nonresponse (yes, no)
  - Secondary nonresponse (yes, no)
  - Intolerance (yes, no)

g. Subjects without biologic failure (bio-naïve, bio-experienced [but not documented failure])

5. Other:
   a. SNP-positive status (yes, no)
   b. Current fistula at baseline (yes, no)

2.4. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - date of Day 1, if visit date <date of Day 1

There is no 'Day 0'.

2.5. Baseline

Baseline is defined as the last observation prior to the start of the first study agent administration.

2.6. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an AE 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 date
  - 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 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 AE 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 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 AE is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an AE 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 death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an AE will be set to the earlier of:
  - 00:01 as long as the onset date is after the study agent start date
  - The time of the study agent start if this is the same day the AE occurred.
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analysis is planned for Part II.

An external data monitoring committee (DMC), which consists of at least one medical expert in the relevant therapeutic area and at least one statistician, will be established to monitor safety data on an ongoing basis to ensure the continuing safety of the subjects randomized in Part II. Until study unblinding, the committee will meet periodically to review interim safety data and make recommendations regarding the continuation of these studies.

4. SUBJECT INFORMATION

The number of subjects in each analysis dataset will be summarized by treatment group, combined JNJ-64304500 treatment group, and overall. In addition, the distribution of subjects by center location, country, and site ID will be presented.

4.1. Demographics and Baseline Characteristics

Demographic data and baseline Crohn's disease characteristic data will be summarized by treatment group (Table 4) for the FAS.

Table 4: Demographic and Baseline Crohn's Disease Characteristic 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)	
Crohn's Disease Duration (years)	
CDAI	
PRO-2 (defined as the sum of the abdominal pain and stool frequency subscores of the CDAI score)	
PRO-3 (defined as the sum of abdominal pain, stool frequency, and general well-being subscores of the CDAI score)	
SES-CD	
CRP Concentration (mg/L)	
Fecal Calprotectin (mg/kg)	
Categorical Variables	
Race ([White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not Reported, and Unknown])	Frequency distribution with the number and percentage of subjects in each category.
Sex ([Male, Female])	
Involved GI areas ([Ileum only, Colon only, Ileum and colon, Proximal gastrointestinal tract, and Perianal])	
Extra intestinal manifestations ([Absent, Present])	
Endoscopic disease severity (SES-CD score) ([Remission (0-2), Mild inflammation (3-6), Moderate inflammation (7-16) and Severe inflammation (>16)])	
Abnormal CRP (>3 mg/L) ([Yes, No])	
Abnormal fecal calprotectin (>250 mg/kg) ([Yes, No])	
Crohn's disease complications (Intra-abdominal abscess, Sinus tracts /perforation, Fistula, Bowel Stricturing]	
SNP-positive status ([Yes, No])	

4.2. Disposition Information

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

- Subjects randomized
- Subjects receiving study agent
- 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 through Week 12, through Week 24, and through the final safety visit. 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

The number of subjects receiving each scheduled administration will be summarized by treatment group for the randomization analysis set. Compliance with randomized study agent versus actual received agent will be summarized by treatment group for the randomization analysis set.

In addition, a list of subjects who were assigned treatment but were never treated and a list of subjects who were unblinded during the study will be provided.

4.4. Extent of Exposure

The number and percentage of subjects who received study agent will be summarized by treatment group based on the efficacy analysis set.

The cumulative dose of JNJ-64304500 and ustekinumab received will be summarized by treatment group based on the safety analysis set.

In addition, the number of administrations of study agent and average duration of follow-up (weeks) will be summarized by treatment group.

4.5. Protocol Deviations

Major protocol deviations will be summarized by treatment group based on the FAS. The major protocol deviations will include the following categories:

- Subjects who entered the trial but did not satisfy entry criteria
- Subjects who developed withdrawal criteria during the trial but were not withdrawn
- Subjects who received the wrong medication or incorrect dose

- Subjects who received disallowed medication
- Other major protocol deviations

In addition, a listing will be provided for subjects who had any major protocol deviations, who did not meet study inclusion/exclusion criteria by category, and who received wrong study agent. A listing will also be provided for subjects who had any COVID-19 related protocol deviations.

4.6. Prior and Concomitant Medications

Summary of Crohn's disease medication history (subjects who took medications for Crohn's disease and their length of exposure prior to the study), CD-related conventional therapy (i.e., 6-MP, AZA, MTX, or corticosteroids) or advanced therapy (i.e., TNF antagonists [infliximab, adalimumab, or certolizumab] or vedolizumab) history will be summarized by treatment group based on the FAS. Prior medications are defined as any therapy used before the day of first dose of study agent.

Crohn's disease specific concomitant medications at baseline (including corticosteroids, immunomodulators, 5-aminosalicylates [5-ASAs], and antibiotics) will be summarized by treatment group based on the FAS. 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.

5. EFFICACY

5.1. General Method of Analysis

Descriptive statistics (i.e., mean, median, standard deviation [SD], interquartile [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., line plots) may also be used to summarize the data.

Analyses suitable for categorical data (e.g., chi-square tests, Cochran-Mantel-Haenszel chi-square tests, or logistic regression, as appropriate) will be used to compare the proportions of subjects achieving selected endpoints (e.g., clinical response). In cases of rare events, Fisher's exact test will be used for treatment comparisons. Continuous response parameters will be compared using Mixed-Effect Model Repeated Measure (MMRM) model. If the normality assumption is in question, an appropriate transformation may be implemented before fitting the MMRM model. Analysis of covariance (ANCOVA) will be used if continuous data are collected at only one post-baseline visit.

5.2. Analysis Specifications

5.2.1. Level of Significance

All statistical tests will be at a 2-sided 0.05 level of significance. A multiple comparisons procedure is specified to control the overall Type 1 error rate for the primary endpoint analysis; the analyses for major secondary endpoints and other endpoints are not adjusted for multiplicity. Nominal p-values are provided for all analyses.

5.3. Primary Efficacy Endpoint

5.3.1. Definition

The primary endpoint is change from baseline in the CDAI score at Week 12 (Week 12 minus baseline).

The CDAI is a validated multi-item measure of severity of illness derived as a weighted sum of 8 different Crohn's disease-related variables. These 8 variables are: extra-intestinal manifestations, abdominal mass, weight, hematocrit, use of antidiarrheal drug(s) and/or opiates, total number of liquid or very soft stools, abdominal pain/cramps, and general well-being. The last 3 variables are scored over 7 days by the subject on a diary card. For the total number of liquid or very soft stools, abdominal pain/cramps, and general well-being, if only 5 days or 6 days of data are available for the calculation, the weights of 7/5 and 7/6, respectively, will be used for the calculation; if the values are recorded for less than 5 days, the components will not be calculated. The CDAI score calculation algorithm is presented in the protocol Attachment 4.

The CDAI score will 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. If the CDAI score cannot be calculated (i.e., < 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:

Treatment by Week 12:

Experimental:

- Active dose 1: JNJ-64304500 400 mg SC at Week 0 and 200 mg SC at Weeks 2, 4, and 8
- Active dose 2: JNJ-64304500 150 mg SC at Week 0 and 75 mg SC at Weeks 2, 4, and 8
- Active dose 3: JNJ-64304500 50 mg SC at Week 0 and 25 mg SC at Weeks 2, 4, and 8

Control: Placebo SC at Weeks 0, 2, 4, and 8

Note: Part II of this study also has an ustekinumab reference group which is not included in this Estimand.

Population: subjects 18 years or older with moderately to severely active Crohn's disease.

Variable (Endpoint): change from baseline in the CDAI score at Week 12. Subjects who have intercurrent events in categories 1-3 (defined below) prior to the Week 12 visit will have a zero change from baseline in the CDAI score assigned, regardless of the observed data.

Intercurrent Events and Corresponding Strategies:

The following are the intercurrent events considered for this trial:

1. A Crohn's disease-related surgery (with the exception of drainage of an abscess or seton placement).
2. A prohibited change in Crohn's disease medication (described in Attachment 1).
3. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease.
4. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection).
5. Discontinuation of study intervention due to reasons other than lack of efficacy or an AE of worsening Crohn's disease (including COVID-19 infection).

Intercurrent events (ICEs) in categories 1-3 will be handled by the composite strategy, and ICE category 4 will be handled by the hypothetical strategy (as if subjects would have not experienced this intercurrent event), and ICE category 5 will be handled by the treatment policy strategy. This estimand acknowledges that having an intercurrent event in categories 1-3 is an unfavorable outcome. For subjects experiencing ICE 4, CDAI data at all visits after an ICE will be set to missing. For subjects experiencing ICE 5, observed values of the variable will be used, if available. For subjects experiencing multiple ICEs, the overall strategy will be based on the first ICE.

Population-level summary: Difference in means between each JNJ-64304500 treatment group and the placebo treatment 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 2.2.2) will be analyzed according to the randomized study intervention regardless of the study intervention they actually received.

The objective of the primary analysis is to detect a dose-response signal and then identify the minimum effective dose (MED).

Data used in the primary analysis includes all values for change from baseline in CDAI score collected up to and including Week 12 for all subjects in the FAS. Any CDAI score collected after experiencing ICEs 1-3 will be replaced by the baseline observation for CDAI. For example, if the ICE occurs between the Week 8 and Week 10 visit, the baseline CDAI will be used as the Weeks 10 and 12 CDAI scores. Any CDAI score collected after experiencing ICE 4 will be set to missing. A subject experiencing ICE 5 will use their observed data through Week 12 (if available), including those collected after the ICE; otherwise their data after the ICE will be missing. For subjects experiencing multiple ICEs, the overall strategy will be based on the first ICE. In addition, intermediate missing data is possible due to missed visits, missed data collections, etc.

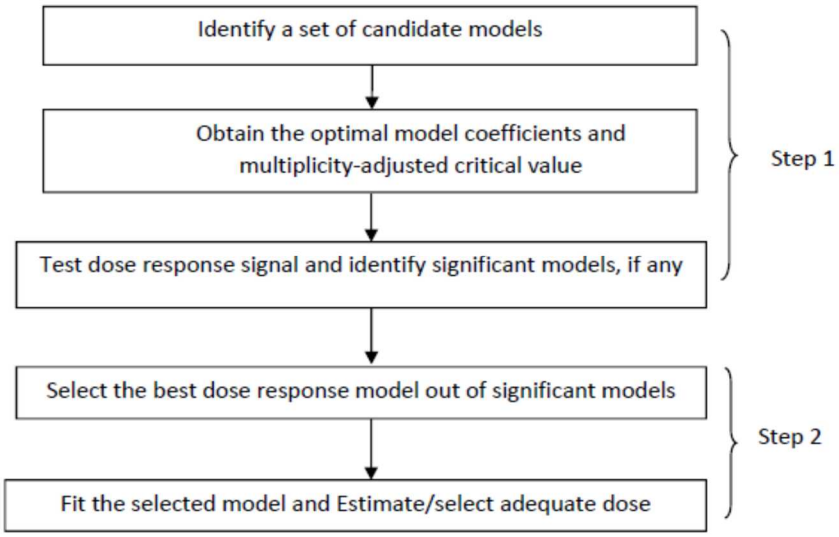
The Mixed-Effect Model Repeat Measures (MMRM) (see Section 5.3.3.1.1) will be used to estimate the mean change from baseline at Week 12 for each of the treatment arms (i.e., placebo and 3 active doses). This estimate will be used in MCP-Mod.

A unified dose-finding strategy called MCP-Mod that combines multiple comparison procedures with modeling techniques will be used to analyze the dose response data. This approach consists of 2 major steps. The first step consists of testing the dose response signal via multiple contrast tests while controlling the overall Type 1 error. If a dose response signal is detected (i.e., statistical significance is observed in at least one of the contrast tests of the first step), the second step is to select a model that best describes the observed data and use it to estimate/select an adequate dose with associated precision.

The road map for the MCP-Mod method is shown in Figure 4.

Step 1 starts with a set of candidate models (see Table 1 in Section 1.4) for representing the dose response relationship. For this step, doses under consideration are placebo, JNJ-64304500 high dose, JNJ-64304500 middle dose, and JNJ-64304500 low dose.

Figure 4: Process for the MCP-mod method



For each candidate model, its significance will be evaluated as follows: first, the optimum contrast coefficients will be computed; then a single contrast test for each model will be performed based on the optimal contrast coefficients applied to the estimated mean changes from baseline in CDAI score per dose, adjusting for baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), and Bio-IR status (yes or no). If the maximum of the contrast test statistics is larger than a computed critical value q, a significant dose-response signal is established. The critical value q will be calculated at the time of the analysis based on the multivariate t-distribution, so that the overall Type 1 error rate is controlled at the 0.05 (2-sided) level.

If none of the contrast test statistics corresponding to the candidate models are significant, it will be concluded that no dose response signal is detected for the given sample size and candidate models, and the second step of the MCP-Mod procedure will not be undertaken.

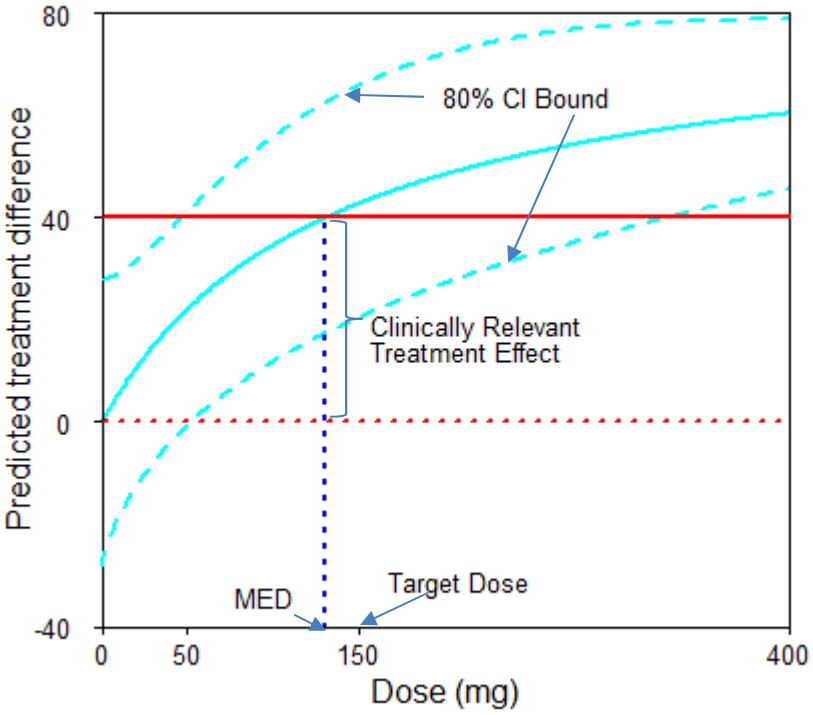
If at least 1 model contrast test statistic is significant, a reference set of good (statistically significant) models is obtained. The model associated with the minimum p value in the reference set may be selected as the most adequate dose response model unless there are issues with fitting this selected model in the second step (e.g., the fitted model is not convergent). Since each model in the reference set is statistically significant and may approximate the true model satisfactorily, other models in the reference set may also be selected as the most adequate dose response model, giving consideration to other criteria such as model convergence and/or interpretation.

Once an adequate model has been selected, the next step of MCP-Mod consists of fitting the selected model to the data with baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), and Bio-IR status (yes or no) as covariates and estimating the target dose of interest. For this step, data from all the doses will be used. The target dose will be based on the estimation of the MED, defined as the smallest dose within the dose range that shows a clinically relevant and statistically significant effect. The MED can be any value on a continuous scale. To be more specific, the MED is defined as the smallest dose that meets both of the following criteria after adjusting for baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), and Bio-IR status (yes or no). Figure 5 illustrates the estimation of the target dose.

- The estimated placebo-corrected treatment difference is at least 40 points (i.e., a clinically relevant treatment effect) above that of the placebo level.
- The lower bound of the 80% confidence interval (CI) for the estimated placebo-corrected response is greater than zero (i.e., a statistically significant effect).

If no dose meets both of these criteria, then the MED is not defined. If the MED can be estimated, the target dose is chosen to be the smallest dose under study whose predicted treatment difference is greater than or equal to that of the MED. By definition, the MED is ≤ the target dose.

Figure 5: Estimation of the target dose based on fitted model



If a dose-response relationship cannot be established (i.e. not achieving statistical significance) from the dose-response analysis, the totality of data (efficacy, safety, PK data from Part I, part II, as well as the available data for JNJ-64304500 from other indications) will be evaluated and the reason for lack of a dose-response signal will be investigated to decide whether to proceed with the dose selection.

Missing Data Handling Rules

- To avoid the need for data imputation for subjects who have insufficient data to calculate their CDAI score at Week 12 (i.e. <4 components of the CDAI are available), the MMRM will be used to estimate the mean change from baseline at Week 12 for each of the treatment arms (i.e., placebo and active doses) based on the observed data only. The generalized MCP-Mod procedure (Pinheiro et al, 2014)[8] will be applied to estimated mean changes from baseline at Week 12, as previously described.

Part II will be considered positive if a dose-response signal for the primary endpoint is detected.

In addition, pooled Part I and Part II data might be used for the analyses.

5.3.3.1.1. Pairwise Comparisons

In addition to the dose-response analysis, pairwise comparisons of each JNJ-64304500 treatment group versus the placebo group will be performed for the change from baseline in the CDAI score at Week 12 by MMRM. Pairwise comparisons will not be adjusted for multiplicity.

Pairwise comparisons of the ustekinumab treatment group with each JNJ-64304500 treatment group or with placebo are not planned; however, summary statistics will be provided for the ustekinumab treatment group.

Missing data for CDAI scores will be addressed by MMRM. In MMRM, missing data for the CDAI scores will not be imputed but missing data will be accounted for through correlation of repeated measures in the model under the assumption of missing at random (MAR). The explanatory variables of the model will include treatment group, SNP-positive status (yes or no), Bio-IR status (yes or no), baseline CDAI score, visit, and an interaction term of visit with treatment group. The model will include data from all 3 JNJ-64304500 treatment groups and placebo group through Week 12. An unstructured covariance matrix for repeated measure within a subject will be used. The F-test will use Kenward-Roger's approximation for degrees of freedom. In case of lack of convergence, empirical structured covariances will be used in the following order until convergence is reached: 1) Toeplitz 2) first order Autoregressive Moving Average.

The treatment difference between each JNJ-64304500 treatment group and the placebo group will be estimated by the difference in the least squares means (LSmeans). The 95% 2-sided confidence interval (CI) for the differences in LSmeans and p-values will be calculated based on the MMRM.

5.3.3.2. Subgroup Analyses

The subgroup analyses for the primary endpoint will focus on the pairwise comparisons of each JNJ-64304500 treatment group versus the placebo group.

To evaluate the consistency of the efficacy of the primary endpoint over different subgroups (demographic, baseline disease characteristics, baseline concomitant medications, and history of CD-related medications), the change from baseline in CDAI at Week 12 will be analyzed for the subgroups defined in Section 2.3 when the number of subjects in the subgroups permits. The same analysis methods and same data handling rules as specified in Section 5.3.3.1.1 will be applied. The 95% 2-sided confidence interval (CI) for the differences in LSmeans and p-values will be calculated based on the MMRM.

5.3.4. Supplementary Estimands for the Primary Endpoint

5.3.4.1. Estimand 2

The components of this supplementary estimand are the same as those for the primary estimand with the exception of the Variable (Endpoint) and the ICE strategy, which are described as follows:

Variable (Endpoint): change from baseline in the CDAI score at Week 12. Subjects who have an intercurrent event described by categories 1-5 will have a zero change from baseline in the CDAI score assigned, regardless of the observed data.

ICE strategy: all ICEs are addressed by the composite 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 Variable (Endpoint) and the ICE strategy, which are described as follows:

Variable (Endpoint): Change from baseline in the CDAI score at Week 12.

ICE strategy: all intercurrent events are addressed by the hypothetical strategy: as if subjects would have not experienced these intercurrent events. This supplementary estimand defines the treatment effect as if the treatment was taken as directed and no intercurrent events would have occurred; therefore, CDAI data at all visits after an ICE will be set to missing.

5.3.5. 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 and 3. The missing CDAI scores will be addressed by MMRM which is accounted for through correlation of repeated measures in the model under the assumption of missing at random (MAR).

5.3.6. Summary of Analyses Related to the Primary Endpoint

Table 5: Summary of Analyses Related to the Primary Endpoint of Change from Baseline in the CDAI Score at Week 12

Analysis (Analysis Set)	Missing data	Analysis method/Summary statistics
Analyses based on **Primary Estimand (Estimand 1)**, where ICEs 1-3 (CD-related surgery, prohibited change in CD medication, and discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease) are handled by the composite strategy, ICE 4 (discontinuation of study intervention due to COVID-19) is handled by the hypothetical strategy, and ICE 5 (discontinuation of study intervention due to other reasons) is handled by the treatment policy strategy		
Primary Analysis (FAS)	Missing data due to missed visits or missed data collection, due to ICE 4, or due to ICE 5 in the absence of observed data. Missing data is not imputed, but is handled through the MMRM assuming MAR.	• Descriptive summary statistics • MMRM model for o LS mean (SD) for each treatment group o Treatment differences in LS means (95% CI) o P-values for comparing LS means • MCP-MOD for o List of contrasts for each pre-specified model o P-values for multiple contrast test o Dose-response curve to find MED based on selected model
Subgroup Analyses (Individual subgroup levels defined in Section 2.3, FAS)	Missing data due to missed visits or missed data collection, due to ICE 4, or due to ICE 5 in the absence of observed data. Missing data is not imputed, but is handled through the MMRM assuming MAR.	• Descriptive summary statistics • MMRM model for o LS mean (SD) for each treatment group o Treatment differences in LS means (95% CI) o P-values for comparing LS means
Analyses based on **Supplementary Estimand 2**, where all ICEs are addressed by the composite strategy.		
Supplementary Analysis 1 (FAS)	Missing data due to missed visits or missed data collection. Missing data is not imputed, but is handled through the MMRM assuming MAR.	• Descriptive summary statistics • MMRM model for o LS mean (SD) for each treatment group o Treatment differences in LS means (95% CI) o P-values for comparing LS means • MCP-MOD for o List of contrasts for each pre-specified model o P-values for multiple contrast test o Dose-response curve to find MED based on selected model
Analyses based on **Supplementary Estimand 3**, where all ICEs are handled by the hypothetical strategy.		
Supplementary Analysis 2 (FAS)	Data is considered missing after the occurrence of an ICE and also due to missed visits or missed data collection. Missing data is not imputed, but is handled through the MMRM assuming MAR.	• Descriptive summary statistics • MMRM model for o LS mean (SD) for each treatment group o Treatment differences in LS means (95% CI) o P-values for comparing LS means • MCP-MOD for o List of contrasts for each pre-specified model o P-values for multiple contrast test o Dose-response curve to find MED based on selected model

5.4. Major Secondary Endpoints

The testing of the major secondary endpoints will occur regardless of the significance of the primary endpoint. The testing of these major secondary 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.

In the analysis of the major secondary endpoints, data from all subjects in the FAS will be analyzed according to the randomized study intervention regardless of the study intervention they actually received.

The major secondary endpoints are:

- Clinical remission at Week 12 as measured by CDAI.
- Clinical response at Week 12 as measured by CDAI.
- Change from baseline in PRO-2 at Week 12.
- Clinical remission at Week 12 as measured by PRO-2.
- Clinical response at Week 12 as measured by PRO-2.
- Change from baseline in SES-CD at Week 12 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score).

5.4.1. Definitions

Clinical remission as measured by CDAI

Clinical remission as measured by CDAI is defined as a CDAI score <150.

Clinical response as measured by CDAI

Clinical response as measured by CDAI is defined as a ≥100-point reduction from baseline in CDAI or clinical remission (CDAI<150).

PRO-2 score

PRO-2 score is defined as the sum of the abdominal pain and stool frequency components of the CDAI score (Note: these components have the weighting used in the calculation of the CDAI). If one of these two components cannot be evaluated, then the PRO-2 score will be set to missing.

Clinical remission as measured by PRO-2

Clinical remission as measured by PRO-2 is defined as a PRO-2 score <75.

Clinical response as measured by PRO-2

Clinical response as measured by PRO-2 is defined as a ≥50-point reduction from baseline in PRO-2 or PRO-2 <75.

Simple endoscopic activity score for Crohn's disease

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 and size of ulcers, the proportion of mucosal surface covered by ulcers, the proportion of mucosal surface affected by any other lesions, and the presence/ type of narrowing (also commonly referred to as strictures/stenosis clinically). Each endoscopic component is scored from 0 to 3 for each segment, and a total score is calculated as a sum of all the component scores across all the segments, as outlined in Table 6. The total SES-CD score ranges from 0 to 56.

Calculation of the SES-CD score:

Main approach (SES-CD calculated based on all segments available):

The total SES-CD score at each 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.

Alternative approach (baseline segments matched approach):

To calculate the SES-CD score at a visit, the sum of the segments that were present at baseline will be used. For segments that were present at baseline but missing post-baseline, the last available score for the missing segment(s) will be carried forward. In the event that a segment is missing at baseline but non-missing at post-baseline, the non-missing post-baseline score is not used in the calculation of SES-CD.

Table 6: 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 narrowing (0-3)						11 max*
					Total 1 + 2 + 3 + 4 =	SES-CD (56 max)

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

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

5.4.2. Main Estimands for the Major Secondary Endpoints

The following describes the attributes of the main estimands for the major secondary endpoints (corresponding to Estimands 4-9):

Treatment by Week 12: Same as Estimand 1, ie:

Experimental:

- Active dose 1: JNJ-64304500 400 mg SC at Week 0 and 200 mg SC at Weeks 2, 4, and 8
- Active dose 2: JNJ-64304500 150 mg SC at Week 0 and 75 mg SC at Weeks 2, 4, and 8
- Active dose 3: JNJ-64304500 50 mg SC at Week 0 and 25 mg SC at Weeks 2, 4, and 8

Control: Placebo SC at Weeks 0, 2, 4, and 8

Note: Part II of this study also has an ustekinumab reference group which is not included in this Estimand.

Population: subjects 18 years or older with moderately to severely active Crohn's disease.

Variables and Population-level Summary

Table 7: Variables and Population-level Summary for the main estimand for each Major Secondary Endpoint

Estimand	Variable (Endpoint)	Population-level summary
4	Clinical remission at Week 12 as measured by CDAI (CDAI score <150 and no ICE 1-3 by Week 12).	Difference in percentage of subjects who achieved clinical remission at Week 12 as measured by CDAI between each JNJ-64304500 treatment group and the placebo treatment group.
5	Clinical response at Week 12 as measured by CDAI (≥100-point reduction from baseline in CDAI score or CDAI score <150 and no ICE 1-3 by Week 12).	Difference in percentage of subjects who achieved clinical response at Week 12 as measured by CDAI between each JNJ-64304500 treatment group and the placebo treatment group.
6	Change from baseline in PRO-2 at Week 12. Subjects who have ICE 1-3 prior to the Week 12 visit will have a zero change from baseline in the PRO-2 score assigned.	Difference in the mean change from baseline in PRO-2 at Week 12 between each JNJ-64304500 treatment group and the placebo treatment group.
7	Clinical remission at Week 12 as measured by PRO-2 (PRO-2 score <75 and no ICE 1-3 by Week 12).	Difference in percentage of subjects who achieved clinical remission at Week 12 as measured by PRO-2 between each JNJ-64304500 treatment group and the placebo treatment group.
8	Clinical response at Week 12 as measured by PRO-2 (≥50-point reduction from baseline in PRO-2 or PRO-2 <75 and no ICE 1-3 by Week 12).	Difference in percentage of subjects who achieved Clinical response at Week 12 as measured by PRO-2 between each JNJ-64304500 treatment group and the placebo treatment group.
9	Change from baseline in SES-CD at Week 12 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score). Subjects who have ICE 1-3 prior to the Week 12 visit will have a zero change from baseline in the SES-CD score assigned.	Difference in the mean change from baseline in SES-CD at Week 12 between each JNJ-64304500 treatment group and the placebo treatment group.

Intercurrent Events and Corresponding Strategies:

The intercurrent events for all major secondary endpoints are the same as those used in the primary estimand, and are as follows:

1. A Crohn's disease-related surgery (with the exception of drainage of an abscess or seton placement).
2. A prohibited change in Crohn's disease medication (described in Attachment 1).
3. Discontinuation of study intervention due to lack of efficacy or an AE of worsening Crohn's disease.

4. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection).
5. Discontinuation of study intervention due to reasons other than lack of efficacy or an AE of worsening Crohn's disease (including COVID-19 infection).

ICEs 1-3 are handled by the composite strategy, and ICE category 4 is handled by the hypothetical strategy (as if subjects would have not experienced these intercurrent events), and ICE 5 is addressed by the treatment policy strategy. If a subject had any of the ICE categories 1-3 prior to Week 12, the subject will be considered not to be in clinical remission at Week 12 as measured by CDAI, clinical response at Week 12 as measured by CDAI, clinical remission at Week 12 as measured by PRO-2, and clinical response at Week 12 as measured by PRO-2; in addition, a zero change from baseline in the PRO-2 and SES-CD scores will be assigned for subjects experiencing ICEs 1-3 and data at all visits after an ICE 4 will be set to missing. For subjects experiencing ICE 5, observed values of the variable will be used for all major secondary endpoints, if available. For subjects experiencing multiple ICEs, the overall strategy will be based on the first ICE.

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

5.4.3.1. Estimators (Analyses) for the Main Estimands

In the analysis of the major secondary endpoints, data from all subjects in the FAS will be analyzed according to the randomized study intervention regardless of the study intervention they 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 binary variables.

The major secondary endpoints of clinical remission and clinical response at Week 12 (defined by either CDAI or PRO-2) will be compared between each of the JNJ-64304500 treatment groups and the placebo group using the Cochran-Mantel-Haenszel (CMH) chi-square test (2-sided) stratified by baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), and Bio-IR status (yes or no). The adjusted treatment difference (with Cochran-Mantel-Haenszel weight) between each of the JNJ-64304500 treatment groups and the placebo group, as well as the associated 95% confidence interval, will be presented.

The change from baseline in PRO-2 at Week 12 will be compared between each of the JNJ-64304500 treatment groups and the placebo group using MMRM method. The explanatory variables of the model will include treatment group, SNP-positive status (yes or no), Bio-IR status (yes or no), baseline PRO-2 score, visit, and an interaction term of visit with treatment group.

The change from baseline in SES-CD score at Week 12 (this is the only scheduled post-baseline visit for SES-CD data collection) will be compared between each of the JNJ-64304500 treatment groups and the placebo group using an analysis of covariance (ANCOVA) with treatment as a fixed factor and respective baseline score and baseline CDAI score (≤300 or >300), Bio-IR status

(yes or no), and SNP-positive status (yes or no) as covariates. The main approach will be used to calculate the SES-CD. An analysis will also be performed using the alternative approach to calculate the SES-CD.

For SES-CD analysis using ANCOVA, multiple imputation (imputed 200 times to generate 200 complete data sets using the Markov chain Monte Carlo method, assuming missing at random and a multivariate normal distribution) will be used to impute the missing SES-CD data.

- Weeks 0 and 12 SES-CD values and design variables (treatment assignment, baseline CDAI score (≤300 or >300), Bio-IR status (yes or no), and SNP-positive status (yes or no)) will be used to impute the missing SES-CD values.

For the major secondary endpoints, pairwise comparisons of the ustekinumab treatment group with each JNJ-64304500 treatment group or with placebo are not planned; however, summary statistics will be provided for the ustekinumab treatment group.

5.4.3.1.1. Additional Missing Data Rules for the Main Estimands

After accounting for the intercurrent events, any missing data for the binary major secondary endpoints will be handled with nonresponder imputation. In particular, the following rules will be used:

- Subjects who have a missing CDAI score (i.e. <4 components of the CDAI score) at Week 12 will be considered not to be in clinical remission or clinical response, as measured by the CDAI score.

- Subjects who have a missing PRO-2 score (i.e. at least one component score of the PRO-2 is missing) at Week 12 will be considered not to be in clinical remission or clinical response as measured by the PRO-2 score.

Missing data for the change from baseline in the PRO-2 score will be addressed by MMRM. In MMRM, missing data for the scores will not be imputed but missing data will be accounted for through correlation of repeated measures in the model under the assumption of missing at random (MAR).

5.4.4. Supplementary Estimands for the Major Secondary Endpoints

Supplementary estimands 10-15 will be used to complement Estimands 4-9.

The attributes of the supplementary estimands are the same as those for the main estimands for the major secondary endpoints, with the exception of the variable (endpoint), which is described as follows:

Variable (Endpoint):

Estimand	Variable (Endpoint)
10	Clinical remission at Week 12 as measured by CDAI (CDAI score <150 and no ICE by Week 12).
11	Clinical response at Week 12 as measured by CDAI (≥100-point reduction from baseline in CDAI score or CDAI score <150 and no ICE by Week 12).
12	Change from baseline in PRO-2 at Week 12. Subjects who have any ICE prior to the Week 12 visit will have a zero change from baseline in the PRO-2 score assigned.
13	Clinical remission at Week 12 as measured by PRO-2 (PRO-2 score <75 and no ICE by Week 12).
14	Clinical response at Week 12 as measured by PRO-2 (≥50-point reduction from baseline in PRO-2 or PRO-2 <75 and no ICE by Week 12).
15	Change from baseline in SES-CD at Week 12 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score). Subjects who have any ICE prior to the Week 12 visit will have a zero change from baseline in the SES-CD score assigned.

All ICEs are handled by the composite strategy. If a subject had any ICEs prior to Week 12, the subject will be considered not to be in clinical remission at Week 12 as measured by CDAI, clinical response at Week 12 as measured by CDAI, clinical remission at Week 12 as measured by PRO-2, and clinical response at Week 12 as measured by PRO-2. In addition, a zero change from baseline in the PRO-2 and SES-CD scores will be assigned for subjects experiencing any ICEs.

5.4.5. Estimators for the Supplementary Estimands of the Major Secondary Endpoints

The same analysis methods for the main estimands described in Sections 5.4.3.1 and 5.4.3.1.1 will be used for the supplementary estimands of the major secondary endpoints.

5.4.6. Summary of Analyses Related to Major Secondary Endpoints

Table 8 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 8: Summary of Analyses Related to Major Secondary Endpoints		
Endpoints (Analysis Set)	**Missing data**	**Analysis method/Summary statistics**
Analyses based on **Main Estimands 4-9**, where ICEs 1-3 are handled by the composite strategy, ICE 4 is handled by the hypothetical strategy, and ICE 5 is handled by the treatment policy strategy		
• Clinical remission at Week 12 as measured by CDAI (FAS) • Clinical response at Week 12 as measured by CDAI (FAS) • Clinical remission at Week 12 as measured by PRO-2 (FAS) • Clinical response at Week 12 as measured by PRO-2 (FAS)	Missing data due to missed visits or missed data collection, due to ICE 4, or due to ICE 5 in the absence of observed data. Subjects with missing data are considered to be non-responders (NRI)	• Summaries of the proportion of subjects who achieved the endpoint • Treatment difference (JNJ-64304500 group-placebo group) and 95% CI • P-value from the CMH test stratified by baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), and Bio-IR status (yes or no)
• Change from baseline in PRO-2 at Week 12 (FAS) • Change from baseline in SES-CD at Week 12 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score) (FAS)	Missing data due to missed visits or missed data collection, due to ICE 4, or due to ICE 5 in the absence of observed data. Missing data is not imputed, but is handled through the MMRM assuming MAR.	• Descriptive summary statistics • MMRM model for PRO-2; ANCOVA for SES-CD o LS mean (SD) for each treatment group o Treatment differences in LS means (95% CI) • P-values for comparing LS means
Analyses based on **Supplementary Estimands 10-15**, where all ICEs are addressed by the composite strategy.		
• Clinical remission at Week 12 as measured by CDAI (FAS) • Clinical response at Week 12 as measured by CDAI (FAS) • Clinical remission at Week 12 as measured by PRO-2 (FAS) • Clinical response at Week 12 as measured by PRO-2 (FAS)	Missing data due to missed visits or missed data collection. Subjects with missing data are considered to be non-responders (NRI)	• Summaries of the proportion of subjects who achieved the endpoint • Treatment difference (JNJ-64304500 group-placebo group) and 95% CI • P-value from the CMH test stratified by baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), and Bio-IR status (yes or no)
• Change from baseline in PRO-2 at Week 12 (FAS) • Change from baseline in SES-CD at Week 12 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score) (FAS)	Missing data due to missed visits or missed data collection. Missing data is not imputed, but is handled through the MMRM assuming MAR.	• Descriptive summary statistics • MMRM model for PRO-2; ANCOVA for SES-CD o LS mean (SD) for each treatment group o Treatment differences in LS means (95% CI) • P-values for comparing LS means

5.5. Other Endpoints

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

The endpoints in the following list will be analyzed.

- Change from baseline in CDAI at Week 12 for subjects who had baseline SES-CD ≥3 (excluding the contribution of the narrowing component score), for subjects who had baseline SES-CD ≥6 (excluding the contribution of the narrowing component score), for subjects who had isolated ileal disease with baseline SES-CD ≥4 or subjects who had colonic or ileocolonic disease with baseline SES-CD ≥6, and for subjects who had baseline abdominal pain mean daily score ≥1 and stool frequency mean daily score ≥1.5.
- Clinical remission at Week 12 as measured by CDAI (CDAI <150) for subjects who had baseline SES-CD ≥3 (excluding the contribution of the narrowing component score), for subjects who had baseline SES-CD ≥6 (excluding the contribution of the narrowing component score), for subjects who had isolated ileal disease with baseline SES-CD ≥4 or subjects who had colonic or ileocolonic disease with baseline SES-CD ≥6, and for subjects who had baseline abdominal pain mean daily score ≥1 and stool frequency mean daily score ≥1.5.
- Clinical response at Week 12 as measured by CDAI (≥100-point reduction from baseline in CDAI or CDAI <150) for subjects who had baseline SES-CD ≥3 (excluding the contribution of the narrowing component score), for subjects who had baseline SES-CD ≥6 (excluding the contribution of the narrowing component score), for subjects who had isolated ileal disease with baseline SES-CD ≥4 or subjects who had colonic or ileocolonic disease with baseline SES-CD ≥6, and for subjects who had baseline abdominal pain mean daily score ≥1 and stool frequency mean daily score ≥1.5.
- Change from baseline in PRO-2 at Week 12 for subjects who had baseline SES-CD ≥3 (excluding the contribution of the narrowing component score), for subjects who had baseline SES-CD ≥6 (excluding the contribution of the narrowing component score), for subjects who had isolated ileal disease with baseline SES-CD ≥4 or subjects who had colonic or ileocolonic disease with baseline SES-CD ≥6, and for subjects who had baseline abdominal pain mean daily score ≥1 and stool frequency mean daily score ≥1.5.
- Clinical remission at Week 12 as measured by PRO-2 (PRO-2 <75) for subjects who had baseline SES-CD ≥3 (excluding the contribution of the narrowing component score), for subjects who had baseline SES-CD ≥6 (excluding the contribution of the narrowing component score), for subjects who had isolated ileal disease with baseline SES-CD ≥4 or subjects who had colonic or ileocolonic disease with baseline SES-CD ≥6, and for subjects who had baseline abdominal pain mean daily score ≥1 and stool frequency mean daily score ≥1.5.
- Clinical response at Week 12 as measured by PRO-2 (≥50-point reduction from baseline in PRO-2 or PRO-2 <75) for subjects who had baseline SES-CD ≥3 (excluding the contribution of the narrowing component score), for subjects who had baseline SES-CD ≥6 (excluding the contribution of the narrowing component score), for subjects who had isolated ileal disease with baseline SES-CD ≥4 or subjects who had colonic or ileocolonic disease with baseline SES-CD ≥6, and for subjects who had baseline abdominal pain mean daily score ≥1 and stool frequency mean daily score ≥1.5.
- Change from baseline in CDAI at all postbaseline visits.

- Change from baseline in CDAI at all postbaseline visits for subjects who had daily average stool frequency score >=4 or daily average abdominal pain score >=2 at baseline based on the CDAI assessment.
- Clinical remission based on CDAI at all postbaseline visits.
- Clinical remission based on CDAI at all postbaseline visits for subjects who had daily average stool frequency score >=4 or daily average abdominal pain score >=2 at baseline based on the CDAI assessment.
- Clinical response based on CDAI at all postbaseline visits.
- Clinical response based on CDAI at all postbaseline visits for subjects who had daily average stool frequency score >=4 or daily average abdominal pain score >=2 at baseline based on the CDAI assessment.
- Change from baseline in PRO-2 at all postbaseline visits.
- Change from baseline in abdominal pain score (daily average based on the CDAI assessment) at all postbaseline visits.
- Change from baseline in stool frequency score (daily average based on the CDAI assessment) at all postbaseline visits.
- Clinical remission based on PRO-2 at all postbaseline visits.
- Clinical response based on PRO-2 at all postbaseline visits.
- Clinical remission based on unweighted PRO-2 (defined as daily average abdominal pain score ≤ 1 AND daily average stool frequency score ≤ 3) at all postbaseline visits.
- Abdominal pain score (daily average based on the CDAI assessment) ≤1 at all postbaseline visits for subjects who had daily average abdominal pain score >1 at baseline.
- Number of liquid or very soft stools (daily average based on the CDAI assessment) ≤3 at all postbaseline visits for subjects who had daily average number of liquid or very soft stools >3 at baseline.
- Change from baseline in PRO-3 (the sum of abdominal pain, stool frequency, and general well-being subscores of the CDAI score) at all postbaseline visits.
- Change from baseline in weighted CDAI component scores at all postbaseline visits.
- Clinical response based on CDAI at Week 24 among subjects in clinical response at Week 12.
- Clinical remission based on CDAI at Week 24 among subjects in clinical response at Week 12.
- Clinical remission based on CDAI at Week 24 among subjects in clinical remission at Week 12.
- Change from baseline in SES-CD score at Week 12 for subjects who had baseline SES-CD score ≥6 (excluding the contribution of the narrowing component score).
- Endoscopic improvement at Week 12 based on a reduction from baseline in SES-CD score ≥3 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score) and for subjects who had baseline SES-CD score ≥6 (excluding the contribution of the narrowing component score).

- Endoscopic response at Week 12 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score) and for subjects who had baseline SES-CD score ≥6 (excluding the contribution of the narrowing component score).
- Endoscopic healing (defined as the absence of mucosal ulcerations) at Week 12 for subjects who had ulcerations at baseline and baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score) and for subjects who had ulcerations at baseline and baseline SES-CD score ≥6 (excluding the contribution of the narrowing component score).
- Endoscopic remission (defined as a SES-CD score of 0-2) at Week 12 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score) and for subjects who had baseline SES-CD score ≥6 (excluding the contribution of the narrowing component score).
- Change from baseline in total GHAS at Week 12.
- Histologic Response (≥ 50% reduction in total GHAS score from baseline) at Week 12.
- Histo-Endoscopic Response (histologic response and endoscopic response) at Week 12 for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score) and for subjects who had baseline SES-CD score ≥6 (excluding the contribution of the narrowing component score).
- Fistula response at all postbaseline visits, defined as a ≥50% reduction from baseline in the number of draining for subjects with draining fistulas at baseline.
- Complete fistula response at all post-baseline visits for subjects with draining fistulas at baseline.
- Change from baseline in daily average number of BSFS types 6 and 7 stools through Week 12.
- A ≥2 reduction in daily average number of BSFS types 6 and 7 stools from baseline through Week 12 for subjects who had baseline daily average number of BSFS types 6 and 7 stools >=2.
- A ≥3 reduction in daily average number of BSFS types 6 and 7 stools from baseline through Week 12 for subjects who had baseline daily average number of BSFS types 6 and 7 stools >=3.
- Change from baseline in daily average number of BSFS types 5, 6, and 7 stools through Week 12.
- A ≥2 reduction in daily average number of BSFS types 5, 6, and 7 stools from baseline through Week 12 for subjects who had baseline daily number of BSFS types 5, 6, and 7 stools >=2
- A ≥3 reduction in daily average number of BSFS types 5, 6, and 7 stools from baseline through Week 12 for subjects who had baseline daily number of BSFS types 5, 6, and 7 stools >=3.
- Change from baseline in abdominal pain score (daily average based on a 0-10 NRS) at all postbaseline visits.
- A ≥2-point reduction in abdominal pain score (daily average based on a 0-10 NRS) from baseline at all postbaseline visits for subjects who had baseline daily average based on a 0-10 NRS >=2.

- A ≥3-point reduction in abdominal pain (daily average based on a 0-10 NRS) from baseline at all postbaseline visits for subjects who had baseline daily average based on a 0-10 NRS >=3.
- A ≥3-point reduction in abdominal pain score (daily average based on a 0-10 NRS) and a ≥3 reduction in daily average number of BSFS types 6 and 7 stools from baseline through Week 12 for subjects who had baseline daily average based on a 0-10 NRS >=3 and baseline daily average number of BSFS types 6 and 7 stools >=3.
- Subjects with abdominal pain score (daily average based on a 0-10 NRS) <3 and daily average number of BSFS types 6 and 7 stools <3 through Week 12.
- Change from baseline in IBDQ score at Weeks 8, 12, and 24.
- Clinical remission based on IBDQ (≥170) at Weeks 8, 12, and 24.
- A ≥16-point improvement in IBDQ from baseline at Weeks 8, 12, and 24.
- Change from baseline in the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of the 36-item Short Form Health Survey (SF-36) at Weeks 8, 12, and 24.
- A ≥5-point improvement in PCS or MCS scores of the SF-36 at Weeks 8, 12, and 24.
- Change from baseline in CRP at all postbaseline visits.
- Normalization in CRP at all postbaseline visits for subjects with abnormal CRP at baseline.
- Change from baseline in fecal calprotectin at Weeks 2, 8, 12, and 24.
- Normalization in fecal calprotectin at Weeks 2, 8, 12, and 24 for subjects with abnormal fecal calprotectin at baseline.
- Change from baseline in fecal lactoferrin at Weeks 2, 8, 12, and 24.
- Normalization in fecal lactoferrin at Weeks 2, 8, 12, and 24 for subjects with abnormal fecal lactoferrin at baseline.
- Clinical-biomarker response at Week 12.
- Change from baseline in the CDAI at all postbaseline visits by SNP status.
- Clinical remission based on CDAI at all postbaseline visits by SNP status.
- Clinical response based on CDAI at all postbaseline visits by SNP status.
- Change from baseline in SES-CD score at Week 12 by SNP status for subjects who had baseline SES-CD score ≥3 (excluding the contribution of the narrowing component score) and for subjects who had baseline SES-CD score ≥6 (excluding the contribution of the narrowing component score).
- Change from baseline in PGIS of Crohn's disease at Weeks 4, 8, 12, and 24.
- A ≥1-point improvement from baseline in PGIS of Crohn's disease or PGIS=1 (absent) at Weeks 4, 8, 12, and 24.
- A ≥2-point improvement from baseline in PGIS of Crohn's disease or PGIS=1 (absent) at Weeks 4, 8, 12, and 24.

- Agreement between PGIS (absent: yes or no) and clinical remission based on CDAI (yes or no) at Week 12.
- Agreement between PGIS (absent or mild: yes or no) and clinical remission based on CDAI (yes or no) at Week 12.
- Agreement between clinical remission based on unweighted PRO-2 (defined as daily average abdominal pain score ≤ 1 AND daily average stool frequency score ≤ 3 based on CDAI assessment) and subjects with abdominal pain score (daily average based on a 0-10 NRS) <3 and daily average number of BSFS types 6 and 7 stools <3 at Week 12.
- Empirical Cumulative Distribution Function (eCDF) curves of change from baseline in abdominal pain score (daily average based on a 0-10 NRS) at Week 12 by change in PGIS of Crohn's disease at Week 12.
- Empirical Cumulative Distribution Function (eCDF) curves of change from baseline in daily average number of BSFS types 6 and 7 stools at Week 12 by change in PGIS of Crohn's disease at Week 12.
- PGIS of Crohn's disease in each category at Weeks 0, 4, 8, 12, and 24.
- A ≥1-point improvement (a little better now, somewhat better now, or a lot better now) in PGIC of severity of Crohn's disease at Weeks 4, 8, 12, and 24.
- A ≥2-point improvement (somewhat better now or a lot better now) in PGIC of severity of Crohn's disease at Weeks 4, 8, 12, and 24.
- PGIC of severity of Crohn's disease in each category at Weeks 4, 8, 12, and 24.

5.5.1. Definitions

Daily average abdominal pain score

Daily average abdominal pain score is defined as: the sum of abdominal pain/cramps ratings in previous 7 days in a dairy card ÷ total days assessment performed. Daily average abdominal pain score at a scheduled visit will not be calculated if total days of assessment is less than 5.

Daily average stool frequency score

Daily average stool frequency score is defined as: total number of liquid or very soft stools in previous 7 days in a dairy card ÷ total days assessment performed. Daily average stool frequency score at a scheduled visit will not be calculated if total days of assessment is less than 5.

Daily average abdominal pain score based on a 0-10 NRS

Daily average abdominal pain score based on a 0-10 NRS is defined as: the sum of abdominal pain score based a 0-10 NRS in previous 7 days in a dairy card ÷ total days assessment performed. Daily average abdominal pain score at a scheduled visit will not be calculated if total days of assessment is less than 5.

Average number of BSFS types 6 and 7 stools per day

Average number of BSFS types 6 and 7 stools per day is defined as: the sum of number of BSFS types 6 and 7 stools in previous 7 days in a dairy card ÷ total days assessment performed. Average

number of BSFS types 6 and 7 stools per day at a scheduled visit will not be calculated if total days of assessment is less than 5.

Clinical remission as measured by unweighted PRO-2

Clinical remission as measured by unweighted PRO-2 is defined as the unweighted CDAI component of daily average abdominal pain (AP) score at or below 1 AND the unweighted CDAI component of daily average stool frequency (SF) score at or below 3, ie, AP ≤ 1 and SF ≤ 3.

PRO-3 score

PRO-3 score is defined as: the sum of abdominal pain, stool frequency, and general well-being components of the CDAI score (Note: these components have the weighting used in the calculation of the CDAI). If one of these three components cannot be evaluated, then the PRO-3 score will be set to missing.

Clinical-biomarker response

Clinical-biomarker response at Week 12 is defined as clinical response based on CDAI score and ≥50% reduction from baseline in CRP or fecal calprotectin

Fistula response

Fistula response is defined as: ≥50% reduction from baseline in the number of draining fistulas.

Complete Fistula response

Complete fistula response is defined as the complete absence of draining fistulas.

Endoscopic improvement

Endoscopic improvement is defined as ≥3 points reduction from baseline in SES-CD score.

Endoscopic response

Endoscopic response is defined as a reduction from baseline in SES-CD score of ≥50% or a SES-CD score ≤2.

Endoscopic healing

Endoscopic healing is defined as the complete absence of mucosal ulcerations in any ileocolonic segment among subjects who presented with ulceration in at least one ileocolonic segment at baseline.

Endoscopic remission

Endoscopic remission is defined as a SES-CD score ≤2.

IBDQ

The Inflammatory Bowel Disease Questionnaire (Irvine et al, 1994)[4] is a 32-item questionnaire specifically designed for subjects with IBD. The range of the IBDQ score is 32 to 224. Higher scores indicate better quality of life. The IBDQ has 4 dimension scores (bowel, systemic, social,

and emotional). Each of the individual IBDQ dimensions will be calculated when ≤ 1 item is missing in the dimension. The missing item will be estimated using the average value across the nonmissing items. If any one of the dimensions within the IBDQ cannot be calculated, then the total IBDQ score cannot be calculated.

SF-36

The SF-36 was developed as part of the Rand Health Insurance Experiment and consists of 8 multi-item scales:

- Limitations in physical functioning due to health problems
- Limitations in usual role activities due to physical health problems
- Bodily pain
- General mental health (psychological distress and well-being)
- Limitations in usual role activities due to personal or emotional problems
- Limitations in social functioning due to physical or mental health problems
- Vitality (energy and fatigue)
- General health perception

These scales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These summary scores are also scaled with higher scores indicating better health but are scored using a norm-based system where linear transformations are performed to transform scores to a mean of 50 and standard deviation of 10, based upon general US population norms (Ware et al, 1994).[9] The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments (Ware and Sherbourne, 1992).[10] Eight subscales are calculated whenever ≥ 50% of the items that comprise the individual subscale are available (nonmissing). Any missing items will be estimated using the average value across the nonmissing items for that subscale. If < 50% of the items that comprise the subscale is available, the subscale will not be calculated. If any of the individual subscales that comprise the physical component summary score or the mental component summary score are missing, then the physical or mental component summary scores cannot be calculated.

Histologic assessment and Global Histology Activity Score

Histologic assessment will be performed using biopsy samples collected during endoscopy. Up to 2 biopsy samples will be collected at screening and Week 12 from each of 3 predefined anatomic locations: the terminal ileum, splenic flexure, and rectum. Biopsies will be collected from representative areas from each of the predefined locations that are consistent with the inflammation status visually observed during endoscopy. Histologic assessment will be conducted by a single central reader who is blinded to treatment assignment and visit information. The modified Global Histology Activity Score (GHAS) will be used to evaluate histologic improvement.

Global Histology Activity Score

The Global Histology Activity Score was first described in 1998, and has been subsequently utilized in a number of studies resulting in peer-reviewed publications (DHaens, 1998; DHaens, 1999; Mojtahed, 2014; Baert, 1999; Laharie, 2011; Mantzaris, 2009).[2,3,7,1,5,6] The GHAS components and related scores are listed in Table 9.

All biopsies will be scored in a blinded manner using GHAS for each region, with minor adaptations for the circumstances of this study:

- At each time point, all biopsies (up to 2 biopsies per region) obtained from each of the predefined anatomic regions will be scored separately for each of the 6 histological features: epithelial damage, architectural changes, infiltration of mononuclear cells into the lamina propria, polymorphonuclear cells in the lamina propria (all scored 0-2); polymorphonuclear cells in the epithelium (scored 0-3); the presence of erosions/ulcers (1 for presence and 0 for absence)
- The component of presence of granulomas in the original GHAS will be excluded due to the rarity and potentially sporadic nature of granulomas, particularly in individual biopsy specimens (prevalence ~2%)
- The component of number of biopsies affected in the original GHAS will also be excluded because only up to 2 biopsies will be taken from each anatomic region in this study, while the component score was constructed based on the assumption that 6 biopsies per region are available
- The single highest scoring biopsy from each of the anatomic regions will be used as the final score for that region.

At each visit, the overall total histologic score will be derived based on the sum of the 3 regional scores. The overall GHAS can be calculated when all 3 regional scores are available. A regional score for a biopsy will be missing if any of the 6 histological features is missing.

Table 9: Scoring System for Histologic Abnormalities in Crohn's Disease Mucosal Biopsy Specimens

Histologic findings	Score
Epithelial damage	0, Normal 1, Focal pathology 2, Extensive pathology
Architectural changes	0, Normal 1, Moderately disturbed (<50%) 2, Severely disturbed (>50%)
Infiltration of mononuclear cells in the lamina propria	0, Normal 1, Moderate increase 2, Severe increase
Polymorphonuclear cells in the lamina propria	0, Normal 1, Moderate increase 2, Severe increase
Polymorphonuclear cells in epithelium	1, In surface epithelium 2, Cryptitis 3, Crypt abscess
Presence of erosion and/or ulcers	0, No 1, Yes
Presence of granuloma	0, No 1, Yes
No. of biopsy specimens affected	0, None (0 of 6) 1, ≤33% (1 or 2 of 6) 2, 33%–66% (3 or 4 of 6) 3, >66% (5 or 6 of 6)
Total	

NOTE. Each topic should be scored independently. Moderate increase, up to twice the number of cells that can normally be expected; severe increase, more than twice the normal of cells. Reprinted with permission from D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastro-

Patient's Global Impression of Severity (PGIS) of Crohn's disease

The PGIS of Crohn's disease is a 5-point scale ("None", "Mild", "Moderate", "Severe" and "Very Severe") to rate Crohn's disease intensity.

Patient's Global Impression of Change (PGIC) of Severity of Crohn's disease

The PGIC of severity of Crohn's disease is a 7-point scale ranging from "a lot better now" to "a lot worse now" with a neutral center point ("neither better nor worse") to measure perceived change (improvement or deterioration) in severity of Crohn's disease.

SNP-positive

Subjects who are positive in at least 1 of 2 SNPs (NKG2D or MICB) will be considered to be SNP-positive. Otherwise subjects are SNP-negative.

Abnormal CRP

Abnormal CRP is defined as CRP concentration >3.0 mg/L.

Abnormal fecal lactoferrin

Abnormal fecal lactoferrin is defined as fecal lactoferrin concentration >7.24 mg/kg.

Abnormal fecal calprotectin

Abnormal fecal calprotectin is defined as fecal calprotectin concentration > 250 mg/kg.

5.5.2. Analysis Methods

Other endpoints listed and defined in Section 5.5 and Section 5.5.1 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., line plots) may also be used to summarize the data.

In general, for the analyses through Week 12, comparisons between each JNJ-64304500 treatment group and the placebo treatment group will be performed based on the overall efficacy analysis set and by Bio-IR status (yes or no) (i.e., Bio-IR and Bio-NF). Pairwise comparisons of the ustekinumab treatment group with the each JNJ-64304500 treatment group or with placebo are not planned. In addition, for the efficacy analyses beyond Week 12, only descriptive statistics will be provided.

The main 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 1-3 (as specified in Section 5.3.2) will be considered to not have achieved the binary endpoints. For subjects experiencing an intercurrent event category 4, data at all visits after an ICE 4 will be set to missing. For subjects experiencing an intercurrent event in category 5, their observed values will be used, if available. For subjects experiencing multiple ICEs, the overall strategy will be based on the first ICE. In addition, for endpoints beyond Week 12, subjects in the placebo group who crossover to JNJ-64304500 treatment group will be considered to have not achieved the binary endpoints. Subjects with missing data for an endpoint will be considered to have not achieved the associated binary endpoint.

For endpoints through Week 12, the proportion of subjects achieving each endpoint will be compared between each JNJ-64304500 treatment group and the placebo group using the Cochran-Mantel-Haenszel (CMH) chi-square test (2-sided) stratified by baseline CDAI score (≤300 or >300), Bio-IR status (yes or no), and SNP-positive status (yes or no).

Additional analysis based on observed data (after the intercurrent event rules applied) will be performed for histologic assessment.

Continuous Endpoints

Baseline values (at Week 0) will be assigned from the point of an intercurrent event categories 1-3 onward, regardless of the observed data if a subject has an intercurrent event in categories 1-3 (as specified in Section 5.3.2). For subjects experiencing an intercurrent event category 4, data at all visits after an ICE 4 will be set to missing. For subjects experiencing an intercurrent event category 5, their observed values will be used, if available. In addition, for analyses beyond Week 12, baseline values (at Week 0) will be assigned from the point of crossover for subjects in the placebo group who crossover to the JNJ-64304500 treatment group.

To account for the missing data for continuous endpoints of change from baseline, the MMRM method will be used, under the assumption of missing at random (MAR), to test the difference between each JNJ-64304500 treatment group and placebo group. In MMRM, missing data will not be imputed but rather missing data will be accounted for through correlation of repeated measures in the model. Additionally, if the MMRM normality assumption is in question, an appropriate transformation may be implemented before fitting the MMRM model. The explanatory variables of the model will include treatment group, baseline CDAI score (≤300 or >300), SNP-positive status (yes or no), Bio-IR status (yes or no), respective baseline score, visit, and an interaction term of visit with treatment group. For CDAI-related endpoints (CDAI, PRO-2, PRO-3, abdominal pain score based on the CDAI assessment, and stool frequency score based on the CDAI assessment), baseline CDAI score (≤300 or >300) will not be included as an explanatory variable.

Endpoints based on SES-CD and GHAS that are measured at only one post-baseline visit will be compared between each JNJ-64304500 treatment group and placebo group using an analysis of covariance (ANCOVA) with treatment as a fixed factor and respective baseline score and baseline CDAI score (≤300 or >300), Bio-IR status (yes or no), and SNP-positive status (yes or no) as covariates.

For analyses using ANCOVA, multiple imputation (imputed 200 times to generate 200 complete data sets using the Markov chain Monte Carlo method, assuming missing at random and a multivariate normal distribution) will be used to impute the missing data.

- Weeks 0 and 12 values and design variables (treatment assignment, baseline CDAI score (≤300 or >300), Bio-IR status (yes or no), and SNP-positive status (yes or no)) will be used to impute the missing values.

6. SAFETY

All safety analyses will be based on the safety analysis set. In general, subjects will be analyzed according to the treatment they actually received.

The safety of JNJ-64304500 in subjects with Crohn's disease will be assessed by summarizing the frequency and type of AEs and changes from baseline in clinical laboratory parameters for hematology and chemistry.

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). Any AE occurring at or after the initial administration of study agent is considered to be treatment emergent (ie, TEAE). 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 will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

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

- Frequency and type of AEs
- Frequency and type of SAEs
- Frequency and type of reasonably related AEs as assessed by the investigator
- Frequency and type of AEs leading to discontinuation of study intervention
- Frequency and type of infections, including serious infections and infections requiring oral or parenteral antimicrobial treatment.
- Frequency and type of AEs temporally associated with infusion.
- Frequency and type of injection-site reactions.

These summary tables will provide the count and percentage of subjects with 1 or more of the specified TEAEs (including COVID-19 related TEAEs) by treatment group, system-organ class and preferred term.

Tables that summarize key safety events (AEs, SAEs, reasonably related AEs, AEs leading to discontinuation of study intervention, infections, and serious infections) will also be provided for frequency of events, events per 100 subject years of follow-up, and subjects with events per 100 subject years of follow-up.

In addition to the summary tables, listings of subjects with SAEs and TEAEs leading to discontinuation of study intervention will be provided. Any deaths, possible anaphylactic or serum-sickness like reactions, or malignancies, will either be presented in a listing or described in the clinical study report.

Definitions

- A reasonably related AE is defined as any event with a relationship to study intervention of 'Very likely', 'Probable', or 'Possible' on the AE eCRF page or if the relationship to study agent is missing.
- An infection is defined as any AE that was recorded as an infection by the investigator on the eCRF.
- An AE that is temporally associated with the infusion of study intervention is one that occurs during or within 1 hour of completion of the infusion, with the exception of laboratory abnormalities.
- A study intervention injection-site reaction is any reaction at an SC study intervention injection site that was recorded as an injection-site reaction by the investigator on the eCRF.

6.2. Clinical Laboratory Tests

Clinical laboratory values are to be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. The laboratory data to be summarized are as follows:

- **Hematology assessments:** hematocrit, hemoglobin, platelet count, total (leukocytes) and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and WBC count
- **Blood chemistry assessments:** ALT, AST, alkaline phosphatase, albumin, total and direct bilirubin, blood urea nitrogen, calcium, chloride, creatinine, phosphate, potassium, total protein, and sodium.

The following data analyses will be performed:

- Summary of maximum NCI-CTCAE toxicity grade for postbaseline laboratory values through Week 12, through Week 24, and through the final efficacy and safety visit for clinical laboratory parameters listed in Attachment 2.
- Shift tables for selected clinical laboratory parameters (ALT, AST, alkaline phosphatase and total bilirubin) at Week 12.
- Summary of maximum postbaseline measurement through Week 12, through Week 24, and through the final efficacy and safety visit for ALT, AST and alkaline phosphatase and total bilirubin relative to ULN.

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

The baseline value for a subject is the value closest to but prior to the first dose of study agent (Week 0). Change from baseline is defined to be the assessment at the postbaseline visit minus the assessment at baseline. Summaries of laboratory data will be completed using all the available laboratory data at the time point of interest without imputing missing data. Shift tables summarize the number of subjects with low, normal, and high values (determined by the laboratory normal ranges) at the post baseline visit for each of the classifications of low, normal, and high at baseline.

6.3. Vital Signs and Physical Examination Findings

Vital signs are measured at every visit. However, since vital signs and physical examination data were not collected on the eCRF, no summaries will be provided for vital signs and physical examination findings.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

PK analyses will be based on the pharmacokinetics analysis set (Section 2.2.4).

7.1.1. Serum Concentrations

Blood samples for determining the serum JNJ-64304500 and ustekinumab concentrations will be drawn from all subjects according to the schedule in the Protocol Time and Events Schedule. Serum JNJ-64304500 and ustekinumab concentrations will be used to evaluate various PK parameters.

Serum JNJ-64304500 and ustekinumab concentrations will be summarized using descriptive statistics (i.e., n, arithmetic mean, standard deviation [SD], coefficient of variation [%CV], median, range [minimum and maximum], and interquartile [IQ] range) at each visit. PK data may be displayed graphically.

The following analyses will be performed for each treatment group.

- Summary of serum JNJ-64304500 and ustekinumab concentrations over time by treatment group
- Proportion of subjects with serum JNJ-64304500 and ustekinumab concentrations below the lowest quantifiable concentration in a sample at each visit by treatment group.
- Summary of serum JNJ-64304500 and ustekinumab concentrations over time by treatment group and by baseline body weight (quartiles). Additional analyses by Bio-IR status (yes or no; i.e. Bio-IR and Bio-NF), immunomodulator use (yes or no), and ileal dominant Crohn's disease (yes or no) will also be performed.
- Plots of median serum JNJ-64304500 concentrations over time by treatment group.
- Plots of median serum JNJ-64304500 concentrations over time by treatment group and by baseline body weight (≤median, >median).

7.1.1.1. Data Handling Rules

Unless otherwise specified, the following data handling rules will apply to PK analyses:

- Serum concentration summaries will be based on the actual treatment received.
- All serum concentration summaries for a particular timepoint will include data obtained from treated subjects at the timepoint of interest without imputing any missing data.
- A concentration not quantifiable (below the lower limit of quantification) will be treated as 0 in the summary statistics and shown as the lower limit of quantification (< LLOQ) in the data listings.
- The data from a subject who meets at least 1 of the following dosing deviation criteria will be excluded from the by-visit data analyses from the point of the dosing deviation onwards:
  - Discontinued study agent administrations
  - Skipped an administration
  - Received an incomplete/ incorrect dose
  - Received an incorrect study agent
  - Received an additional dose
  - Received an administration outside the dosing window specified in Table 10.

Table 10: Dosing Window

Visit	Window
Week 0 through Week 24	± 5 days from scheduled visit day
Final Safety/Efficacy Follow-up visits	± 14 days from scheduled visit day

7.1.2. PK vs Efficacy

To explore the relationship between JNJ-64304500 serum concentrations and efficacy endpoints, the following analyses will be explored:

- The relationship between JNJ-64304500 serum concentrations (quartiles) at Week 12 and change from baseline in CDAI score, clinical response and clinical remission status (based on CDAI), endoscopic response and remission status, and PRO-2 change from baseline at Week 12 will be explored.
- The relationship between JNJ-64304500 serum concentrations (quartiles) at Week 24 and change from baseline in CDAI score, clinical response and clinical remission status (based on CDAI), endoscopic response and remission status, and PRO-2 change from baseline at Week 24 will be explored.
- Summaries by Bio-IR status (yes or no, i.e., Bio-IR and Bio-NF) will also be provided.

7.1.3. Population PK Analysis

When appropriate, population PK analysis will be performed using serum concentration-time data of JNJ-64304500 in all randomized subjects with the nonlinear mixed-effects modeling (NONMEM) approach. Details will be provided in a separate technical report.

7.2. Immune Response

Immune response analyses will be based on the immunogenicity analysis set (Section 2.2.5).

7.2.1. Antibodies to Study Agents

The antibodies to JNJ-64304500 and antibodies to ustekinumab status (positive at any time, negative) and titers will be summarized by treatment group for subjects who receive a dose of JNJ-64304500 or ustekinumab and have appropriate samples for detection of antibodies to JNJ-64304500 or antibodies to ustekinumab (ie, subjects with at least 1 sample obtained after their first dose of JNJ-64304500 or ustekinumab). The maximum titers of antibodies to JNJ-64304500 or antibodies to ustekinumab will be provided for subjects who are positive for antibodies to JNJ-64304500 or ustekinumab respectively.

A listing of subjects who are positive for antibodies to JNJ-64304500 or ustekinumab will be provided. The sample antibodies status, the titer, and the neutralizing antibodies status to JNJ-64304500 or ustekinumab will be listed by visit. This listing will also provide information regarding immunomodulator use at baseline, dose administered, injection-site/infusion reactions, JNJ-64304500 or ustekinumab serum concentration, and CDAI for all visits. In addition, a list of antibodies status in subjects who discontinued study agent (JNJ-64304500 or ustekinumab) early will be provided.

7.2.1.1. Neutralized Antibodies to Study Agents

The incidence of neutralizing antibodies (NAbs) to JNJ-64304500 or ustekinumab will be summarized for subjects who are positive for antibodies to JNJ-64304500 or ustekinumab and have samples evaluable for NAbs to JNJ-64304500 or ustekinumab.

7.2.2. Antibodies vs Efficacy/PK

Serum JNJ-64304500 concentrations, clinical remission/response status, and change from baseline in the CDAI score over time may be summarized by antibodies to JNJ-64304500 status if sufficient numbers of subjects are positive for antibodies. Serum ustekinumab concentrations may also be summarized by antibodies to ustekinumab status if sufficient numbers of subjects are positive for antibodies. Plots of median serum JNJ-64304500 concentrations over time by antibodies to JNJ-64304500 status and treatment group may also be provided.

7.2.3. Antibodies vs Safety

Injection site reactions will be summarized by antibodies to JNJ-64304500 or ustekinumab status if sufficient numbers of subjects are positive for antibodies.

7.3. Receptor Occupancy and Immunophenotyping

NKG2D Receptor occupancy (RO%) over time will be summarized for each treatment group (excluding ustekinumab treatment group) using descriptive statistics (number of observations, mean, SD, %CV, median, minimum and maximum, IQR). Plots for NKG2D RO percentage (median) over time by treatment will be produced. Plots by Bio-IR status (yes or no) (i.e., Bio-IR and Bio-NF) over time may also be provided.

The absolute numbers and percentages of peripheral blood NK cells and T cells (including CD4+ and CD8+) expressing NKG2D receptor over time will be summarized for each treatment group (excluding ustekinumab treatment group) using descriptive statistics (number of observations, mean, SD, %CV, median, minimum and maximum, IQR). Plots for immunophenotyping results (median) over time by treatment will be produced. Plots by Bio-IR status (yes or no) (i.e., Bio-IR and Bio-NF) over time may also be provided.

7.4. Pharmacodynamic/Biomarker Analyses

Biomarker assessments will be made to examine the biological response to treatment and to identify biomarkers that are relevant to JNJ-64304500 treatment and/or Crohn's disease. Assessments include the evaluation of relevant biomarkers in serum, whole blood (for RNA analysis), stool, and mucosal biopsy samples (for RNA and histology analysis) collected according to the Time and Events Schedule.

Biomarker analyses will characterize the effects of JNJ-64304500 on the measured biomarkers to identify biomarkers relevant to treatment and to determine if these biomarkers can predict response to JNJ-64304500. Results will be reported in separate technical reports.

CRP, fecal lactoferrin and fecal calprotectin are included in the efficacy analysis Section 5.5.

7.5. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between serum concentration of JNJ-64304500 and PD will be analyzed graphically. For example, individual NKG2D RO% measurements may be plotted against serum JNJ-64304500 concentration data at the corresponding nominal sampling time. If any visual trend is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship. In the latter case, the results of the PK/PD modeling analysis will be presented in a separate technical report. PK/PD relationships for clinical efficacy endpoints will also be investigated, including but not limited to, clinical response and clinical remission (based on CDAI). Results of the PK/PD modeling analysis for the efficacy endpoints will be presented in the separate technical report.

7.6. Pharmacogenomic Analyses

Whole blood sample collection for SNPs and DNA analysis will be collected from all subjects at Screening. All subjects will be tested for the NKG2D SNP rs2255336 and the MICB (NKG2D ligand) SNP rs2239705 at screening. Selected efficacy endpoints will be assessed by SNP status, which are included in the efficacy analysis Section 5.3. For subjects who have signed an optional pharmacogenomics consent form, DNA testing will be done to search for links of specific genes

to disease or response. Exploratory genetic analyses on DNA collection from subjects who signed the optional DNA consent will be presented in a separate technical report.

8. HEALTH ECONOMICS

The medical resource utilization analysis will be based on the efficacy analysis set. The medical resource utilization data will be analyzed according to the treatment group to which they were assigned regardless of the treatment they actually received.

For Crohn's disease-related hospitalizations and surgeries, comparison between the JNJ-64304500 treatment group and the placebo treatment group will be performed for efficacy analysis set and by Bio-IR status (yes or no) (i.e., Bio-IR and Bio-NF) through Week 12. Only descriptive statistics will be provided to summarize the data beyond Week 12.

Crohn's disease-related hospitalizations

The proportion of subjects with a Crohn's disease-related hospitalization through Week 12 will be summarized and compared between each of the JNJ-64304500 treatment groups and the placebo group using a 2-sided Cochran Mantel-Haenszel Chi-square test, stratified by baseline CDAI score (<=300 or >300), Bio-IR status (yes or no), and SNP-positive status (yes or no), at a significance level of 0.05. In case of rare events, Fisher's exact test will be used for treatment comparisons.

Crohn's disease-related surgeries

The proportion of subjects with a Crohn's disease-related surgery through Week 12 will be summarized and compared between each of the JNJ-64304500 treatment groups and the placebo group using a 2-sided Cochran Mantel-Haenszel Chi-square test, stratified by baseline CDAI score (<=300 or >300), Bio-IR status (yes or no), and SNP-positive status (Yes or no), at a significance level of 0.05. In case of rare events, Fisher's exact test will be used for treatment comparisons.

Crohn's disease-related hospitalizations or surgeries The proportion of subjects with a Crohn's disease-related hospitalization or surgery through Week 12 will be summarized and compared between each of the JNJ-64304500 treatment groups and the placebo group using a 2-sided Cochran Mantel-Haenszel Chi-square test, stratified by baseline CDAI score (<=300 or >300), Bio-IR status (yes or no), and SNP-positive status (Yes or no), at a significance level of 0.05. In case of rare events, Fisher's exact test will be used for treatment comparisons.

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ATTACHMENTS

Attachment 1 Detailed prohibited changes in CD medication (category 2 of the Intercurrent events)

- Initiation of prohibited medications:
  - 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).
  - Immunomodulatory biologic agents (including but not limited to TNF antagonists, natalizumab, abatacept, vedolizumab).
  - Experimental Crohn's disease medications (including but not limited to thalidomide, briakinumab, traficet, brodalumab [AMG 827]).
- Initiation of oral corticosteroids (including budesonide and beclomethasone dipropionate) due to worsening of Crohn's disease.
- Initiation of oral corticosteroids (including budesonide and beclomethasone dipropionate) for more than 7 days due to reasons other than worsening Crohn's disease.
- Increase in the dose of oral corticosteroids (excluding budesonide and beclomethasone dipropionate) > 5 mg/day (prednisone equivalent) above the baseline dose due to worsening of Crohn's disease.
- Increase in the dose of oral corticosteroids (excluding budesonide and beclomethasone dipropionate) > 5 mg/day (prednisone equivalent) above the baseline dose for more than 7 days due to reasons other than worsening Crohn's disease.
- Increase in the dose of oral budesonide > 3 mg/day above the baseline dose due to worsening of Crohn's disease.
- Increase in the dose of oral beclomethasone dipropionate > 5 mg/day above the baseline dose due to worsening of Crohn's disease.
- Initiation of parenteral or rectal corticosteroids due to worsening Crohn's disease.
- Any switch among oral budesonide, oral beclomethasone dipropionate or other oral corticosteroids (excluding prednisone equivalent changes) due to worsening of Crohn's disease.
- Initiation of oral or rectal 5-ASA compounds due to worsening of Crohn's disease
- Increase above baseline in the dosage of oral 5-ASA compounds due to worsening of Crohn's disease
- Change from one oral 5-ASA compound to another 5-ASA compound due to worsening of Crohn's disease
- Initiation of 6-MP/AZA/MTX due to worsening of Crohn's disease

- Increase above baseline in the dosage of 6-MP/AZA/MTX due to worsening of Crohn's disease
- Any switch between 6-MP/AZA and MTX due to worsening of Crohn's disease.
- Initiation of antibiotics due to worsening Crohn's disease.

Attachment 2: Grading Criteria for Clinical Laboratory Tests [CTCAE Version 4.03]					
Hematology Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Hemoglobin (g/L)	Decrease	≥100 - <LLN	≥80 - <100.0	≥65 - <80	<65
Neutrophils (10^9/L)	Decrease	≥1.5 - <LLN	≥1.0 - <1.5	≥0.5 - <1.0	<0.5
Platelets (10^9/L)	Decrease	≥75.0 - <LLN	≥50.0 - <75.0	≥25.0 - <50.0	<25.0
Total WBC count (Leukocytes 10^9/L)	Decrease	≥3.0 - <LLN	≥2.0 - <3.0	≥1.0 - <2.0	<1.0
Lymphocytes (10^9/L)	Decrease	≥0.8 - <LLN	≥0.5 - <0.8	≥0.2 - <0.5	<0.2
Chemistry Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
ALT	Increase	>ULN - ≤3.0 xULN	>3.0 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
AST	Increase	>ULN - ≤3.0 xULN	>3.0 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
Albumin (g/L)	Decrease	≥30 - <LLN	≥20 - <30	<20	
Alkaline Phosphatase	Increase	>ULN - ≤2.5 xULN	>2.5 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
Bilirubin (total)	Increase	>ULN - ≤1.5 xULN	>1.5 xULN - ≤3.0 xULN	>3.0 xULN - ≤10.0 xULN	>10.0 xULN
Calcium (mmol/L)	Increase	>ULN - ≤2.9	>2.9 - ≤3.1	>3.1 - ≤3.4	>3.4
Calcium (mmol/L)	Decrease	[Albumin ≥40 g/L or missing and calcium ≥2.0 - <LLN]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥2.0 - <LLN]	[Albumin ≥40 g/L or missing and calcium ≥1.75 - <2.0]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥1.75 - <2.0]	[Albumin ≥40 g/L or missing and calcium ≥1.5 - <1.75]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥1.5 - <1.75]	[Albumin ≥40 g/L or missing and calcium <1.5]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) <1.5]
Creatinine	Increase	>ULN - ≤1.5 xULN	>1.5 xULN - ≤3.0 xULN	>3.0 xULN - ≤6.0 xULN	>6.0 xULN
Phosphate (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - ≤6.0	>6.0 - ≤7.0	>7.0
Phosphate (mmol/L)	Decrease	≥0.8 - <LLN	≥0.6 - <0.8	≥0.3 - <0.6	<0.3
Potassium (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - ≤6.0	>6.0 - ≤7.0	>7.0
Potassium (mmol/L)	Decrease	≥3.0 - <LLN		≥2.5 - <3.0	<2.5
Sodium (mmol/L)	Increase	>ULN - ≤150	>150 - ≤155	>155 - ≤160	>160
Sodium (mmol/L)	Decrease	≥130 - <LLN		≥120 - <130	<120