**Janssen Research & Development ***

**Clinical Protocol**

**Intervention Specific Appendix to Master Clinical Protocol PLATFORMPACRD2001**

**PRISM-SCARLET**

**Protocol 67864238PACRD2001; Phase 2a**
**AMENDMENT 5**

**JNJ-67864238**

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

**EudraCT NUMBER:** 2019-003335-37

**Status:** Approved
**Date:** 11 May 2021
**Prepared by:** Janssen Research & Development, LLC
**EDMS number:** EDMS-ERI-154159369, 7.0

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

## PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 5 | 11 May 2021 |
| Amendment 4 | 14 December 2020 |
| Amendment 3 | 17 September 2020 |
| Amendment COVID-19 Appendix | 20 May 2020 |
| Amendment 2 | 13 November 2019 |
| Amendment 1 | 14 August 2019 |
| Original Protocol | 06 June 2019 |

### Amendment 5: 11 May 2021

**Overall Rationale for the Amendment:** The overall rationale for the amendment is to allow for additional ad hoc interim analyses to augment decision making for this JNJ-67864238 cohort.

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis;<br>4.1 Overall Design;<br>9.2.1 Decision-Making Framework;<br>9.5. Interim Analysis | Additional ad hoc interim analyses may be conducted if deemed necessary. | To augment decision making for this JNJ-67864238 intervention cohort. |
| Synopsis;<br>9.2.1 Decision-Making Framework;<br>9.5. Interim Analysis | The number of participants to be included in the interim analysis was updated from at least 45 participants to approximately 45 participants. | To provide flexibility regarding the number of participants required to conduct the interim analysis. |
| 9.2.2.2 Decision-Making Specifics at the Completion of the Intervention Cohort; | A decision-making framework based solely on Crohn's Disease Activity Index scores was added. | To add decision-making criteria based on the primary endpoint of the change in the Crohn's Disease Activity Index from baseline at Week 12. |
| 5.2 Exclusion Criteria, A01;<br><br>10.8. Appendix 8: Definition of Minimal Exposure to Ustekinumab | Exclusion criterion A01 was updated to indicate that participants who have had limited exposure to ustekinumab as defined in Appendix 8 may be eligible for this JNJ-67864238 intervention cohort.<br><br>Appendix 8 was added to specify the definition of minimal exposure to ustekinumab. | To clarify that limited prior exposure to ustekinumab may not disqualify a participant from participating in this JNJ-67864238 intervention cohort. |
| 5.1 Inclusion Criteria<br><br>6.5 Concomitant Therapy | Inclusion criterion A06 was added to address the use of COVID-19 vaccines.<br><br>Guidance was added to address the use of COVID-19 vaccines. | COVID-19 vaccines are provisionally authorized (ie, emergency-use authorization or conditional marketing authorization) and are in use. |
| 10.4 Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments | The liver safety stopping algorithm and follow-up assessments were updated. | To align with health authority guidance for liver safety. |
| 8.3.7. Adverse Events of Special Interest; | The definition of a possible Hy's law case was added. | To align with health authority guidance for liver safety. |

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.5 Appendix 5: Clinical Laboratory Tests | | |
| 8.3.7. Adverse Events of Special Interest; | Text was updated to indicate that adverse events of special interest should be reported to the sponsor in an expedited manner. | To clarify the procedures for reporting adverse events of special interest. |
| 1.3 Schedule of Activities | Footnote bb was added to indicate that at the screening visit only, the CDAI will be calculated using participant recall. The investigator will complete the variable assessments required to calculate the CDAI total score as conducted in the other visits. | To clarify the procedures for obtaining the components of the CDAI. |
| 1.3 Schedule of Activities | Footnote cc was added to indicate that for visits other than Week 0, the most recent hematocrit value obtained before a visit will be used to calculate the CDAI for that visit. | To clarify the procedures for the calculation of CDAI using the hematocrit value. |
| 5.2 Exclusion Criteria, A01;<br>7.1 Discontinuation of Study Intervention | Experimental compound MEDI2070 is now named brazikumab. | To align with current compound names. |
| 5.2 Exclusion Criteria, A01; | Experimental compound LY3074828 is now named mirikizumab. | To align with current compound names. |
| Synopsis;<br>4.1 Overall Design | For the single database lock, the term study was updated to intervention cohort. | To clarify that the single database lock applies to this JNJ-67864238 intervention cohort. |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. | Minor errors were noted. |

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### TABLES



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# 1. PROTOCOL SUMARY

## 1.1. Synopsis

**Intervention Specific Appendix to Master Clinical Protocol PLATFORMPACRD2001**

The following terms are used throughout the Master PLATFORMPACRD2001 synopsis and this 67864238PACRD2001 synopsis:

- "Participant" refers to the common term "subject"
- "Study intervention" refers to study agent, either active or placebo
- "Intervention cohort" refers to a cohort of adult participants with moderately to severely active Crohn's disease who receive a specific active study intervention or the comparator (ie, placebo and/or an active comparator) and in whom the efficacy and safety of that active study intervention is evaluated
- "JNJ-active" and "placebo" refer to the active study intervention and the inactive study intervention, respectively, being tested in an intervention cohort
  - In this intervention cohort, JNJ-active is JNJ-67864238
- "Treatment arm" refers to the treatment assignment within an intervention cohort, eg, JNJ-active, an active comparator, or placebo
- "Control arm" refers to the comparator for JNJ-active, either an active comparator or placebo
- "Intervention Specific Appendix (ISA)" refers to this 67864238PACRD2001 companion protocol to Master protocol PLATFORMPACRD2001, which describes the background information for JNJ-67864238 (eg, preclinical and clinical data), JNJ-67864238 entry criteria or assessments, JNJ-67864238 statistical assessments (eg, sample size, randomization method and ratio), and JNJ-67864238 dosage and administration information.

A platform study is a study with multiple targeted therapies investigated in a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm. This ISA describes the Phase 2a study for JNJ-67864238. It is a companion document to the Master protocol PLATFORMPACRD2001, which describes the sponsor's platform study in participants with moderately to severely active Crohn's disease. The Master protocol PLATFORMPACRD2001 describes the common study design elements and this ISA describes additional protocol elements specific to JNJ-67864238.

JNJ-67864238 is an oral antagonist of the interleukin (IL)-23 receptor (IL-23R) being developed for the treatment of moderately to severely active Crohn's disease. CCI [redacted] Targeting of the IL-23 pathway has shown to be effective in the treatment of Crohn's disease in clinical studies. Selective inhibition of IL-23R with an oral compound offers an additional opportunity to uniquely inhibit IL-23 driven pathology.

JNJ-67864238 is also known as PTG-200 and will be referred to as JNJ-67864238 in this ISA protocol synopsis.

**OBJECTIVES AND ENDPOINTS**

Refer to the synopsis of the Master protocol PLATFORMPACRD2001 for study objectives and endpoints.

**Hypothesis**

Refer to the synopsis of the Master protocol PLATFORMPACRD2001 for the study hypothesis.

## OVERALL DESIGN, INTERVENTION COHORT AND DURATION, AND NUMBER OF PARTICIPANTS

The overall study design and target population are presented in the synopsis of the Master protocol PLATFORMPACRD2001. This ISA is designed to assess the effects of a predominantly gastrointestinal-restricted anti-IL-23R compound, JNJ-67864238, for moderately to severely active Crohn's disease. This 12-week Phase 2a study is focused on proof-of-concept and will assess the safety and efficacy of an orally administered high dose of JNJ-67864238 compared with placebo in participants with Crohn's disease. Since the inhibition of the IL-23 pathway has been validated as a mechanism for treating Crohn's disease, a high dose was chosen to assess the efficacy of a locally acting anti-IL-23 inhibitor.

Participants may be biologic intolerant or refractory (Bio-IR) or biologic nonfailures (Bio-NF) populations as defined in the synopsis of the Master protocol PLATFORMPACRD2001.

A target of 90 Bio-IR and Bio-NF participants will be randomized to receive JNJ-67864238 CCI [redacted] or placebo in a 3:2 ratio using permuted block randomization, stratified by baseline Crohn's Disease Activity Index (CDAI) score (≤300, >300) and biological refractory status (Bio-IR, Bio-NF). The treatment arms for this study will be as follows:

- JNJ-67864238 CCI [redacted] (N=54)
- Placebo (N=36)

Of note, the sample size has been chosen to assess a level of efficacy consistent with that observed with systemically available biological therapies for Crohn's disease.

There is 1 database lock planned at the end of this intervention cohort. In addition, there will be a planned Interim Analysis (IA) to enable early termination of the intervention cohort if JNJ-67864238 (CCI [redacted]) is futile. Additional ad hoc IA(s) may be conducted if deemed necessary. No database locks are planned for any of the IA(s).

Refer to the synopsis of the Master protocol PLATFORMPACRD2001 for a description of the Data Monitoring Committee.

### End of Study Definition

The end of the JNJ-67864238 intervention cohort is considered as the last visit for the last participant in the intervention cohort. Refer to the synopsis of the Master protocol PLATFORMPACRD2001 for the end of study definition.

**Description of Study Interventions**

| Dosage and Administration Specifics for JNJ-67864238 and Matching Placebo | | |
|---|---|---|
| | **JNJ-67864238** | **Placebo** |
| **Dosage formulation** | A solid dosage formulation of JNJ-67864238 supplied as 300 mg oral tablets<br><br>Refer to the Investigator's Brochure for a list of excipients | Matching placebo oral tablets |
| **Unit dose strength(s)/ Dosage levels:** | 300 mg oral tablets | Matching placebo oral tablets |
| **Route of administration** | Oral | Oral |
| **Dosage instructions** | JNJ-67864238 CCI [redacted] | Matching placebo CCI [redacted] |
| **Packaging and labeling** | JNJ-67864238 will be packaged in blister packs. The study supplies will be packaged according to the randomization code and each unit will be labeled with a medication ID number.<br><br>JNJ-67864238 will be dispensed in child-resistant packaging.<br><br>JNJ-67864238 labels will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container. | Matching placebo will be packaged in blister packs. The study supplies will be packaged according to the randomization code and each unit will be labeled with a medication ID number.<br><br>Matching placebo will be dispensed in child-resistant packaging.<br><br>Matching placebo labels will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container. |
| **Preparation, handling, and storage** | All JNJ-67864238 will be stored in a secure area with restricted access. The JNJ-67864238 solid dosage formulation must be stored at controlled temperatures as indicated on the product specific labeling. | All matching placebo will be stored in a secure area with restricted access. The matching placebo must be stored at controlled temperatures as indicated on the product specific labeling. |

## EFFICACY EVALUATIONS

There are no intervention-specific efficacy evaluations. Refer to the synopsis of the Master protocol PLATFORMPACRD2001 for efficacy evaluations.

## PHARMACOKINETIC EVALUATIONS

Plasma and fecal samples will be used to evaluate the systemic and local colon exposure, respectively, of JNJ-67864238. Plasma collected for pharmacokinetics may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. In addition, biopsy samples will be used for the measurement of JNJ-67864238 tissue concentration.

## IMMUNOGENICITY EVALUATIONS

Immunogenicity will not be assessed in the JNJ-67864238 intervention cohort. Samples collected for immunogenicity would only be analyzed if required to assess other data or analyses, such as pharmacokinetics or adverse events.

## PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Pharmacodynamic assessments will be made to examine the biological response to treatment and to identify genes and proteins that are relevant to JNJ-67864238 treatment and/or Crohn's disease. Serum, fecal, and whole blood samples will be collected from all participants to study the effect of JNJ-67864238 on proteins (serum and fecal samples) and RNA expression (whole blood and biopsy samples). Stool and saliva samples will also be collected to evaluate the effects of JNJ-67864238 on the microbiome.

## PHARMACOGENOMIC (DNA) EVALUATIONS

Among participants who consent separately to this component of the study, whole genome analyses will be performed to detect associations between specific gene polymorphisms to the disease or JNJ-67864238 response. DNA analysis will be restricted to JNJ-67864238-related effects or to the diseases for which JNJ-67864238 is being developed.

## SAFETY EVALUATIONS

Participants will be screened for tuberculosis (TB) at study entry. In addition, to aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits.

Refer to the synopsis of the Master protocol PLATFORMPACRD2001 for other safety evaluations.

## STATISTICAL METHODS

### Sample Size Determination

The decision-making framework is applied to a total of 5000 virtual studies with simulated CDAI and change in the Simplified Endoscopic Score for Crohn's disease (SES-CD) data. With 90 participants (54 participants receiving JNJ-67864238 CCI [redacted] and 36 participants receiving placebo), under the alternative hypothesis, the probability of JNJ-67864238 meeting the success criteria is approximately 87%, and the probability of dropping JNJ-67864238 for futility is approximately 1%. When there is no treatment difference, the probability of JNJ-67864238 meeting the success criteria is approximately 5% and the probability of dropping JNJ-67864238 for futility is approximately 77%. There is approximately a 32% chance that the futility criteria are met at the IA.

For reference, without factoring in the interim futility analysis, the sample size of 90 participants (54 participants in the JNJ-67864238 CCI [redacted] treatment arm and 36 participants in the placebo treatment arm) will provide 90% power to detect a treatment difference at $\alpha$=0.1 (2-sided) when the true treatment difference is 60 (placebo – JNJ-67864238) in the change in CDAI at Week 12 for both Bio-IR and Bio-NF populations.

### Efficacy Analyses

There are no JNJ-67864238-specific efficacy analyses. Refer to the synopsis of the Master protocol PLATFORMPACRD2001 for efficacy analyses.

**Safety Analyses**

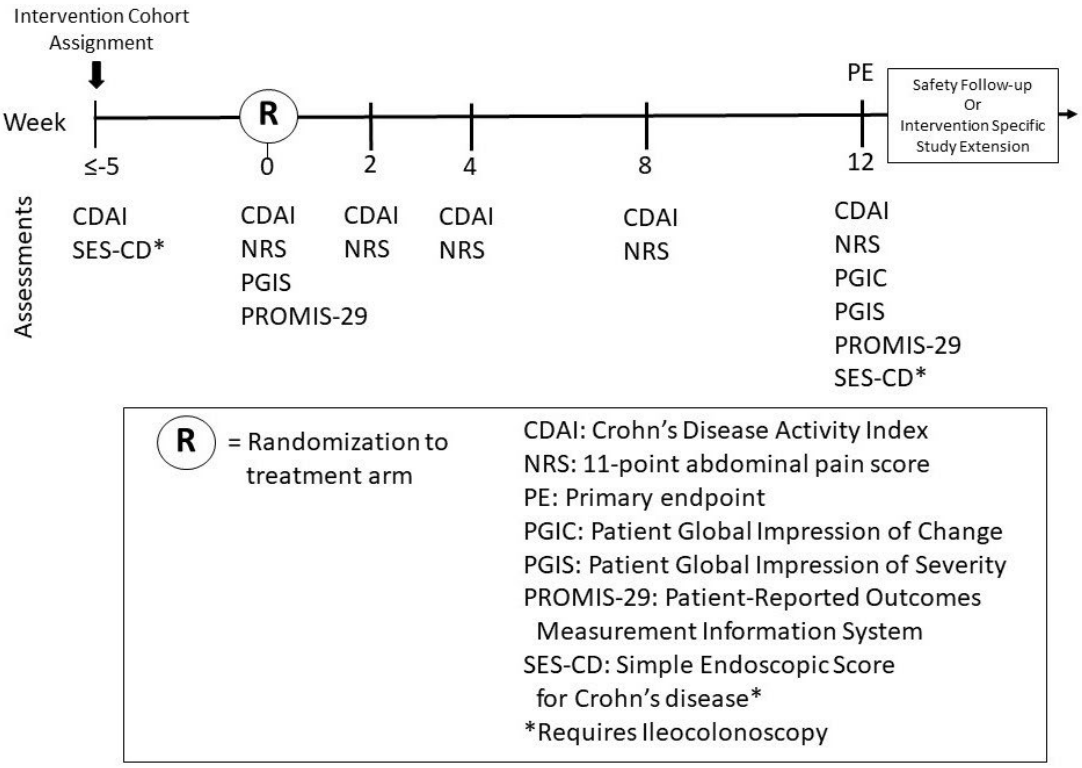
There are no JNJ-67864238-specific safety analyses. Refer to the synopsis of the Master protocol PLATFORMPACRD2001 for safety analyses.

**Interim Analyses**

One IA is planned. It will take place when approximately 45 participants have completed their Week 12 assessments or have withdrawn early from the intervention cohort. Additional ad hoc IA(s) may be conducted if deemed necessary. The objective of the IA(s) is to enable early termination of the intervention cohort if JNJ-67864238 is futile and plan for future intervention cohorts. At the time of the IA(s), the study team will remain blinded. The planned IA (and any additional IA[s]) will be described in the IA SAP.

## 1.2. Schema

**Figure 1: Schematic Overview of Study Design**



## 1.3. Schedule of Activities

A consolidated Schedule of Activities for the Master protocol PLATFORMPACRD2001 and this ISA is presented in Table 1.

**Table 1: Consolidated Schedule of Activities - PLATFORMPACRD2001 and 67864238PACRD2001**

| 67864238PACRD2001 specific events | Period | Screening[a] | Treatment Phase[b] | | | | | Early Termination[c] | Final Safety Follow-up[d] |
|---|---|---|---|---|---|---|---|---|---|
| | Week | -5 weeks | 0 | 2 | 4 | 8 | 12 | | |
| | **Study Procedures** | | | | | | | | |
| | **Screening/Administrative** | | | | | | | | |
| | Informed consent[e] | X | | | | | | | |
| | Master protocol inclusion/exclusion criteria[f] | X | X | | | | | | |
| X | JNJ-67864238 inclusion/exclusion criteria[f] | X | X | | | | | | |
| | Medical history and demographics | X | | | | | | | |
| | Immunization history | X | | | | | | | |
| | Stool studies to evaluate for enteric pathogens[g] | X | | | | | | | |
| | Height | X | | | | | | | |
| X[v] | QuantiFERON-TB test | X | | | | | | | |
| X[w] | Chest radiograph | X | | | | | | | |
| | HIV, HBV and HCV testing | X | | | | | | | |
| | Follicle stimulating hormone test (optional at the discretion of the investigator) | X | | | | | | | |
| | Serum pregnancy test[h] | X | | | | | | | |
| X (Week 4 only) | 12-lead ECG | X | | | X | | X | | X |
| | Training on diary completion | X | | | | | | | |
| | Randomization | | X | | | | | | |
| | **Study Intervention Administration** | | | | | | | | |
| X | Dispense study intervention | | X | X | X | X | | | |
| X | Administer study intervention | | Daily Self-Administration | | | | | | |
| X | Study intervention accountability | | | X | X | X | X | X | |
| | **Safety Assessments** | | | | | | | | |
| | Physical examination | X | | | | | X | X | X |

| Table 1: Consolidated Schedule of Activities - PLATFORMPACRD2001 and 67864238PACRD2001 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **67864238PACRD2001 specific events** | **Period** | **Screening[a]** | **Treatment Phase[b]** | | | | | **Early Termination[c]** | **Final Safety Follow-up[d]** |
| | **Week** | **-5 weeks** | **0** | **2** | **4** | **8** | **12** | | |
| | **Study Procedures** | | | | | | | | |
| | Body weight | X | X | X | X | X | X | X | X |
| | Vital signs [i] | X | X | X | X | X | X | X | X |
| | Urine pregnancy test [j] | | X | X | X | X | X | X | X |
| | Concomitant therapy review | X | X | X | X | X | X | X | X |
| | Adverse events review | X | X | X | X | X | X | X | X |
| X [x] | Tuberculosis evaluation/other infection assessment | X | X | X | X | X | X | X | X |
| | **Efficacy Assessments** | | | | | | | | |
| | Collect and review diary entries [k] | | X | X | X | X | X | X | |
| X [bb, cc] | CDAI assessments [l, m] | X | X | X | X | X | X | X | |
| | Fistula exam | | X | X | X | X | X | X | |
| | Abdominal pain NRS assessment [n] | | X | X | X | X | X | X | |
| | Stool sample (fecal lactoferrin and calprotectin) [o] | X | X | X | X | X | X | X | |
| X [y] | Video ileocolonoscopy with biopsies for RNA and histology [p] | X | | | | | X | X | |
| | PROMIS-29 [q] | | X | | | | X | X | |
| | PGIC | | | | | | X | X | |
| | PGIS | | X | | | | X | X | |
| | **Clinical Laboratory Assessments** | | | | | | | | |
| | Hematology [r, s] | X | X | X | X | X | X | X | X |
| | Chemistry [r, s] | X | X | X | X | X | X | X | X |
| | CRP | X | X | X | X | X | X | X | X |
| | **Pharmacokinetics/Immunogenicity** | | | | | | | | |
| X [z] | Plasma JNJ-67864238 concentration [t] | | X | X | X | X | X | X | |
| X [z] | Serum antibodies to JNJ-67864238 [t] | | X | | X | | X | X | X |
| X [aa] | Fecal samples for stool concentrations of JNJ-67864238 [t] | | | X | X | X | X | X | |
| | **Pharmacodynamics/Biomarkers** | | | | | | | | |
| | Whole blood samples for biomarkers [t] | X | X | X | X | X | X | X | X |
| | Serum samples for biomarkers [t] | X | X | X | X | X | X | X | X |
| X [aa] | Fecal samples for biomarkers [t] | X [p] | X | X | X | X | X [p] | X | X |
| | Saliva samples for microbiome [t] | | X | | | | X | X | X |

| Table 1: Consolidated Schedule of Activities - PLATFORMPACRD2001 and 67864238PACRD2001 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **67864238PACRD2001 specific events** | **Period** | **Screening[a]** | **Treatment Phase[b]** | | | | | **Early Termination[c]** | **Final Safety Follow-up[d]** |
| | **Week** | **-5 weeks** | **0** | **2** | **4** | **8** | **12** | | |
| | **Study Procedures** | | | | | | | | |
| | **Pharmacogenomics (DNA)** | | | | | | | | |
| | Whole blood samples for DNA analysis[u] | | X | | | | | | |

Abbreviations: CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; DNA=deoxyribonucleic acid; ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; NRS=numeric rating scale; PGIC= Patient's Global Impression of Change; PGIS= Patient's Global Impression of Severity; PROMIS=Patient-Reported Outcomes Measurement Information System; RNA=ribonucleic acid; TB=tuberculosis.

**Footnotes:**

a. The screening period should be a minimum of 7 days to allow for collection of CDAI data. Participants who are rescreened do not need to have a minimum of 7 days, provided that they have enough data to support CDAI calculation. The screening period should be a maximum of 5 weeks.
b. Visit windows should be ± 4 days for each visit.
c. A participant will not be automatically withdrawn if they discontinue the study intervention before the end of the intervention cohort. Participants should return for all scheduled visits including the final safety follow-up visit.
d. All participants should complete a final safety follow-up visit after their last study intervention administration. The safety follow-up period after the last dose of the study intervention should be 4 weeks.
e. Informed consents for both the Master protocol and the Intervention Specific Appendix must be signed before first study-related activity.
f. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix 5 of the Master protocol PLATFORMPACRD2001, Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study intervention.
g. Stool studies for enteric pathogens may be performed at either the central or a local laboratory and must include a stool culture and Clostridium difficile toxin assay. These must have been performed within 4 months before Week 0. Additional testing, such as ova and parasites or Escherichia coli O157:H7 assessment may be performed at the investigator's clinical discretion.
h. Must be performed before any administration of the study intervention for female participants of childbearing potential.
i. Temperature, pulse/heart rate, respiratory rate, and blood pressure.
j. Must be performed at every visit for female participants of childbearing potential.
k. For all visits up to and including Week 12, daily diary information should be collected for every day prior to each visit.
l. Hematocrit value obtained during screening will be used to calculate CDAI at Week 0.
m. CDAI will calculated using the total number of liquid or very soft stools in the previous 7 days. During the screening visit, participants should be trained on how to complete the CDAI diary, including instructions that only liquid and very loose stools should be scored using the Bristol Stool Form Scale as a reference.
n. Participant will complete the abdominal pain numeric rating scale (NRS) assessment as a daily diary entry, beginning during screening, and bring the diary to each visit. For all visits up to and including Week 12, daily diary information should be collected for every day prior to the visits. Patient-reported outcome components of the CDAI should be performed first (ie, before the NRS).
o. Stool samples required for the visits with a video ileocolonoscopy should be obtained before the start of the bowel preparation for the video ileocolonoscopy that is also scheduled for the visit.
p. Because these procedures must not interfere with the collection of CDAI data, if performed on the day of these visits, the 7 days before the initiation of the colonoscopy preparation should be used to calculate CDAI scores for these visits. If the video ileocolonoscopic examination is not performed on the day of the

visit, it must be performed at least 8 days before the Week 0 visit and no more than 8 days before the Week 12 visit or early termination visit. The Simplified Endoscopic Score for Crohn's disease (SES-CD) will be calculated by the central reader.

q. The PROMIS surveys should be administered before any clinical procedures or tests are performed. PROMIS surveys will only be collected in countries where translations are available.
r. Hematology and chemistry tests at Week 0 are not required if screening laboratory tests were performed within 2 weeks before the Week 0 visit.
s. Blood samples should be collected after PROs are administered and vital signs collected. All reasonable attempts should be made to collect samples at the scheduled timepoints and record the actual times of sample collections.
t. All reasonable attempts should be made to collect samples at the scheduled timepoints and record the actual dates and times of sample collections.
u. Requires completion of a separate informed consent.

**67864238PACRD2001 specific**

v. All participants will undergo QuantiFERON-TB testing. In countries where the QuantiFERON-TB test is not registered/approved, TB skin testing will also be required (recommended but not required for study centers in Ukraine if tuberculin is not available).
w. Chest radiograph (posterior-anterior view) must be obtained within 3 months before the Week 0 visit.
x. If TB is suspected at any time, a chest radiograph and QuantiFERON-TB test should be performed. In countries where the QuantiFERON-TB test is not registered/approved, TB skin testing should also be performed (recommended but not required for study centers in Ukraine if tuberculin is not available).
y. Biopsy samples will also be used for the measurement of JNJ-67864238 tissue concentration.
z. Venous blood samples of sufficient volume for the measurement of JNJ-67864238 plasma concentrations and to assess serum antibodies to JNJ-67864238 will be collected from all randomized participants as follows:
    - Before study intervention administration (ie, predose) at Week 0, Week 2, Week 4, Week 8, and Week 12
        i. The Weeks 2 and 8 sample should be of sufficient volume to assess the plasma concentration of JNJ-67864238 (and a backup sample).
        ii. The Weeks 0, 4, and 12 samples should be of sufficient volume to assess the plasma concentration of JNJ-67864238 (and a backup sample) and to assess serum antibodies to JNJ-67864238.
    - After study intervention administration (ie, postdose) at Week 12 within 2 to 4 hours
    - At the early termination visit (if applicable)
aa. A single stool sample (ie, bowel movement) will be collected at each visit to assess JNJ-67864238 stool concentration and biomarkers.
bb. At the screening visit only, the CDAI will be calculated using participant recall. The investigator will complete the variable assessments required to calculate the CDAI total score as conducted in the other visits.
cc. For visits other than Week 0, the most recent hematocrit value obtained before a visit will be used to calculate the CDAI for that visit.

# 2. INTRODUCTION

## Background

There is significant unmet medical need for patients with Crohn's disease. To rapidly identify efficacious and novel treatment options for these patients, a large number of Phase 2 therapies need to be evaluated.

A platform study is a study with multiple targeted therapies investigated in a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm.[14] Therefore, Crohn's disease is ideally suited for a platform study, as the general design and endpoints required for Phase 2 development are common across compounds.

Master protocol PLATFORMPACRD2001 describes the common study design elements in the sponsor's platform program in participants with moderately to severely active Crohn's disease. This Intervention Specific Appendix describes the Phase 2a 67864238PACRD2001 study for JNJ-67864238 and additional protocol elements specific to this Intervention Specific Appendix (ISA). For complete study information, refer to both the PLATFORMPACRD2001 and the 67864238PACRD2001 protocols.

JNJ-67864238 is an oral antagonist of the interleukin (IL)-23 receptor (IL-23R) being developed for the treatment of moderately to severely active Crohn's disease. CCI [redacted] Targeting of the IL-23 pathway has shown to be effective in the treatment of Crohn's disease in clinical studies.[11,6,4,12]

JNJ-67864238, also known as PTG-200, is being jointly developed by Janssen Research & Development and Protagonist Therapeutics and will be referred to as JNJ-67864238 in this ISA protocol.

For the most comprehensive nonclinical and clinical information regarding JNJ-67864238, refer to the latest version of the Investigator's Brochure (IB) and Addenda for JNJ-67864238.

## Terminology

The following terms are used throughout the Master protocol PLATFORMPACRD2001 and this 67864238PACRD2001 protocol:

- "Participant" refers to the common term "subject"
- "Study intervention" refers to study agent, either active or placebo
- "Intervention cohort" refers to a cohort of adult participants with moderately to severely active Crohn's disease who receive a specific active study intervention or the comparator (ie, placebo and/or an active comparator) and in whom the efficacy and safety of that active study intervention is evaluated

- "JNJ-active" and "placebo" refer to the active study intervention and the inactive study intervention, respectively, being tested in an intervention cohort
  - In this intervention cohort, JNJ-active is JNJ-67864238
- "Treatment arm" refers to the treatment assignment within an intervention cohort, eg, JNJ-active, an active comparator, or placebo
- "Control arm" refers to the comparator for JNJ-active, either an active comparator or placebo
- "Intervention Specific Appendix (ISA)" refers to this 67864238PACRD2001 companion protocol to Master protocol PLATFORMPACRD2001, which describes the background information for JNJ-67864238 (eg, preclinical and clinical data), JNJ-67864238 entry criteria or assessments, JNJ-67864238 statistical assessments (eg, sample size, randomization method and ratio), and JNJ-67864238 dosage and administration information.
- "Sponsor" refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

## 2.1. Study Rationale

Initial observations from genetic and animal model data suggest that Crohn's disease is mediated by IL-12 and/or IL-23, potentially through the induction of Th1 and Th17 pathways.[10] However, increasing evidence suggests a predominant role for IL-23 in Crohn's disease. Genome-wide association studies identified polymorphisms in the IL-23R gene that are associated with Crohn's disease.[2] The role of IL-23 in driving intestinal inflammation has been shown in several mouse models of inflammatory bowel disease (IBD). Mice treated with anti-IL-23 antibodies exhibited attenuated inflammation,[10] and mice with a genetic deletion of the p19 subunit of IL-23 are protected in several models of intestinal inflammation.[9]

The potential therapeutic role of IL-23 in Crohn's disease was first established by clinical studies of the IL-12/23p40 antagonist ustekinumab.[13] While these studies demonstrated that blockade of both IL-12 and IL-23 is effective in treating Crohn's disease, it could not ascertain the relative contributions of the 2 cytokines. More recent studies of 2 anti-IL-23 antagonists risankizumab[4,5] and brazikumab[12] reported Phase 2 results demonstrating efficacy of IL-23 blockade alone in participants with moderately to severely active Crohn's disease.

Selective inhibition of IL-23R with an oral compound offers an additional opportunity to uniquely inhibit IL-23 driven pathology. JNJ-67864238, an IL-23 receptor (IL-23R) antagonist, is being developed as an oral treatment for patients with IBD. In vitro studies have shown that JNJ-67864238 binds selectively to IL-23R, blocks IL-23 mediated phosphorylation of Stat3 in a transformed cell line and in whole blood, and reduces the production of cytokines in primary cells. In vivo studies in a rat colitis model showed dose-dependent and significant attenuation of disease parameters with high concentrations of JNJ-67864238 detected in the gastrointestinal (GI) tissue and stool and with low systemic exposure.

Following oral administration, CCI [redacted] Thus,

JNJ-67864238 offers an opportunity for differentiation from the injectable monoclonal antibody therapeutics and represents an innovative approach to the treatment of patients with IBD.

## 2.2. Background

### Nonclinical Studies

#### *Pharmacologic Profile*

In vitro and in vivo studies have been conducted to assess the activity, pharmacokinetics (PK) and toxicology of JNJ-67864238. In vitro, JNJ-67864238 is a potent and selective antagonist of the IL-23 receptor and blocks IL-23 mediated phosphorylation of Stat3 in a transformed cell line and in whole blood and reduces the production of cytokine in primary cells (refer to Section 3 of the IB for details). CCI [redacted]

In vitro stability studies and the CCI [redacted]

In vivo, JNJ-67864238 is efficacious in attenuating colitis in a 2,4,6 trinitrobenzene sulfonic acid (TNBS)-induced rat model of IBD by reducing the ratio of colon weight to length and improving the gross pathology and histopathology of the diseased colon comparable to treatment with an anti-IL-23p19 monoclonal antibody. The efficacy of JNJ-67864238 in the colitis model was associated with detectable drug in the stool corresponding with high concentrations of the drug in the GI tissue but low systemic exposure.

#### *Safety Pharmacology*

JNJ-67864238 has been evaluated for cardiovascular safety in the in vitro human ether-à-go-go-related gene (hERG) assay and by an in vivo radio telemetry study in monkeys.

JNJ-67864238 did not induce any meaningful inhibition of the hERG potassium current.

Cardiovascular assessments were also included in a 90-day monkey study near the end of the dosing period and no treatment-related changes were seen in electrocardiogram (ECG) parameters, heart rate, blood pressure, and body temperature. Effects on respiratory and neurobehavioral function were also assessed in rats and no adverse changes were reported.

#### *Toxicology*

The potential toxicity of JNJ-67864238 was evaluated in repeated dose studies in rats (up to 6 months in duration) and monkeys (for up to 9 months in duration) and in a standard battery of safety pharmacology and genetic toxicity studies. Potential effects on reproductive safety were assessed in rats and rabbits. No JNJ-67864238-related adverse changes were observed in any study, and the no observed effect level (NOEL) or the no observed adverse effect level (NOAEL) in each study was typically the highest dose level evaluated.

Embryo-fetal developmental safety was evaluated in rats and rabbits, and no untoward effects were detected at CCI [redacted] (the highest dose tested). JNJ-67864238 was evaluated in rats for effects on male and female fertility and no adverse findings were noted at CCI [redacted] (the highest dose tested). JNJ-67864238 was not genotoxic in a standard panel of genotoxicity assays.

***Pharmacokinetic Profile***

After a single oral dose to rats and monkeys, absorption was rapid, with a $T_{max}$ of ≤0.5 hour and 1 hour in the rat and monkey, respectively. Absolute bioavailability was less than 0.15% and 0.03% in the rat and monkey, respectively.

The retention of JNJ-67864238 in selected GI tissues was assessed after repeated oral dosing in rats and monkeys. These studies demonstrated a comparatively high GI tissue exposure and low plasma exposure of JNJ-67864238. The observed high tissue:plasma ratios after repeated doses (in rat) supports the assumption that the activity of JNJ-67864238 will be restricted to the GI tract.

JNJ-67864238 was also assessed for its ability to inhibit the cytochrome (CYP) drug metabolizing isozymes. JNJ-67864238 is not an inhibitor of CYP activity and, coupled with the very low systemic exposure after oral administration, that there is no concern for drug-drug interactions through CYP inhibition.

In vitro studies evaluated JNJ-67864238 as a potential inhibitor of human P-glycoprotein (P-gp or Multidrug Resistance 1 [MDR1] protein), the efflux transporter involved in the intestinal absorption and biliary and renal excretion of drugs. The inhibitory effect of JNJ-67864238 on the MDR1-mediated efflux of digoxin was determined at seven concentrations of JNJ-67864238 (0.82-600 μM). JNJ-67864238 did not decrease the net efflux ratio of digoxin, a P-gp substrate, indicating that JNJ-67864238 is not an inhibitor of MDR1/P-gp. It is concluded that drug-drug interactions with co-administered drugs which are P-gp substrates are unlikely.

Immunogenicity was not tested in animals.

**Clinical Studies**

***Human Pharmacokinetics, Pharmacokinetics, Safety, and Tolerability***

Study PTG-200-01

Study PTG-200-01 was a Phase 1, randomized, double-blind, placebo-controlled, first-in-human (FIH) study to assess the safety, tolerability, and PK of JNJ-67864238 in healthy study participants. The study was done in 2 parts: Part 1 Single Ascending Dose and Part 2 Multiple Ascending Dose.

Safety Summary

Part 1 Single Ascending Dose: Thirty-one healthy male participants enrolled in 3 single ascending dose cohorts: CCI [redacted]. There were no deaths or serious adverse events (SAEs) reported. With the exception of 1 adverse event (AE; nausea) that was reported to be moderate in

intensity, all AEs were reported to be mild in severity, transient in nature and generally resolved while the study participant was at the study site.

Part 2 Multiple Ascending Dose: Fifty-one healthy male participants enrolled in 5 dose cohorts and received PTG-200 as follows [redacted] Five participants (3 treated with PTG-200 and 2 treated with placebo) reported a total of 7 moderate AEs including 3 events of headache (PTG-200 groups only) and single events of vasovagal syncope, ligament sprain, triglyceride increase and constipation. All other AEs were mild in severity, transient in nature and generally resolved while the study participant was at the study site.

Overall, there were no SAEs, no severe AEs, life-threatening AEs, or AEs that led to withdrawal from the study. There was no evidence of a dose-dependent effect.

No clinically relevant changes were observed in physical examinations, vital signs, ECGs or safety laboratory assessments in either the single or multiple dose cohorts.

Pharmacokinetic Summary

Part 1 Single Ascending Dose: Following single-dose oral administration of JNJ-67864238 of [redacted] This is consistent with the nonclinical profile of the drug intended for local intestinal action and the estimated absolute oral bioavailability in the rat at approximately 0.1% of fecal recovery of JNJ-67864238, and plasma elimination half-life.

[redacted]

Part 2 Multiple Ascending Dose: After repeated oral administrations of JNJ-67864238 at 5 ascending dosages [redacted] Comparisons of AUC and $C_{max}$ values between Day 1 and Day 14 suggest accumulation in the plasma did not occur between scheduled doses for dose levels up to and including the [redacted] group. There was no evidence of excretion of JNJ-67864238 via urine for dose levels up to [redacted], with only 1 subject in the [redacted] group having quantifiable drug concentrations above the urine assay limit. Median fecal concentration of intact JNJ-67864238 increased with dose level and frequency.

## 2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of JNJ-67864238 may be found in the IB.

### 2.3.1. Risks for Study Participation

| Potential Risks of Clinical Significance | Summary of Data/ Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Non-response to oral anti-IL23. | This is the first study examining JNJ-67864238 in participants with Crohn's disease. | Participants should continue treatment of Crohn's disease with certain concomitant medications (Section 5.1 of this ISA). Participants will be withdrawn from the study if continuation is not in their best interest or if they need to initiate protocol-prohibited medications including certain biologics or immunomodulators (Section 7.1 of this ISA). |
| **Risks Due to JNJ-67864238** | | |
| Risk of infection, including tuberculosis (TB). | Available animal and human data suggest that systemic blockade of IL-23 may be associated with an increased infection risk. However, unlike a systemically administered anti-IL-23 molecule, JNJ-67864238 is designed to be GI restricted and exhibits minimal plasma exposure. Therefore, the potential that JNJ-67864238 may increase the risk of infections or reactivation of latent infections is considered to be low (Section 5.8 of the IB). | Systemic exposure with JNJ-67864238 is far below that required for pharmacodynamic (PD) effect, therefore risk of infection or TB reactivation is not expected.<br><br>Participants with either a chronic infection, a prior history of recurrent infection, or a clinically important active infection should not receive JNJ-67864238. Participants will be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a participant develops a serious infection they will be closely monitored and JNJ-67864238 will not be administered during the infection. Following resolution of a serious infection, JNJ-67864238 may be reinitiated at the discretion of the investigator and/or the medical monitor.<br><br>Participants with evidence of active or latent TB will be excluded. |

| Potential Risks of Clinical Significance | Summary of Data/ Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Vaccine responsiveness may be blunted by concurrent anti-IL-23 treatment. | The theoretical risk of systemic anti-IL-23 reducing primary or secondary vaccine responses has been considered but has not been demonstrated to date. | Prior to initiating therapy, participants should have completed all age-appropriate immunizations according to current immunization guidelines. Immunization history will be assessed at screening. Participants must agree not to receive a live attenuated virus vaccination during the study and for 30 days after receiving the last dose of JNJ-67864238. |
| **Risks Due to Study Procedures** | | |
| A colonoscopy procedure will be performed at enrollment and at 12 weeks post dosing (the primary endpoint time point). | Serious complications of colonoscopy such as a perforation are rare (less than 1/1000); other risks associated with colonoscopies include abdominal pain, diarrhea, bleeding, flatulence, anal bleeding, and bloating. | All participants must sign a consent form to have a colonoscopy as part of this study, which will include an explanation of the risks and benefits of the procedure. Standard of care will be practiced by the investigator performing the procedure to minimize risks. |

### 2.3.2. Benefits for Study Participation

JNJ-67864238 is predominantly GI restricted, thereby minimizing the risk of systemic side effects that could occur due to systemic exposure to high concentrations of an IL-23 inhibitor. This potentially gives oral JNJ-67864238 an advantage over the injectable therapeutics that target the same immune pathway (IL-23) because most of it does not enter or last in the systemic circulation at high concentrations. Thus, JNJ-67864238 offers an opportunity for differentiation from the injectable, systemic anti-IL-23 monoclonal antibody therapeutics and represents an innovative approach to the treatment of patients with IBD.

The clinical efficacy of JNJ-67864238 has not been evaluated in patients with Crohn's disease. Therefore, the benefit of JNJ-67864238 in Crohn's disease is not yet known. However, studies of systemic anti-IL-23 compounds have shown efficacy for both clinical and endoscopic improvement in up to ~30% of patients. In addition, approved anti-IL-12/23 or anti-IL-23 drugs (ie, STELARA® [ustekinumab], TREMFYA® [guselkumab]) have been generally safe and well tolerated by patients in the approved indications of psoriasis and Crohn's disease for STELARA and psoriasis for TREMFYA. Thus, the potential benefit of participating in this study is that JNJ-67864238 could induce clinical response and remission of Crohn's disease. Participants will also have regular follow-up with their physician during this study, and this type of monitoring (ie, physical exams and laboratory assessments) may result in improved care of their disease.

JNJ-67864238 is not an injectable medication (ie, not a subcutaneous [SC] injection or intravenous [IV] infusion) but is an oral tablet that will be administered at CCI [redacted]. If approved, it will be a convenient treatment for patients, reducing the burden of missing school or work for a drug infusion or dealing with the pain and inconvenience of injections.

Participants in the study will also help in furthering development of this and other oral drugs specifically designed to treat Crohn's disease. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering with Crohn's disease by developing better, more potent, and safer medications for this disease.

### 2.3.3. Benefit-Risk Assessment for Study Participation

The dose regimen of JNJ-67864238 selected for this study demonstrated a favorable safety profile in a Phase 1 FIH healthy volunteer study. There were no adverse drug reactions reported.

Available animal and human data support the critical role of IL-23 in the pathogenesis of Crohn's disease, and studies with other anti-IL-23 monoclonal antibodies (mAbs) suggest that selective targeting of IL-23 may achieve higher levels of efficacy than that observed with other mechanisms of action in patients with moderately to severely active Crohn's disease. Participants with Crohn's disease with evidence of active disease and an inadequate response or loss of response to biologics (ie, anti-tumor necrosis factor [TNF] agents, anti-integrins) or immunomodulators (ie, 6-mercaptopurine, azathioprine, or methotrexate) are eligible for this study. Given their history with other agents, many of these participants may have few other treatment options to induce and/or maintain remission of active disease. Anti-IL-12/23 drug therapy (ustekinumab) has demonstrated efficacy in patients who are naïve to anti-TNF therapy or who have received anti-TNF therapy. Due to the unique design of JNJ-67864238, most of it is concentrated in the GI tract with very little of it reaching the systemic circulation. Thus, the low risk of infection associated with the systemic anti-IL23 drug compounds, as described in Section 5.8 of the IB, are significantly minimized with JNJ-67864238. Although an efficacy response with JNJ-67864238 in Crohn's disease has not been established, given the low systemic exposure and risk of infection, there is a potential benefit to participants who may respond to treatment with investigational JNJ-67864238.

Some participants will receive placebo for the duration of the study, which will eliminate exposure to JNJ-67864238 and any possible benefit or adverse effects associated with it. All participants should continue to receive protocol-permitted, existing background medications for Crohn's disease. In addition, if participants experience worsening of their Crohn's disease, they have the option to discontinue the study intervention and initiate other treatment at the discretion of their physician.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with JNJ-67864238 are justified by the anticipated benefits that may be afforded to participants with Crohn's disease.

# 3. OBJECTIVES AND ENDPOINTS

Refer to Section 3 of the Master protocol PLATFORMPACRD2001 for study objectives and endpoints.

**HYPOTHESIS**

Refer to Section 3 of the Master protocol PLATFORMPACRD2001 for the study hypothesis.

# 4. STUDY DESIGN

## 4.1. Overall Design

This ISA is designed to assess the effects of a predominantly gastrointestinal-restricted anti-IL-23R compound for moderately to severely active Crohn's disease. This 12-week Phase 2a study is focused on proof-of-concept and will assess the safety and efficacy of an orally administered high dose of JNJ-67864238 compared with placebo in participants with Crohn's disease. Since the inhibition of the IL-23 pathway has been validated as a mechanism for treating Crohn's disease, a high dose was chosen to assess the efficacy of a locally acting anti-IL-23 inhibitor.

The target population for this intervention cohort is defined in Section 4.1.2 of the Master protocol PLATFORMPACRD2001 (ie, men or women 18 to 75 years of age with moderately to severely active Crohn's disease of at least 3 months' duration, defined as a Crohn's Disease Activity Index (CDAI) score ≥220 but ≤450 at Week 0, with a Simplified Endoscopic Score for Crohn's disease (SES-CD) score ≥3 by central endoscopy read OR an elevated C-reactive protein (CRP; >0.3 mg/dL or 3.0 mg/L) or elevated fecal calprotectin (>250 µg/mg). In this intervention cohort, however, participants with a screening SES-CD score <3 who have an elevated CRP or elevated fecal calprotectin will be limited to 20% of the participant population.

Participants may be biologic intolerant or refractory (Bio-IR) or biologic nonfailures (Bio-NF) populations as defined in Section 4.1.2 of the Master protocol PLATFORMPACRD2001.

A target of 90 Bio-IR and Bio-NF participants will be randomized to receive JNJ-67864238 CCI or placebo in a 3:2 ratio using permuted block randomization, stratified by baseline CDAI score (≤300, >300) and biological refractory status (Bio-IR, Bio-NF). The treatment arms for this study will be as follows:

- JNJ-67864238 CCI (N=54)
- Placebo (N=36)

Of note, the sample size has been chosen to assess a level of efficacy consistent with that observed with systemically available biological therapies for Crohn's disease (Section 2.1 of this ISA).

There is 1 database lock (DBL) planned at the end of this intervention cohort. In addition, there will be a planned Interim Analysis (IA) to enable early termination of the intervention cohort if JNJ-67864238 (CCI) is futile. Additional ad hoc IA(s) may be conducted if deemed necessary. No DBLs are planned for any of the IA(s).

The Data Monitoring Committee (DMC) and Interim Analysis Committee for the study are described in Section 9.5.1, Section 9.6 and Appendix 5, Regulatory, Ethical, and Study Oversight Considerations, all in the Master protocol PLATFORMPACRD2001.

A diagram of the study design is provided in Section 1.2 of this ISA, Schema.

## 4.2. Scientific Rationale for Study Design

JNJ-67864238 is the first JNJ-active compound in the Crohn's disease platform study described in the Master protocol PLATFORMPACRD2001.

Refer to Section 4.2 of the Master protocol PLATFORMPACRD2001 for a full description of the scientific rationale for the study design.

### 4.2.1. Study-Specific Ethical Design Considerations

The primary ethical concern is that participants enrolled in an intervention cohort will be randomized to receive either active study intervention or placebo for 12 weeks, with no therapeutic benefit for this portion of the study. While patients with Crohn's disease do traditionally benefit from inclusion in clinical studies independent of the assigned therapy and many improve even while on placebo (up to 30-50%), the duration of the placebo-controlled induction period has been limited to the extent possible while still maintaining sufficient scientific rigor for meaningful evaluation of critical endoscopic endpoints. Also, participants will be closely monitored during this 12-week period and will continue to receive existing background therapy for Crohn's disease. Participants with worsening Crohn's disease can discontinue the study intervention at any time, and the study intervention should be discontinued if a participant requires additional therapy for Crohn's disease.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study and is described Section 8 of this ISA.

Refer to Section 4.2.1 of the Master protocol PLATFORMPACRD2001 for other study-specific ethical design considerations.

## 4.3. Justification for Dose

JNJ-67864238 is administered orally for local action in the intestinal tract with very little systemic exposure (absolute bioavailability approximately 0.1% in the rat and approximately 0.03% in the monkey). The human equivalent dose approach and relative in vitro (IC50 for IL 23R) and ex vivo (white blood cell pSTAT3 IC50) potency in preclinical species versus humans was used to select the JNJ-67864238 doses evaluated in the FIH study (PTG-200-01). The JNJ-67864238 doses evaluated in the single ascending dose part were CCI [redacted]; the doses evaluated in the multiple ascending dose part were CCI [redacted] The dosage selected for this proof-of-concept study is the highest dosage tested in the FIH study (ie, CCI [redacted]). This dosage also produced consistent fecal JNJ-67864238 concentrations in humans which, on average, greatly

exceed the estimated EC80 concentrations or the 50% probability of obtaining a favorable colonic score shown to be efficacious in a TNBS-induced rat model of colitis.

The FIH study in healthy subjects demonstrated that CCI [redacted] are safe and generally well tolerated. After multiple dosing, fecal samples showed that only those subjects administered JNJ-67864238 CCI [redacted] had substantially higher (~24-fold) median fecal JNJ-67864238 concentrations than the 15,000 ng/mL threshold target.

In view of these results and to maximize the likelihood of a positive outcome in this study, the JNJ-67864238 dose selected is CCI [redacted]. This dose is also supported by a preclinical exposure-response analysis of the efficacy of JNJ-67864238 in treating rats with TNBS-induced colitis, as well as safety data following daily dosing for up to 6 months in rats and 9 months in monkeys.

In summary, a dosage of JNJ-67864238 CCI [redacted] is selected for this study, as it is supported by preclinical exposure-response modeling, human safety/tolerability from the FIH study, and the toxicology margins established in the Good Laboratory Practice studies.

### 4.4. End of Study Definition

The end of the JNJ-67864238 intervention cohort is considered as the last visit for the last participant in the intervention cohort. Refer to Section 4.4 of the Master protocol PLATFORMPACRD2001 for a full description of the end of study definition.

## 5. STUDY POPULATION

To be eligible to participate in the JNJ-67864238 intervention cohort, potential participants must meet all inclusion and exclusion criteria described in Section 5.1 and Section 5.2, respectively, of the Master protocol PLATFORMPACRD2001, which are also listed below. Potential participants must also meet the additional JNJ-67864238-specific inclusion and exclusion criteria presented in Section 5.1 and Section 5.2 of this ISA, respectively, to participate in the JNJ-67864238 intervention cohort.

Considerations specific to JNJ-67864238 include the following:

- Participants who have failed anti-IL-12/23 and anti-IL-23 agents will be excluded.
- Participants with known allergies, hypersensitivity, or intolerance to JNJ-67864238 or its excipients will be excluded.
- As reactivation of latent tuberculosis (TB) has been reported with systemic IL-23 inhibition, participants with evidence of active or latent TB will be excluded. However, because systemic exposure with JNJ-67864238 is far below that required for a pharmacodynamic (PD) effect, the risk for TB reactivation is expected to be low.

Screening for eligible participants will be performed within 5 weeks before administration of the study intervention. Refer to Section 5.4 of this ISA, Screen Failures, for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in the Master protocol PLATFORMPACRD2001 and this ISA are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

## 5.1. Inclusion Criteria

Each potential participant must satisfy all of the following Master PLATFORMPACRD2001 protocol and these ISA-specific criteria to be enrolled in the JNJ-67864238 intervention cohort.

Master PLATFORMPACRD2001 protocol inclusion criteria are listed below.

1. Male or female

2. 18 to 75 years of age, inclusive

**Disease Characteristics**

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

4. Have active Crohn's disease, defined as a baseline CDAI score of ≥220 and ≤450

5. Have evidence of active ileocolonic Crohn's disease as assessed by:
    a. An SES-CD score ≥3 at screening by central endoscopy reading

       OR

    b. An elevated screening CRP (>0.3 mg/dL or 3.0 mg/L) or an elevated screening fecal calprotectin (>250 µg/mg)

6. A participant with a family history of colorectal cancer, personal history of increased risk of colorectal cancer, age >50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance (may be performed during screening). Adenomatous polyps must be removed before the first administration of the study intervention.

7. A participant who has had extensive colitis for ≥8 years, or disease limited to the left side of the colon for ≥12 years, must either have had a colonoscopy to assess for the presence of dysplasia within 1 year before the first administration of the study intervention or a colonoscopy to assess for the presence of malignancy at the screening visit, with no evidence of malignancy

**Concomitant or Previous Medical Therapies Received**

8. Meet the following requirements for prior or current medications for Crohn's disease:
    a. Has previously demonstrated inadequate response to, loss of response to, or intolerance to an approved biologic therapy (unless otherwise specified in the JNJ-67864238 intervention cohort specific criteria below, ie, anti-TNFα agents [eg, infliximab, adalimumab, certolizumab pegol], anti-IL-12/23 agents [eg, ustekinumab], or anti-integrin agents [eg, vedolizumab]), ie, the Bio-IR population (Appendix 2 of the Master protocol PLATFORMPACRD2001 [Definition of Inadequate Initial Response, Loss of Response, or Intolerance to TNF Antagonist Therapies (Infliximab, Adalimumab, or Certolizumab Pegol), Vedolizumab, or Ustekinumab] and Section 5.2 of this ISA)

    **OR**

    b. Has previously demonstrated an inadequate response to or failed to tolerate corticosteroids or immunomodulators (ie, 6-MP, AZA, and MTX) but not a biologic, ie, the Bio-NF population (Appendix 3 of the Master protocol PLATFORMPACRD2001, Definitions of Inadequate Response to or Intolerance of Corticosteroids or AZA/6 MP and Corticosteroid Dependence)

9. Therapy for the treatment of Crohn's disease must include at least 1 of the following medications, which should have been maintained at stable doses prior to the baseline (Week 0) visit:
    a. Oral 5-aminosalicylic acid (5-ASA) compounds
    b. Oral corticosteroids at a prednisone-equivalent dose ≤25 mg/day, or 9 mg/day of budesonide, or 5 mg/day beclomethasone dipropionate
    c. Antibiotics being used as a primary treatment of Crohn's disease
    d. Conventional immunomodulators (ie, AZA, 6-MP, or MTX) if participants have been taking them for at least 12 weeks and have been at a stable dose for at least 4 weeks prior to baseline

**Laboratory Parameters**

10. Have screening laboratory test results within the following parameters:
    a. Hemoglobin ≥8.0 g/dL

b. White blood cell count (WBCs) $\geq 3.0 \times 10^3/\mu L$

c. Neutrophils $\geq 1.5 \times 10^3/\mu L$

d. Platelets $\geq 100 \times 10^3/\mu L$

e. Serum creatinine <1.7 mg/dL

f. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations must be within 2 times the upper limit of the normal range for the laboratory conducting the test

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

**Pregnancy Testing**

11. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) pregnancy test result at screening and a negative urine pregnancy test result at Week 0.

**Other**

12. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study

13. Must sign a separate ICF if he or she agrees to provide optional DNA samples for research (where local regulations permit). Refusal to give consent for the optional DNA research samples does not exclude a participant from participation in the study

14. Willing and able to adhere to the lifestyle restrictions specified in this protocol

JNJ-67864238 intervention cohort specific inclusion criteria start with the letter A and are listed below.

A01. A woman using oral contraceptives must use an additional contraceptive method (above that required in Inclusion Criterion A02).

A02. A woman must be (as defined in Appendix 2 of this ISA, Contraceptive and Barrier Guidance and Collection of Pregnancy Information)

a. Not of childbearing potential

b. Of childbearing potential and

- Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 30 days

after last dose - the end of relevant systemic exposure. Examples of highly effective methods of contraception are located in Appendix 2 of this ISA, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

A03. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 30 days after receiving the last dose of study intervention.

A04. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person.

A05. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 90 days after receiving the last dose of study intervention.

A06. It is recommended that participants are up to date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. For study participants who received locally approved (and including emergency use-authorized) COVID-19 vaccines recently prior to study entry, follow applicable local vaccine labeling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.5 Concomitant Therapy).

## 5.2. Exclusion Criteria

Any potential participant who meets any of the following Master PLATFORMPACRD2001 protocol and these ISA-specific criteria will be excluded from participating in the JNJ-67864238 intervention cohort.

Master PLATFORMPACRD2001 protocol exclusion criteria are listed below.

**Disease Characteristics**

1. Has complications of Crohn's disease such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation that might be anticipated to require surgery, could preclude the use of the CDAI to assess response to therapy, or would possibly confound the ability to assess the effect of treatment with JNJ-67864238
2. Currently has or is suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained and adequately treated at least 3 weeks before baseline, or 8 weeks before baseline for intra-abdominal abscesses, provided that there is no anticipated need for any further surgery. Participants with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses identified.
3. Has had any kind of bowel resection within 6 months or any other intra-abdominal surgery within 3 months before baseline

4. Has a draining (ie, functioning) stoma or ostomy

**Concomitant or Previous Medical Therapies Received**

5. Has received any of the following prescribed medications or therapies within the specified period:

| Compound | Exclusionary Period |
|---|---|
| a. Intravenous corticosteroids | <3 weeks before baseline |
| b. Oral immunomodulatory agents including 6-thioguanine (6-TG), cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil, tofacitinib and other Janus kinase (JAK) inhibitors | <6 weeks or within 5 half-lives of agent before baseline, whichever is longer |
| c. Natalizumab or biologic agents that deplete B or T cells (eg, rituximab or alemtuzumab) | <12 weeks before baseline |

6. Has received a TNFα-antagonist biologic agents (eg, monoclonal antibody therapies) within 8 weeks prior the first administration of the study intervention or vedolizumab within 16 weeks prior to the first administration of the study intervention OR has received an anti-IL-12/23 (eg, ustekinumab) within 16 weeks prior to the first administration of the study intervention OR has detectable serum concentrations of an advanced therapy (ie, TNFα-antagonist biologic agents, vedolizumab, and tofacitinib)
7. Initiation of total (complete) or partial (supplemental) parenteral nutrition administered through any indwelling catheter <3 weeks before baseline or anticipated to require parenteral nutrition administered through an indwelling catheter during enrollment in the study
8. Initiation of enteral therapy for Crohn's disease (liquid nutritional formula comprising ≥80% of total caloric intake administered through the gastrointestinal tract) <3 weeks before baseline. Subjects who are on a stable regimen of enteral feeds ≥3 weeks before baseline may be considered for enrollment if they plan to continue enteral feeds as treatment for Crohn's disease through the duration of the study.

**Infections or Predisposition to Infections**

9. Has a history of serious infection (eg, sepsis, pneumonia, or pyelonephritis), including any infection requiring hospitalization or IV antibiotics, within 8 weeks before baseline
10. Has a stool culture or other examination positive for an enteric pathogen, including *Clostridium difficile* toxin, in the last 4 months unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen, or has had a fecal transplant in the last 4 months

11. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection, recurrent urinary tract infection (eg, recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers
12. Has current signs or symptoms of infection. Established nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator
13. Has or ever has had a systemic nontuberculous mycobacterial infection or serious opportunistic infection (eg, cytomegalovirus colitis, Pneumocystis carinii, aspergillosis)
14. Is infected with human immunodeficiency virus (HIV; positive serology for HIV antibody). If seropositive, consultation with a physician with expertise in the treatment of HIV is recommended
15. Is seropositive for antibodies to hepatitis C virus (HCV) without a history of successful treatment, defined as being negative for HCV RNA at least 24 weeks after completing antiviral treatment
16. Is infected with hepatitis B virus (HBV; Appendix 4 of the Master protocol PLATFORMPACRD2001, Hepatitis B Virus Screening). For participants who are not eligible for this study due to HBV test results, consultation with a physician with expertise in the treatment of HBV infection is recommended.

**Malignancy or Increased Potential for Malignancy**

17. Has a known history of lymphoproliferative disease, including monoclonal gammopathy of unknown significance, lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly
18. Known malignancy or a history of malignancy before screening (with the exception of basal cell carcinoma; squamous cell carcinoma in situ of the skin; or cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years before screening)

**Coexisting Medical Conditions or Past Medical History**

19. History of liver or renal insufficiency (estimated creatinine clearance below 60 mL/min); significant cardiac, vascular, pulmonary, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances
20. Has a transplanted organ (with exception of a corneal transplant >12 weeks before screening)

**Other**

21. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins
22. Is currently or intending to participate in any other study using an investigational agent or procedure during participation in this study
23. Received an investigational treatment or used an invasive investigational medical device within 5 half-lives of the investigational treatment before baseline before the planned first dose of study intervention
24. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
25. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
26. Participants must not have a history of drug or alcohol abuse according to the Diagnostic and Statistical Manual of Disorders (5th edition) criteria within the last 12 months

JNJ-67864238 intervention cohort specific exclusion criteria start with the letter A and are listed below.

A01. Updated per Amendment 5.

A01.1. Prior exposure to an anti-IL-12/23 (ie, ustekinumab) or anti-IL-23 agents or related compound (including risankizumab, brazikumab, guselkumab, mirikizumab, and related compounds). Exception is made for participants who have had minimal exposure to ustekinumab at its approved labeled dosage AND have met the required wash-out criteria AND have not demonstrated inadequate response or intolerance to ustekinumab as defined in Appendix 8 of this ISA.

A02. Known allergies, hypersensitivity, or intolerance to JNJ-67864238 or its excipients (refer to IB for JNJ-67864238)

A03. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 30 days after the last dose of study intervention.

A04. Plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention

A05. Unable or unwilling to swallow CCI intact study intervention tablets CCI with approximately 240 mL (8 ounces) of water

**Tuberculosis Exclusion Criteria**

A06 Have a history of latent or active TB prior to screening

A07 Have signs or symptoms suggestive of active TB upon medical history and/or physical examination

A08 Have had recent close contact with a person with active TB

A09 QuantiFERON®-TB test criteria:

a. Within 2 months prior to the first administration of study agent, have a positive QuantiFERON®-TB test result; Within 2 months, a positive tuberculin skin test (Appendix 3 of this ISA, Tuberculin Skin Testing) prior to the first administration of study agent is exclusionary if the QuantiFERON®-TB test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

b. Indeterminate results should be handled as outlined in Section 8.11 of this ISA. Participants with persistently indeterminate QuantiFERON®-TB test results may be enrolled without treatment for latent TB, if active TB is ruled out, a chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the participant's source documents and initialed by the investigator.

A10 Have a chest radiograph (posterior-anterior view) taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with evidence of current, active TB or old, inactive TB or that shows an abnormality suggestive of a malignancy or current active infection

A11 Have a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening

A12 Have had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening or any other live bacterial or live viral vaccination within 12 weeks before baseline

**NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4 of this ISA and Section 5.4 of the Master protocol PLATFORMPACRD2001, Screen Failures, describe options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 5 of the Master protocol PLATFORMPACRD2001, Regulatory, Ethical, and Study Oversight Considerations.

### 5.3. Lifestyle Considerations

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

1. Refer to Section 6.5 of this ISA, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

3. Must agree not to receive a live attenuated virus vaccination during the study and for 30 days after receiving the last dose of study intervention.

4. Must agree not to receive a BCG vaccination during the study and for 30 days after receiving the last dose of study intervention.

### 5.4. Screen Failures

Refer to Section 5.4 of the Master protocol PLATFORMPACRD2001 for screening failure considerations.

Participants who meet the entry criteria for inclusion per the Master protocol PLATFORMPACRD2001 but do not meet the entry criteria for participation per this ISA may be rescreened to this or another ISA, depending on the reason for screen failure. Participants who meet exclusion criteria A01 or A02 (Section 5.2 of this ISA) may not be rescreened to this ISA.

## 6. STUDY INTERVENTION

### 6.1. Study Interventions Administered

JNJ-67864238 will be provided as CCI [redacted] for oral administration. Participants will be instructed to take their assigned dose of the study intervention (JNJ-67864238 or matching placebo tablets) CCI [redacted] orally CCI [redacted]. The study intervention is to be taken with approximately 240 mL (8 ounces) of water. The tablets should be swallowed intact with no attempt to dissolve them in water.

The dosage and administration specifics for JNJ-67864238 tablets and the matching placebo tablets are described in Table 2.

| Table 2: Dosage and Administration Specifics for JNJ-67864238 and Matching Placebo | | |
|---|---|---|
| | **JNJ-67864238** | **Placebo** |
| **Dosage formulation** | A solid dosage formulation of JNJ-67864238 supplied as 300 mg oral tablets<br><br>Refer to the IB for a list of excipients | Matching placebo oral tablets |
| **Unit dose strength(s)/ Dosage levels:** | 300 mg oral tablets | Matching placebo oral tablets |
| **Route of administration** | Oral | Oral |
| **Dosage instructions** | JNJ-67864238 CCI [redacted] taken CCI [redacted] | Matching placebo taken CCI [redacted] |
| **Packaging and labeling** | JNJ-67864238 will be packaged in blister packs. The study supplies will be packaged according to the randomization code and each unit will be labeled with a medication ID number.<br><br>JNJ-67864238 will be dispensed in child-resistant packaging.<br><br>JNJ-67864238 labels will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container. | Matching placebo will be packaged in blister packs. The study supplies will be packaged according to the randomization code and each unit will be labeled with a medication ID number.<br><br>Matching placebo will be dispensed in child-resistant packaging.<br><br>Matching placebo labels will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container. |
| **Preparation, handling, and storage** | All JNJ-67864238 will be stored in a secure area with restricted access. The JNJ-67864238 solid dosage formulation must be stored at controlled temperatures as indicated on the product specific labeling. | All matching placebo will be stored in a secure area with restricted access. The matching placebo must be stored at controlled temperatures as indicated on the product specific labeling. |

Study intervention administration (date and time) must be captured in the source documents and the case report form (CRF) or another system selected by the sponsor. Study-site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

JNJ-67864238 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

For a definition of JNJ-67864238 overdose, refer to Section 8.4 of this ISA, Treatment of Overdose.

## 6.2. Preparation/Handling/Storage/Accountability

### Preparation/Handling/Storage

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

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

### Accountability

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

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the study intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the study intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants enrolled in the study. Returned study intervention must not be dispensed again, even to the same participant. Whenever a participant brings his or her study intervention to the study site for pill count, this is not seen as a return of supplies. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

### JNJ-67864238 Intervention Cohort

#### *Randomization*

Central randomization will be implemented in this study. Participants assigned to this intervention cohort and eligible to enroll will be randomized to 1 of 2 treatment arms in a 3:2 ratio

(JNJ-67864238:placebo) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

***Stratification***

The study intervention randomization in this cohort will be balanced by using randomly permuted blocks and will be stratified by the baseline CDAI score (<300 and ≥300) and population (Bio-IR and Bio-NF). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the study intervention treatment arm and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

**Blinding**

After all 90 randomized participants have either completed the Week 12 visit or have terminated study participation before Week 12, the Week 12 DBL will occur and the treatment assignment information will be unblinded to the sponsor for all participants and released to the sponsor for analysis. The final safety DBL will occur when all randomized participants have either completed the final safety visit or have terminated study participation.

Refer to Section 6.3 of the Master protocol PLATFORMPACRD2001 for additional blinding considerations.

## 6.4. Study Intervention Compliance

Participant compliance with the protocol-specified administration of the study intervention (CCI [redacted] by mouth CCI [redacted]) will be assessed by the site at each clinic visit following baseline (Day 1) up to the end of treatment.

Study-site personnel will maintain a log of all study intervention administered. Drug supplies for each participant will be inventoried and accounted for.

## 6.5. Concomitant Therapy

Concomitant therapies must be recorded throughout the study beginning with the signing of the ICF to the last study visit (including the follow-up visit).

Concomitant therapies should also be recorded beyond the follow-up visit only in conjunction with new or worsening AEs and SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1 of this ISA.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of treatment, treatment period, dosing

regimen, route of administration, and its indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

Participants are not to receive the prohibited prestudy therapies listed in Exclusion Criteria 5, 6, and A01.

When considering use of locally approved (and including emergency use-authorized) COVID-19 vaccines in study participants, follow applicable local vaccine labelling, guidelines, and standards of care for participants receiving immune-targeted therapy.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

### 6.5.1. Rescue Medication

Participants may transiently use (ie, for <4 weeks) increased doses of corticosteroids for reasons other than loss of response to treatment for Crohn's disease (eg, stress doses of corticosteroids for surgery, asthma, adrenocortical insufficiency, etc).

Although enrolled participants should not initiate or increase the dose of oral or rectal 5-ASA compounds, immunomodulators (ie, AZA, 6-MP, or MTX), corticosteroids, or antibiotics as a treatment for Crohn's disease so as not to confound the efficacy assessments, it is recognized that the use of such compounds may be medically necessary. In such cases, participants may continue to receive the study intervention, but would be considered a treatment failure. This would not represent a deviation from the study protocol.

### 6.5.2. Crohn's Disease-Specific Therapies

Participants must continue to receive their concomitant, background oral 5-ASA compounds, the immunomodulators AZA, 6-MP, and MTX, oral corticosteroids, and/or antibiotics for the treatment of Crohn's disease during the study (as defined in the inclusion criteria). **Concomitant medications for Crohn's disease at study enrollment should be maintained at a stable dose throughout this study.**

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

- Oral or rectal 5-ASA compounds
- Immunomodulators (ie, AZA, 6-MP, or MTX)
- Parenteral or rectal corticosteroids
- Antibiotics as a treatment for Crohn's disease
- Total parenteral nutrition as a treatment for Crohn's disease

Because protection of human research participants is paramount, it is recognized that initiating or modifying the dose of the above therapies may be medically required. If the above medications are initiated or medication doses are changed, participants may continue to receive the study

intervention, and should continue to attend all study visits and have all assessments. If due to medical necessity in the opinion of the investigator, the above medications are initiated or medication doses are changed, this does not represent a deviation from the study protocol, but may be considered a treatment failure.

Oral corticosteroid should not be initiated during the study.

Concomitant corticosteroids must remain stable through Week 8. Participants receiving corticosteroids at baseline must begin tapering corticosteroids at Week 8. When corticosteroid tapering is commenced, the daily dose of prednisone or the equivalent should be decreased by 5 mg/week until the daily dose is 20 mg, and then by 2.5 mg/week until the daily dose is 0 mg. Participants receiving budesonide must begin tapering starting at Week 8. When budesonide tapering is commenced, the daily dose of budesonide should be decreased by 3 mg every 3 weeks until the daily dose is 0 mg. For participants who experience a worsening of disease activity while tapering oral corticosteroid or budesonide, further dose decreases may be suspended and/or their dose increased if deemed necessary by the investigator. The oral corticosteroid or budesonide dose, however, may not be increased above the baseline dose unless due to medical necessity. These participants will not be considered treatment failures unless their dose of oral corticosteroids or budesonide is increased above the baseline dose.

### 6.5.3. Prohibited Medications

Participants **must not initiate** any of the following prohibited medications:

- Immunomodulatory non-biologic 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 TNFα antagonists, natalizumab, vedolizumab, and ustekinumab)
- Experimental Crohn's disease medications

Because protection of human research participants is paramount, it is recognized that initiating such therapies may be required due to medical necessity. However, initiation of these prohibited medications should be documented as a deviation from the study protocol, and the participant will be discontinued from receiving further study intervention.

Participants must not enroll in any other clinical study with an investigational agent while in this study and must terminate study participation if they do. A participant who intends to enroll in any other clinical study with an investigational agent should undergo an early termination visit before he or she withdraws from study participation.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

### 6.6. Dose Modification

Dose modification is not permitted in this intervention cohort.

### 6.7. Study Intervention After the End of the Study

Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF (refer to Informed Consent in Appendix 5 of the Master protocol PLATFORMPACRD2001, Regulatory, Ethical, and Study Oversight Considerations).

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

## 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1. Discontinuation of Study Intervention

Participants will not be automatically withdrawn from the study if they discontinue the study intervention before the end of the dose regimen.

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, an AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant. Refer to Appendix 2 of this ISA, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
- The participant is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
  - A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB test result and/or an indeterminate QuantiFERON®-TB test result on repeat testing (refer to Section 5.2 of this ISA); and/or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities.
- The participant develops an opportunistic infection, ie, an infection by an organism that usually causes disease only in a host whose resistance is lowered (eg, Pneumocystis jirovecii, coccidioidomycosis, Mycobacterium avium).

- The participant develops a malignancy including squamous cell skin cancer. Consideration may be given to allow participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study agent.
- The participant initiates any of the following protocol-prohibited medications at any time during the study:
  - Immunomodulatory agents other than AZA, 6-MP, or MTX (including, but not limited to, 6-TG, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus).
  - Immunomodulatory biologic agents (including, but not limited to, TNF antagonists, abatacept, anakinra, rituximab, vedolizumab, natalizumab, ustekinumab).
  - Experimental Crohn's disease medications (including, but not limited to, tofacitinib, etrolizumab, guselkumab, risankizumab, brazikumab, or other experimental anti-IL-23 agents).
  - Thalidomide or related agents.
- The participant has any Crohn's disease-related surgeries that represent a lack of efficacy of study agent or will preclude the future ability to assess efficacy through the CDAI
  - Other permitted Crohn's disease-related surgeries (eg, to resolve long-standing complications such as strictures or for symptomatic nonhealing fistulas, in participants experiencing improvement on the study intervention) other than minor procedures (eg, placement of a seton or cutaneous drainage of an abscess) should be postponed until after the Week 12 visit, unless necessary to ensure the participant's well-being and/or safety.
- The participant develops severe hepatic function abnormalities, as described in Section 8.2.4 and Appendix 4, Liver Safety: Suggested Actions and Follow-up Assessments, both of this ISA
- Adverse events of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 will be evaluated by the investigator and the study medical monitor to make a determination on discontinuation of the study intervention. Discontinuation of the study intervention should be considered in participants with worsening Crohn's disease where continuation of the study drug is not in the best interest of the participant.
- Total (complete) or partial (supplemental) parenteral nutrition is initiated through an indwelling catheter at any time during the study.
- A participant has symptoms of anaphylaxis, such as bronchospasm with wheezing and/or dyspnea that requires ventilatory support OR that results in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg following study intervention administration. This may include events of NCI-CTCAE toxicity grade ≥3.
- A participant has a serious adverse allergic reaction that is possibly related to the study intervention.
- The participant (or the participant's representative) withdraws consent for administration of the study intervention.

In the event of any serious infection, the intervention must be held and may not be resumed until the investigator has discussed the case with the study medical monitor.

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered to ensure the protocol-specified number of participants complete the study.

Refer to Section 7.1 of the Master protocol PLATFORMPACRD2001 for additional considerations for discontinuation of study intervention.

## 7.2. Participant Discontinuation/Withdrawal From the Study

Refer to Section 7.2 of the Master protocol PLATFORMPACRD2001 for participant discontinuation or withdrawal considerations.

## 7.3. Lost to Follow-up

Refer to Section 7.3 of the Master protocol PLATFORMPACRD2001 for follow-up considerations.

# 8. STUDY ASSESSMENTS AND PROCEDURES

**Overview**

Participants in the JNJ-67864238 intervention cohort will be assessed using the study evaluations described in Section 8 of the Master protocol PLATFORMPACRD2001. Participants will also be assessed using the following JNJ-67864238-specific assessments and procedures.

The Schedule of Activities (Table 1) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, and safety measurements applicable to this intervention cohort.

**Contraception**

Women of childbearing potential must have a negative serum β-hCG pregnancy test result at screening as described in the Schedule of Activities (Table 1). Participants must be reminded that they are required to use a highly effective method of contraception during the study and must continue using contraception as directed after receiving the last administration of the study intervention (Section 5.1 of this ISA). The method(s) of contraception used by each participant must be documented. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

**Blood Volume**

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 500 mL.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the World Health Organization's *Blood Donor Selection: Guidelines on Assessing Donor Suitability for Blood Donation*, which state that whole blood donation should not exceed 13% of blood volume (ie,

350 mL ± 10% for a donor with a body weight of 45 kg and 450 mL ± 10% for a donor with a body weight of 50 kg). The total blood volume collected in this study is below the amounts recommended for a single blood donation.[14]

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

## 8.1. Efficacy Assessments

Refer to Section 8.1 of the Master protocol PLATFORMPACRD2001 for efficacy assessments.

## 8.2. Safety Assessments

Refer to Section 8.2 of the Master protocol PLATFORMPACRD2001 for safety assessments. Participants in the JNJ-67864238 intervention cohort will also have the safety assessments in the following sections. The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (Table 1).

### 8.2.1. Physical Examinations

Physical examination will be performed as indicated in the Schedule of Activities (Table 1). Clinically significant findings should be reported as AEs.

### 8.2.2. Vital Signs

Temperature, pulse/heart rate, blood pressure, respiratory rate, and body weight will be assessed.

### 8.2.3. Electrocardiograms

During ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before the ECG and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Electrocardiograms will be performed at screening, Week 12, and the final safety visit.

### 8.2.4. Clinical Safety Laboratory Assessments

Clinical laboratory assessments will include hematology assessments, blood chemistry assessments, pregnancy testing, serology (HIV antibody; HBV surface antigen [HBsAg; Appendix 4 of the Master protocol PLATFORMPACRD2001, Hepatitis B Virus Screening]; and HCV antibody), and liver function tests (Appendix 4 of this ISA, Liver Safety: Suggested Actions and Follow-up Assessments) for additional information on monitoring and assessment of abnormal liver function tests.

Pregnancy testing (serum or urine) should be conducted as indicated in the Schedule of Activities (Table 1).

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

### 8.2.5. Signs of Infection

The study intervention should not be administered to a participant with a clinically important, active infection. Investigators are required to evaluate participants for any signs or symptoms of infection, and also review participant's diary entries for signs of infection, at scheduled visits in the Schedule of Activities (Table 1). If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of the study intervention (ie, no further study intervention administrations) must be considered.

## 8.3. Adverse Events and Serious Adverse Events

Refer to Section 8.3 of the Master protocol PLATFORMPACRD2001 for considerations for collecting AEs and SAEs.

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

**All Adverse Events**

All AEs and special reporting situations (Appendix 6 of the Master protocol PLATFORMPACRD2001, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting), whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Beyond the protocol-specified follow-up period, the investigator should report any AEs they consider associated with the use of the study intervention (ie, possibly, probably, or very likely related to the study intervention according to the Attribution Definitions in Appendix 6 of the Master protocol PLATFORMPACRD2001, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting) to Janssen Global Medical Safety.

**Serious Adverse Events**

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician

from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

### 8.3.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 6 of the Master protocol PLATFORMPACRD2001, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

### 8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events:

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

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

### 8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are

considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.

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

### 8.3.5. Concomitant Medication Review

Concomitant medications will be reviewed as indicated in the Schedule of Activities (Table 1).

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

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study treatment, is considered an SAE.

### 8.3.7. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in participants participating in this clinical study are considered AEs of special interest and must be reported by the investigator in an expedited manner according to the procedures in Appendix 6 of the Master protocol PLATFORMPACRD2001, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

A **possible Hy's law case** is defined by the occurrence of ALT/AST ≥3 x the upper limit of normal (ULN), alkaline phosphatase <2 x ULN together with Tbili ≥2 x ULN or international normalized ratio >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and should be reported to the sponsor in an expedited manner using the adverse events of special interest form, even before all other possible causes of liver injury have been excluded (FDA 2009).

A confirmed Hy's law case must be reported as a SAE.

## 8.4. Treatment of Overdose

For this study, any dose of JNJ-67864238 greater than the assigned treatment within a 24-hour time period ±8 hours will be considered an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

Note that overdose is a special reporting situation (Appendix 6 of the Master protocol PLATFORMPACRD2001, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting).

## 8.5. Pharmacokinetics

Pharmacokinetic assessments will be used to understand the disposition of JNJ-67864238 in participants with moderately to severely active Crohn's disease. Plasma and fecal samples will be used to evaluate the systemic and local colon exposure, respectively, of JNJ-67864238. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. In addition, biopsy samples will also be used for the measurement of JNJ-67864238 tissue concentration.

Participant confidentiality will be maintained.

### 8.5.1. Evaluations

Venous blood samples and fecal samples will be collected for the determination of plasma and fecal concentrations of JNJ-67864238 according to the Schedule of Activities (Table 1).

Blood samples for the measurement of JNJ-67864238 plasma concentrations will be collected from all randomized participants as follows:

- Before study intervention administration at Week 0, Week 2, Week 4, Week 8, and Week 12
- After study intervention administration at Week 12 within 2 to 4 hours
- The early termination visit (if applicable)

The exact dates and times of PK blood sampling must be recorded on the laboratory requisition form. Additional information about the collection, handling, and shipment of biological samples can be found in the applicable Laboratory Manual.

Stool samples for the measurement of JNJ-67864238 concentrations will be collected from all randomized participants as follows:

- At Week 2, Week 4, Week 8, and Week 12
- The early termination visit (if applicable)

Biopsy samples collected during video ileocolonoscopy will be used for the measurement of JNJ-67864238 tissue concentration.

### 8.5.2. Analytical Procedures

Plasma, fecal, and biopsy tissue samples will be analyzed to determine concentrations of JNJ-67864238 using validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry methods by or under the supervision of the sponsor.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future analysis of other co-administered treatments and protein binding and the metabolite profile.

### 8.5.3. Pharmacokinetic Parameters and Evaluations

**Parameters**

Sparse samples will be collected for the determination of plasma concentrations of JNJ-67864238. Since a population PK model is not available for JNJ-67864238, PK parameters cannot be estimated.

**Pharmacokinetic/Pharmacodynamic Evaluations**

The relationship between plasma, fecal, and biopsy tissue concentrations of JNJ-67864238 and PD and/or clinical endpoints may be examined if appropriate.

## 8.6. Pharmacodynamics

Pharmacodynamic assessments will be made to examine the biological response to treatment and to identify genes and proteins that are relevant to JNJ-67864238 treatment and/or Crohn's disease. The results will be used to inform Phase 3 study design.

## 8.7. Genetics

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary, where local regulations permit.

Whole genome analyses will be performed to detect associations between specific gene polymorphisms to the disease or JNJ-67864238 response. DNA research will be performed only on samples from participants consenting to DNA analysis and will be restricted to JNJ-67864238-related effects or to the diseases for which JNJ-67864238 is being developed.

A participant may withdraw such consent at any time without affecting their participation in other aspects of the study, or their future participation in the study.

## 8.8. Biomarkers

Serum, fecal, and whole blood samples will be collected from all participants to study the effect of JNJ-67864238 on proteins (serum and fecal samples) and RNA expression (whole blood and

biopsy samples). Protein and RNA expression data will be used to assess and predict effects on clinical disease activity and will support study interpretation and disease understanding. Computational analysis will be performed on a subset of analytes shown by the sponsor to relate to disease activity in IBD to compare effects of JNJ-67864238 to placebo.

Stool and saliva samples will also be collected to evaluate the effects of JNJ-67864238 on the microbiome.

Results will be presented in a separate technical report.

**Serum-based Biomarkers**

Blood samples for serum-based biomarker analyses will be collected from all participants. Assays to be performed may include the following: CCI [redacted]

**Whole Blood-based Biomarkers**

Whole blood samples will be collected from all participants to study the effect of JNJ-67864238 on RNA expression. Whole blood analyses may also examine RNA expression associated with the pathogenesis of Crohn's disease.

**Biopsy-based Biomarkers**

Biopsy samples will be collected during video ileocolonoscopy to study the effect of JNJ-67864238 on gene and protein expression and for the histologic assessment of disease and healing. Biopsy analyses may also examine gene and protein expression associated with the pathogenesis of Crohn's disease.

**Stool-based Biomarkers**

Stool samples will be collected according to the Schedule of Activity (Table 1). Gut biomarkers (ie, the microbiome and other fecal-based protein markers) will be investigated in relation to JNJ-67864238 and/or pathogenesis of Crohn's disease.

**Oral Biomarkers**

Oral microbiome samples will be collected from saliva and analyzed from all participants to further the understanding of Crohn's disease and the potential connection between Crohn's disease activity and changes in oral microbiome.[3,8,1]

### 8.8.1. RNA Transcriptome Research

Transcriptome studies may be conducted using, but not limited to, microarray, and/or alternative technologies, which facilitates the simultaneous measurement of the relative abundances of RNA species resulting in a transcriptome profile. This will enable the evaluation of changes in

transcriptome profiles that may correlate with biological response relating to IBD and medically related conditions or the action of JNJ-67864238.

The same samples may also be used to confirm findings by application of alternative technologies.

### 8.8.2. Proteome Research

Plasma, serum, stool, or biopsy proteome studies may be performed. Proprietary algorithms and standard statistical techniques, such as analysis of variance (ANOVA) and analysis of covariance (ANCOVA), may be used to identify individual proteins exhibiting statistically significantly different changes in their levels between samples and/or between groups of samples. This may enable the evaluation of changes in proteome profiles that may correlate with biological response relating to IBD and medically related conditions or the action of JNJ-67864238.

The samples may also be used to confirm findings by application of alternative technologies.

### 8.8.3. Metabolomic Research

Plasma, serum, stool, or biopsy metabolome studies may be performed by, but not limited to, nuclear magnetic resonance, mass spectrometry, liquid chromatography – mass spectrometry, gas chromatography – mass spectrometry, and/or Fourier transform mass spectrometry, or other methods. This may include analysis of identified or uncharacterized metabolites and lipids that are known to be or emerge in the future as important in the pathogenesis of IBD or a related medical condition, or the participant's response to JNJ-67864238, or AE.

## 8.9. Immunogenicity Assessments

Immunogenicity will not be assessed in the JNJ-67864238 intervention cohort. Samples collected per the consolidated Schedule of Activities (Table 1) for immunogenicity would only be analyzed if required to assess other data or analyses, such as PK or AEs.

## 8.10. Medical Resource Utilization and Health Economics

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

## 8.11. Tuberculosis Assessments

**Screening Assessments**

Participants must undergo testing for TB (see Section 5.2 and Appendix 3, Tuberculin Skin Testing, both of this ISA) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON®-TB test and the tuberculin skin test to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated in order to evaluate a participant who has high risk of having latent TB. If either the QuantiFERON®-TB test or the tuberculin skin test is positive, the participant is considered to have latent TB infection for the purposes of eligibility for this study.

Participants with a negative QuantiFERON®-TB test result (and a negative tuberculin skin test result in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities) are eligible to continue with prerandomization procedures. Participants with a newly identified positive QuantiFERON®-TB (or tuberculin skin) test result must be excluded from the study.

**Treatment Phase**

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the Schedule of Activities [Table 1]) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of > 14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON® TB test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment for latent TB is warranted. If the QuantiFERON® TB test result is indeterminate, the test should be repeated as outlined in the manufacturer's instructions. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol.

# 9. STATISTICAL CONSIDERATIONS

Statistical analyses for the JNJ-67864238 intervention cohort will be performed using the statistical methods described in Section 9 of the Master protocol PLATFORMPACRD2001. In addition, JNJ-67864238-specific statistical considerations are described below.

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

## 9.1. Statistical Hypotheses

The statistical hypothesis is that JNJ-67864238 is superior to placebo as measured by the reduction from baseline in the CDAI at Week 12 in participants with moderately to severely active Crohn's disease.

## 9.2. Sample Size Determination

Sample size is determined to achieve desirable operating characteristics of the decision-making framework for JNJ-67864238 through simulated CDAI and SES-CD data. More details on data simulation are provided in Appendix 6 of this ISA, Data Simulation.

### 9.2.1. Decision-Making Framework

There are a minimum of 2 decision points planned for this ISA protocol:

1. At the IA: The IA will take place when approximately 45 participants have completed their Week 12 assessments or have withdrawn from the study before Week 12. If the futility criteria are met, the decision to terminate enrollment will be made based on a benefit-risk assessment of the totality of data, including overall efficacy assessments, analysis of biomarker and PD data, and a safety review by the external DMC. If the futility criteria are not met and the DMC has not raised any safety issue, enrollment will continue until the planned sample size is reached. To augment decision-making, all available data at this IA, including from those participants without Week 12 assessments, will be analyzed. An Interim Analysis Committee will review the unblinded interim data and formulate recommendations (Section 9.5.1 of the Master protocol PLATFORMPACRD2001).
2. At the completion of this intervention cohort: The overall study success or futility is defined in the Master protocol.

Additional ad hoc IA(s) may be conducted if deemed necessary; any ad hoc IA(s) will be part of the decision-making framework and will follow the same decision-making rules as those of the planned IA.

This decision-making framework is suggestive but not binding. The final decision will be made based on the totality of data.

### 9.2.2. Decision-Making Specifics

#### 9.2.2.1. Decision-Making Specifics at the Interim Analysis

If neither change in CDAI nor change in SES-CD of the JNJ-67864238 CCI CCI treatment arm meets the success criteria, the futility of the JNJ-67864238 treatment arm will be considered. The futility is defined as follows:

- Futility in change in CDAI: if upper bound (UB) (95%) <60 and lower bound (LB) (10%) <40, ie, the 95% upper confidence bound of the true mean treatment difference at Week 12 is less than 60 and its 90% lower confidence bound less than 40; **and**
- Futility in change in SES-CD: if UB (95%) <1.6 and LB (10%) <0.4, ie, the 95% upper confidence bound of the true median treatment difference at Week 12 is less than 1.6 and its 90% lower confidence bound less than 0.4.

The thresholds chosen for futility at the IA correspond to an active study intervention profile with limited benefit.

#### 9.2.2.2. Decision-Making Specifics at the Completion of the Intervention Cohort

The success of the JNJ-67864238 CCI treatment arm is defined as follows:

- Success in change in CDAI: if LB (20%) ≥40, ie, the 80% lower confidence bound of the true mean treatment difference at Week 12 is at least 40; **or**
- Success in change in SES-CD: if LB (20%) ≥0.4, ie, the 80% lower confidence bound of the true median treatment difference at Week 12 is at least 0.4.

The threshold of 40 is selected to provide confidence that a therapy is at least as effective as currently approved therapies (STELARA® [ustekinumab] or adalimumab), where a CDAI change of 40 represents the lower confidence bound for success of the treatment difference between JNJ-67864238 and placebo.

If neither change in CDAI nor change in SES-CD of the JNJ-67864238 CCI CCI treatment arm meets the success criteria, the futility of the JNJ-67864238 treatment arm will be considered. The futility of is defined as follows:

- Futility in change in CDAI: if UB (80%) <60 and LB (20%) <40, ie, the 80% upper confidence bound of the true mean treatment difference at Week 12 is less than 60 and its 80% lower confidence bound less than 40; and
- Futility in change in SES-CD: if UB (90%) <1.6 and LB (20%) <0.4, ie, the 90% upper confidence bound of the true median treatment difference at Week 12 is less than 1.6 and its 80% lower confidence bound less than 0.4.

In addition, a decision-making framework based solely on CDAI scores will also be assessed by combining a benefit-risk assessment of the totality of the data, including analyses of biomarker and PD data. For the case of futility criteria based solely on CDAI scores, the UB of 80% based

on a change in the CDAI for the final analysis will be updated to 95% (ie, UB 95% <60) and the LB will remain the same (ie, LB 20% <40). Details will be provided in the SAP.

### 9.2.3. Sample Size

#### 9.2.3.1. Operating Characteristics of the Intervention Cohort

The decision-making framework outlined in Section 9.2.2 of this ISA is applied to a total of 5000 virtual studies with simulated CDAI and change in SES-CD data. With 90 participants (54 participants receiving JNJ-67864238 CCI [redacted] and 36 participants receiving placebo), under the alternative hypothesis (Appendix 6 of this ISA, Data Simulation), the probability of JNJ-67864238 meeting the success criteria is approximately 87%, and the probability of dropping JNJ-67864238 for futility is approximately 1%. When there is no treatment difference, the probability of JNJ-67864238 meeting the success criteria is approximately 5% and the probability of dropping JNJ-67864238 for futility is approximately 77%. There is approximately a 32% chance that the futility criteria are met at the IA when there is no treatment difference.

#### 9.2.3.2. Power for Detecting Treatment Difference in Change in the CDAI

For reference, without factoring in the interim futility analysis, the sample size of 90 participants (54 participants in the JNJ-67864238 CCI [redacted] treatment arm and 36 participants in the placebo treatment arm) will provide 90% power to detect a treatment difference at $\alpha$=0.1 (2-sided) when the true treatment difference is 60 (placebo – JNJ-67864238) in the change in CDAI at Week 12 for both Bio-IR and Bio-NF populations. The detailed assumptions of the CDAI scores are outlined in Appendix 6 of this ISA, Data Simulation. This evaluation is based on an analysis of covariance model with change in the CDAI score at Week 12 as the response variable and baseline CDAI score as a covariate, with population (Bio-IR and Bio-NF), treatment, and their interaction as fixed factors in the model.

## 9.3. Populations for Analyses

Refer to Section 9.3 of the Master protocol PLATFORMPACRD2001 for populations for analyses.

## 9.4. Statistical Analyses

### 9.4.1. General Considerations

Refer to Section 9.4.1 of the Master protocol PLATFORMPACRD2001 for general considerations.

#### 9.4.1.1. Multiplicity Control

An overall type I error rate of 0.1 (2-sided) will be used.

The hypothesis testing will be conducted in a hierarchical manner with the test on the primary endpoint conducted first and the tests on major secondary endpoints conducted next. Within the major secondary endpoints, the gatekeeping approach in conjunction with graphical multiplicity control procedures will be applied. More details will be provided in the ISA SAP.

As the IA will not lead to an early ISA completion due to success, multiplicity adjustment is not required.

Nominal p-values will be calculated for all treatment comparisons.

### 9.4.2. Primary Endpoint

Refer to Section 9.4.2 of the Master protocol PLATFORMPACRD2001 for the primary endpoint.

### 9.4.3. Secondary Endpoints

Refer to Section 9.4.3 of the Master protocol PLATFORMPACRD2001 for the secondary endpoints.

### 9.4.4. Safety Analyses

Refer to Section 9.4.4 of the Master protocol PLATFORMPACRD2001 for safety analyses.

### 9.4.5. Other Analyses

Refer to Section 9.4.5 of the Master protocol PLATFORMPACRD2001 for additional information for other analyses.

**Pharmacokinetic Analyses**

Data will be listed for all participants with available plasma, fecal, and biopsy tissue concentrations per treatment arm. Participants will be excluded from the descriptive statistics if their data do not allow for accurate assessment of the concentration data (eg, incomplete administration of the study intervention; missing information of dosing and sampling times).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

For each treatment arm, descriptive statistics, including arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum will be calculated.

**Biomarkers Analyses**

Refer to Section 9.4.5 of the Master protocol PLATFORMPACRD2001 for biomarker analyses.

**Immunogenicity Analyses**

The incidence of anti-JNJ-67864238 antibodies will be summarized for all participants who receive at least 1 dose of JNJ-67864238 and have appropriate samples for detection of antibodies to JNJ-67864238 (ie, participants with at least 1 sample obtained after their first dose of JNJ-67864238). Antibodies may be summarized as induced or pre-existing if a predose sample at Week 0 is obtained.

A listing of participants who are positive for antibodies to JNJ-67864238 will be provided. The maximum titers of antibodies to JNJ-67864238 will be summarized for participants who are positive for antibodies to JNJ-67864238.

Systemic JNJ-67864238 concentrations and clinical efficacy/safety endpoints may be summarized by antibody to JNJ-67864238 status if sufficient numbers of participants are positive for antibodies. Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

**Pharmacodynamic and Disease-specific Analyses**

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. Any PD samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, excluded from the PD analysis.

Changes in serum/RNA or other biomarkers over time will be summarized by treatment arm. Associations between baseline levels and changes from baseline in select markers and clinical response will be explored. RNA analyses will be summarized in separate technical reports.

**Pharmacokinetic/Pharmacodynamic Analyses**

Refer to Section 9.4.5 of the Master protocol PLATFORMPACRD2001 for PK/PD analyses.

**Pharmacogenomic Analyses**

Complete genomic testing will be done to search for links of specific genes to disease or response to drug. Only DNA research related to JNJ-67864238 or to the diseases for which this drug is being developed will be performed.

Genome-wide pharmacogenomic testing will be undertaken in participants who have signed a separate informed consent to participate in this portion of the study. Further, a participant may withdraw such consent at any time without affecting their participation in other aspects of the study, or their future participation in the study.

Results will be presented in a separate report.

DNA samples will be analyzed for links to specific genes to disease or the response to JNJ-67864238. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

DNA samples will be used for research related to links to specific genes to disease or the response to JNJ-67864238. They may also be used to develop tests/assays related to JNJ-67864238 and Crohn's disease. Pharmacogenomic research may consist of the analysis of one or more candidate genes or analysis of the entire genome (as appropriate) in relation to JNJ-67864238 or Crohn's disease clinical endpoints.

## 9.5. Interim Analysis

One IA is planned. It will take place when approximately 45 participants have completed their Week 12 assessments or have withdrawn early from the intervention cohort. Additional ad hoc IA(s) may be conducted if deemed necessary. The objective of the IA(s) is to enable early termination of the intervention cohort if JNJ-67864238 ([redacted]) is futile and plan for future intervention cohorts. At the time of the IA(s), the study team will remain blinded. The planned IA (and any additional IA[s]) will be described in the IA SAP.

## 9.6. Data Monitoring Committee or Other Review Board

Refer to Section 9.6 of the Master protocol PLATFORMPACRD2001 for information regarding the DMC.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Abbreviations

| | |
|---|---|
| 6-MP | 6-mercaptopurine |
| AE | adverse event |
| AUC | area under the curve |
| AZA | azathioprine |
| Bio-IR | biologic intolerant or refractory |
| Bio-NF | biologic nonfailures, ie, inadequate response to or failed to tolerate corticosteroids or immunomodulators, but not a biologic |
| CDAI | Crohn's Disease Activity Index |
| CRF | case report form |
| CRP | C-reactive protein |
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| ECG | electrocardiogram |
| FIH | first-in-human |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| hERG | human ether-à-go-go-related gene |
| HIV | human immunodeficiency virus |
| IA | interim analysis |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| IEC | Independent Ethics Committee |
| IL | interleukin |
| IRB | Institutional Review Board |
| ISA | Intervention Specific Appendix |
| IV | intravenous |
| IWRS | interactive web response system |
| LB | lower bound |
| MTX | methotrexate |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NRS | numeric rating scale |
| PD | pharmacodynamic |
| PGIC | Patient's Global Impression of Change |
| PGIS | Patient's Global Impression of Severity |
| P-gp | P-glycoprotein |
| PK | pharmacokinetic(s) |
| PRO | patient-reported outcome |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | subcutaneous |
| SES-CD | Simplified Endoscopic Score for Crohn's Disease |
| TB | tuberculosis |
| TNBS | trinitrobenzene sulfonic acid |
| TNF | tumor necrosis factor |
| UB | upper bound |
| ULN | upper limit of normal |

## 10.2. Appendix 2: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1 of this ISA, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4 of this ISA Pregnancy, and Appendix 6 of the Master protocol PLATFORMPACRD2001, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

**Definitions**

***Woman of Childbearing Potential (WOCBP)***

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

***Woman Not of Childbearing Potential***

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

**Examples of Contraceptives**

| **EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:** |
|---|
| **USER INDEPENDENT**<br>**Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.* |
| • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] |
| • Intrauterine device (IUD) |

| |
|---|
| • Intrauterine hormone-releasing system (IUS) |
| • Bilateral tubal occlusion |
| • Vasectomized partner<br>*(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)* |
| **USER DEPENDENT**<br>**Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.* |
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– intravaginal<br>– transdermal<br>– injectable |
| • Progestogen-only hormone contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| • Sexual abstinence<br>*(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)* |
| **NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)** |
| • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. |
| • Male or female condom with or without spermicide[c] |
| • Cap, diaphragm, or sponge with spermicide |
| • A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c] |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods) |
| • Withdrawal (coitus-interruptus) |
| • Spermicides alone |
| • Lactational amenorrhea method (LAM) |
| a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.<br>b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.<br>c) Male condom and female condom should not be used together (due to risk of failure with friction). |

**Pregnancy During the Study**

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention.

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

## 10.3. Appendix 3: Tuberculin Skin Testing

### Administering the Mantoux Tuberculin Skin Test

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

### Interpreting the Tuberculin Skin Test Results

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

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

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

### Treatment of Latent Tuberculosis

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

### References

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

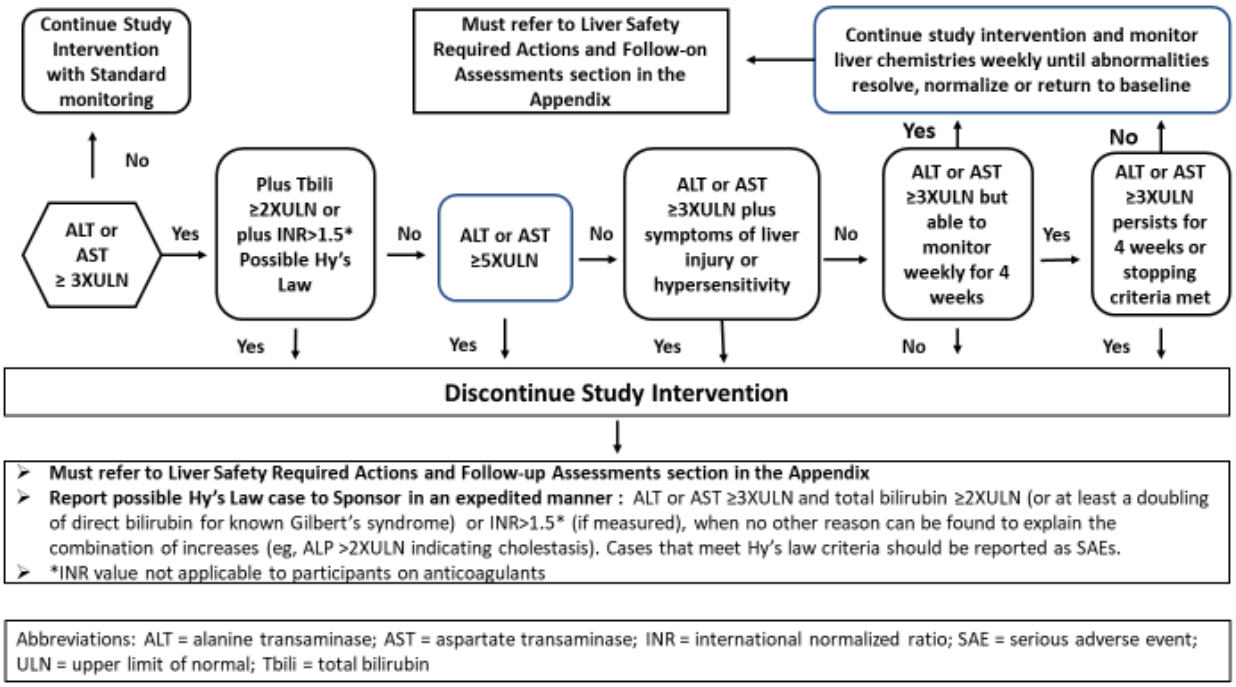
Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

## 10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

### 10.4.1. Stopping Algorithm

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

**Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)**




Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal; Tbili = total bilirubin

### 10.4.2. Follow-up Assessments

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT/AST--absolute</td><td colspan="2">ALT or AST- ≥5xULN</td></tr>
<tr><td>ALT/AST-Increase</td><td colspan="2">If cannot monitor:<br>ALT or AST- ≥3xULN and cannot be monitored weekly for 4 weeks<br><br>Or if able to monitor:<br>ALT or AST- ≥3xULN persists for ≥4 weeks</td></tr>
<tr><td>Total bilirubin[1, 2]</td><td colspan="2">ALT or AST- ≥3xULN and total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert’s syndrome)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT or AST- ≥3xULN and international normalized ratio (INR) >1.5, if INR measured</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT or AST- ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Suggested Actions, Monitoring and Follow-up Assessments</th></tr>
<tr><td colspan="2">Actions</td><td>Follow-up Assessments</td></tr>
<tr><td colspan="2">• Immediately stop study intervention<br>• Report the event to the sponsor within 24 hours<br>• Complete the AE form and the SAE data collection tool if the event also met the criteria for an SAE[2]<br>• Perform follow-up assessments as described in the Follow Up Assessment column<br>• Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see MONITORING)<br>MONITORING:<br>If ALP <2xULN, ALT or AST - ≥3xULN AND total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert’s syndrome) or INR >1.5 (if measured):<br>• Repeat liver chemistry tests (include ALT, AST, ALP, total and direct bilirubin, and INR) and perform liver event follow-up assessments within 24 hours<br>• Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline</td><td>• Viral hepatitis serology[4]<br>• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend<br>• Obtain blood sample for pharmacokinetic (PK) analysis 72 hours after the most recent dose[5]<br>• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), glutamate dehydrogenase (GLDH), and serum albumin<br>• Fractionate bilirubin<br>• Obtain complete blood count with differential to assess eosinophilia<br>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE and SAE forms.<br>• Record use of concomitant medications (including acetaminophen, herbal remedies,</td></tr>
</table>

| | |
|---|---|
| • A specialist or hepatology consultation is recommended<br>**If ALT or AST - ≥3xULN AND total bilirubin <2xULN and INR ≤1.5:**<br>• Repeat liver chemistry tests (include ALT, AST, ALP, total and direct bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours**<br>• Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline<br><br>**RESTART/RECHALLENGE**<br>• **Do not restart/rechallenge** participant with study intervention | recreational drugs and other over-the-counter medications)<br>• Record alcohol use on the substance use alcohol form<br>**<u>If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 (if measured)</u>** obtain the following in addition to the assessments listed above**:**<br>• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins<br>• Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week<br>• Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete the medical encounter form<br>• Liver biopsy may be considered and discussed with local specialist if available:<br>– In participants when serology raises the possibility of autoimmune hepatitis<br>– In participants when suspected drug-induced liver injury progresses or fails to resolve on withdrawal of study intervention<br>– In participants with acute or chronic atypical presentation<br>• If liver biopsy conducted complete the medical encounter form |

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALP <2xULN, ALT **or AST -** ≥3xULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or ALP <2xULN , ALT **or AST -** ≥3xULN **and** INR >1.5 (if

measured) may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria are met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAg and hepatitis B Core Antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Laboratory Manual.

## 10.5. Appendix 5: Clinical Laboratory Tests

The following tests will be performed according to the ISA Schedule of Activities (Table 1) by a sponsor contracted central or specialty laboratory.

**Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | | |
|---|---|---|---|
| Hematology | Platelet count<br>Red blood cell count<br>Hemoglobin<br>Hematocrit | <u>Red Blood Cell (RBC) Indices:</u><br>Mean corpuscular volume<br>Mean corpuscular hemoglobin<br>% Reticulocytes | <u>White Blood Cell (CBC) count with Differential:</u><br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| | Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported. | | |
| Clinical Chemistry | Sodium<br>Potassium<br>Chloride<br>Calcium<br>Phosphate<br>Alkaline phosphatase<br>Blood urea nitrogen (BUN)<br>Creatinine | Albumin<br>Total protein<br>Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic<br>Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic<br>Total and direct bilirubin<br>Cholesterol<br>Glucose | |
| | Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 4: Liver Safety.<br><br>Potential Hy's Law case (ALT/AST ≥3 x ULN, ALP <2 x ULN together with Tbili ≥2 x ULN or INR >1.5 [if measured]) reporting requirements are defined in Section 8.3.7. | | |
| Other Screening Tests | • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)<br>• Serum Pregnancy Testing<br>• Urine Treatment Screen<br>• Follicle stimulating hormone test (optional at the discretion of the investigator) | | |
| Pregnancy Testing | • Female subjects of childbearing potential will undergo a serum β-hCG pregnancy test at screening<br>• Urine pregnancy testing (for women of child bearing potential only) performed locally at all site visits (prior to dosing at dosing visits). | | |

## 10.6. Appendix 6: Data Simulation

To evaluate the operating characteristics of the study design, the following assumptions are made based on 3 completed clinical studies (C0743T26, CNTO1275CRD3001, and CNTO1275CRD3002) conducted by the sponsor:

- The compositions of Bio-IR and Bio-NF populations are 50% each
- For Bio-IR population, the CDAI scores of the JNJ-67864238 CCI treatment arm and placebo treatment arm at Weeks 0, 2, 4, 8, and 12 are assumed to be (323,285,259,247,238) ` and (323,305,300,299,298) `, respectively. Similarly, for Bio-NF population, the CDAI scores of the JNJ-67864238 CCI treatment arm and placebo treatment arm at Weeks 0, 2, 4, 8 and 12 are assumed to be (302,245,208,180,176) ` and (302,271,254,241,236) `, respectively.
- The covariance matrix is assumed to be

$$\begin{pmatrix} 3844 & 3069 & 3100 & 3193 & 3255 \\ 3069 & 8100 & 7200 & 6489 & 5670 \\ 3100 & 7200 & 10000 & 7210 & 5250 \\ 3193 & 6489 & 7210 & 10609 & 7030 \\ 3255 & 5670 & 5250 & 7030 & 11025 \end{pmatrix} \quad \text{and} \quad \begin{pmatrix} 3600 & 2970 & 2565 & 3646 & 2520 \\ 2970 & 8100 & 5558 & 5670 & 4725 \\ 2565 & 5558 & 9025 & 6484 & 4988 \\ 3646 & 5670 & 6484 & 11025 & 7166 \\ 2520 & 4725 & 4988 & 7166 & 11025 \end{pmatrix}$$

  for the Bio-IR and Bio-NF populations, respectively.
- In CNTO1275CRD3001 and CNTO1275CRD3002, an optional endoscopy substudy was conducted in a subset of study participants. Based on the collected data, change in SES-CD is assumed to have a mixture distribution - excessive zeros (no change) and a normal distribution. Therefore, 2 steps were utilized to simulate the change in SES-CD data.
  - Step 1: no change in SES-CD is simulated for 19% of JNJ-67864238 CCI treated participants and 32% placebo treated participants.
  - Step 2: changes in SES-CD based on the normal distributions with mean changes from baseline of -3.26 and -0.22 are generated for the JNJ-67864238 CCI and placebo arms, respectively. The common standard deviation is 3.8. As the change in SES-CD of a participant is an integer, the simulated value then is rounded to the nearest integer. The above assumptions are for the Bio-IR population. The change in SES-CD responses for the Bio-NF population can be simulated similarly with the following assumptions: the proportion of the excessive zeros is 12% for both the active and placebo treatment arm in Step 1. The means of the normal distributions are -4.68 and -2.71 for the JNJ-67864238 CCI and placebo arms, respectively. The common standard deviation is 5.9.
- The correlation coefficients between the change in SES-CD and the CDAI scores are assumed to be -0.15, 0, 0, 0.15, and 0.15 at Weeks 0, 2, 4, 8, and 12 for the Bio-IR population. They are assumed to be 0, 0, 0, 0.15 and 0.15 at Weeks 0, 2, 4, 8, and 12 for the Bio-NF population.

## 10.7. Appendix 7: COVID-19 APPENDIX

## GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

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

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

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

**ADDITIONAL ELEMENTS, WHERE APPLICABLE:**

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

    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures e.g. those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent)

    - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

    - other procedures, eg, imaging, may be conducted at an appropriate facility

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

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

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

- Exclusion: a potential participant with the following features will be excluded from participating in the study protocol:

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

        - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

        (i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, e.g. fever, cough, dyspnea)

AND

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

- NOTES on COVID-related exclusion:

1. If a participant is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.

2. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.

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

## 10.8. Appendix 8: Definition of Minimal Exposure to Ustekinumab

Participants who have had limited exposure to ustekinumab at its approved labeled dosage **AND** have met the required washout criterion **AND** have not demonstrated inadequate response or intolerance to ustekinumab as defined further below **are eligible** for entry into this intervention cohort.

Participants who have had exposure to ustekinumab as an investigational agent (ie, exposure to ustekinumab from participation in prior ustekinumab clinical studies) or exposure to ustekinumab as an off-label treatment at their physician's discretion **are ineligible** for entry into this intervention cohort.

Participants with prior exposure to an anti-IL-12/23 (ie, ustekinumab) or anti-IL-23 agents or related compound (including risankizumab, brazikumab, guselkumab, mirikizumab, and related compounds) **are ineligible** for entry into this intervention cohort. Exception is made for participants who have had minimal exposure to ustekinumab as defined by the 3 criteria below.

**Participants MUST meet all of criteria 1, 2, and 3 below to qualify for entry into this intervention cohort as having had minimal exposure to ustekinumab, and provided that all other entry criteria as described in Section 5.1 and 5.2 have been satisfied.**

1. **The criteria for minimal exposure to ustekinumab at its approved label dosage is defined as follows:**
   - **a.** No more than one induction dose of ustekinumab (ie, an IV dose of 260 mg, 390 mg or 520 mg)
   - b. No more than one maintenance dose of ustekinumab (ie, a 90 mg SC dose) 8 weeks after the single induction dose
2. **The required washout period from ustekinumab is defined as follows:**

   Participants must have been discontinued from ustekinumab for at least 16 weeks prior to the Week 0 dosing visit of this intervention cohort
3. **The following documentation to confirm the discontinuation of ustekinumab treatment for Crohn's disease for reasons other than inadequate response or intolerance MUST be provided:**

   Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization / denial notifications) that:

   a. Provide the dates and doses of ustekinumab for the treatment of Crohn's disease; AND

   b. Provide the date of discontinuation of ustekinumab for the treatment of Crohn's disease; AND

   c. Indicate the participant had discontinued ustekinumab treatment for reasons other than inadequate response and/or intolerance (eg, loss of insurance); AND

   d. Indicate the participant **did not** discontinue ustekinumab treatment for Crohn's disease due to inadequate response and/or intolerance. See further details under the NOTE section below for evidence indicative of inadequate response and/or intolerance.

**NOTE**:

The following are considered evidence of inadequate response and/or intolerance to ustekinumab treatment for Crohn's disease. Participants who meet these criteria **are ineligible** to enter this intervention cohort.

**Evidence of inadequate response to ustekinumab that had precluded continuation of previous treatment with ustekinumab for Crohn's disease:**

- Lack of improvement or worsening in stool frequency
- Lack of improvement or worsening in daily abdominal pain

- Occurrence, lack of improvement, or worsening of fever thought to be related to Crohn's disease
- Lack of improvement or worsening in a draining fistula or development of a new draining fistula
- Lack of improvement or worsening in rectal bleeding
- Initiation or increase in antidiarrheal medication

These signs and symptoms of Crohn's disease are offered only as a benchmark and acknowledges that the Crohn's Disease Activity Index is not routinely recorded in clinical practice.

**Evidence of intolerance to ustekinumab that had precluded continuation of previous treatment with ustekinumab for Crohn's disease:**

Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum sickness-like reaction); or 3) significant injection-site reaction. Definitions of these 3 criteria are provided below.

- **A significant acute infusion/administration reaction is defined as an adverse reaction that:**
  a. Was manifested through ≥1 of the following symptoms.
     - Fever greater than 100°F (37.8°C)
     - Chills or rigors
     - Itching
     - Rash
     - Flushing
     - Urticaria or angioedema
     - Breathing difficulties (dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor)
     - Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure <90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure >20 mm Hg

     **AND**

  b. Occurred ≤24 hours after infusion/administration of ustekinumab

     **AND**

  c. Was considered related to the infusion/administration of ustekinumab
- **A significant delayed infusion/administration reaction is defined as an adverse reaction that:**
  a. Was manifested through 1 or more of the following symptoms:
     - Myalgias
     - Arthralgias
     - Fever greater than 100°F (37.8°C)
     - Malaise
     - Rash

**AND**

b. Occurred >24 hours and <15 days after infusion/administration of ustekinumab

**AND**

c. Was considered related to the infusion/administration of ustekinumab

- **A significant injection-site reaction is defined as an adverse reaction that:**

a. Was manifested through 1 or more of the following symptoms:

- Significant bruising
- Erythema
- Hemorrhage
- Irritation
- Pain
- Pruritus
- "Injection-site reaction"

**AND**

b. Occurred within 24 hours of an SC injection of ustekinumab.

**AND**

c. Was considered related to the SC injection of ustekinumab.

## 10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

### Amendment 4 (14 Dec 2020)

**Overall Rationale for the Amendment:** The overall rationale for the amendment is to incorporate the Coronavirus Disease 2019 (COVID-19) appendix into the protocol.

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.7. Appendix 7 COVID-19 Appendix | The previously approved and submitted COVID-19 appendix was added as Section 10.7 of the protocol. The Protocol Amendment History, previously Section 10.7, is Section 10.8. | The stand-alone COVID-19 appendix was a prior amendment that was added to the body of the protocol to consolidate all protocol amendments. |
| Cover Page | The version number of the protocol was updated from 4.0 to 6.0. | Protocol amendment 3 dated 17 September 2020 was inadvertently labeled version 4.0 instead of version 5.0. |

### Amendment 3 (17 Sep 2020)

**Overall Rationale for the Amendment:** The overall rationale for the amendment is to update fecal samples for the microbiome to fecal samples for biomarkers. Biomarkers is a more inclusive term, and proteins and the microbiome will be analyzed from the same sample.

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1. Synopsis; 2 Introduction | The definition of a platform study and the reference were added. | The term platform study was not defined. |
| | The definition of an intervention cohort was updated to indicate that an intervention cohort may include participants receiving placebo or an active comparator. | The definition of an intervention cohort was clarified. |
| 1.1 Synopsis; 1.3 Schedule of Activities; 8.8 Biomarkers | Fecal samples for microbiome was updated to fecal samples for biomarkers. Footnote dd was also removed to align with this change. | Biomarkers is a more inclusive term, and proteins and the microbiome will be analyzed from the same sample. |
| 1.3 Schedule of Activities | An optional screening follicle stimulating hormone assessment at the discretion of the investigator was added. | This optional screening assessment was inadvertently omitted from the Schedule of Activities. |
| | A fecal sample for stool concentrations and a plasma sample for systemic concentrations of JNJ-67864238 were added at Week 2. | These samples at Week 2 were inadvertently omitted from the Schedule of Activities. |
| | Footnote t was removed as it was a Master protocol footnote and had the sample schedule for pharmacokinetics (PK) and | The PK sampling schedule was inadvertently included in the master protocol. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | immunogenicity, which are ISA specific. The lettering of the remaining footnotes was subsequently updated. | |
| | Footnote u (updated to footnote t with this amendment) was revised as it was a Master protocol footnote and had references to PK sampling, which are ISA specific. | The PK sampling information was inadvertently included in the Master protocol. |
| | Footnote aa (updated to footnote z with this amendment) was revised to include the relevant sampling information that was in footnotes t and u.<br><br>Footnote bb was removed since the information is in footnote aa (updated to footnote z). | Footnote t was removed and footnote u (updated to footnote t with this amendment) was revised to remove references to PK and antibody assessments. |
| | Footnote bb was removed as the antibody sampling schedule was incorporated into footnote aa (updated to footnote z with this amendment). | Footnote bb was redundant. |
| 2.2 Background; Pharmacokinetic Profile;<br>6.5 Concomitant Therapy | Text indicating that narrow therapeutic index drugs that are P-glycoprotein (P-gp) substrates should be avoided was removed. | Data from a sponsor preclinical study (Report FK13558, In vitro Interaction Studies of JNJ-67864238 with human MDR1 Efflux [ABC] Transporter, issued 08 JUL 2019) indicate that there was no effect of JNJ-67864238 on digoxin (a P-gp substrate) efflux and therefore drug interactions with drugs that are P-gp substrates are unlikely. |
| 7.1 Discontinuation of Study Intervention | Text regarding follow-up visits for participants who discontinuation study intervention prior to Week 12 was removed. | Detailed instructions were added to Section 7.1 of Master protocol PLATFORMPACRD2001 to clarify the follow-up visit schedule for participants who discontinuation study intervention prior to Week 12. |
| 8.5.1 Evaluations | A plasma sample for systemic concentrations of JNJ-67864238 was added at Week 2. | This sample at Week 2 was inadvertently omitted. |
| | Details regarding the collection of stool samples for measurement of JNJ-67864238 stool concentrations as outlined in the Schedule of Activities were added. | Details regarding the collection of stool samples were added to align with the Schedule of Activities. |
| 1.1. Synopsis;<br>8.9 Immunogenicity Assessments | Immunogenicity will not be assessed in the JNJ-67864238 intervention cohort. | Samples for immunogenicity will be collected and would only be analyzed if required to assess other data or analyses, such as for PK or AEs. |
| Appendix 2 | The bilateral tubal occlusion/ligation procedures were removed from the definition of permanently sterile. | The text was updated to align the definition of permanently sterile with that of the European Union Clinical Trials Facilitation and Coordination Group. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Appendix 5 | An optional screening follicle stimulating hormone assessment at the discretion of the investigator was added. | This optional screening assessment was inadvertently omitted. |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. | Minor errors were noted. |

## Amendment 2 (13 November 2019)

**Overall Rationale for the Amendment:** To address health authority requested changes.

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1. Inclusion Criteria, #9 | Text was added to indicate that subjects must be receiving treatment for Crohn's disease at study entry. | In this early phase study where some participants will receive placebo and the efficacy of JNJ-67864238 is unknown, participants must receive appropriate therapy for Crohn's disease. |
| 2.3.1. Risks for Study Participation; 2.3.3. Benefit-Risk Assessment for Study Participation; 6.5.2. Crohn's Disease-Specific Therapies | Text was added to indicate that concomitant background therapies should be continued throughout the study. | In this early phase study where some participants will receive placebo and the efficacy of JNJ-67864238 is unknown, participants should continue to receive appropriate concomitant therapy for Crohn's disease. |
| 5.2. Exclusion Criteria | Exclusion criterion #26 was added to clarify that participants must not have a history of drug or alcohol abuse. | The exclusion criterion was added to exclude participants with a history of drug or alcohol abuse. |
| 6.3. Measures to Minimize Bias: Randomization and Blinding | Text was added to specify that treatment assignment will be unblinded to the sponsor at the Week 12 database lock. | The text was updated to clarify unblinding to the sponsor. |
| 9.2.2.2. Decision-Making Specifics at the Completion of the Intervention Cohort | Futility criteria for the change in SES-CD were updated. | The futility criteria were corrected for internal document consistency. |
| 9.5. Interim Analysis | Text was added to indicate that the study team will remain blinded at the Interim Analysis. | The text was updated to clarify that the study team will not be unblinded for the Interim Analysis. |
| 4.1. Overall Design; 5.1. Inclusion Criteria | The units for fecal calprotectin were changed from >250 mg/mL to >250 µg/mg. | The units for fecal calprotectin were corrected. |
| 5.2 Exclusion Criteria | Duplication of exclusion criteria #A05 was corrected. | The number A05 was used twice and was corrected to sequential numbering. |
| 6.2. Preparation/Handling/ Storage/Accountability | Text regarding the disposition of needles and syringes was removed. | Since JNJ-67864238 is an oral intervention, the text is not applicable. |
| 7.1. Discontinuation of Study Intervention | Text regarding severe injection-site or infusion reactions was removed. | Since JNJ-67864238 is an oral intervention, the text is not applicable. |
| 1.2 Scheme; 1.3 Schedule of Activities | The Patient's Global Impression of Change (PGIC) at Week 0 was removed. | PGIC is not applicable at Week 0. |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. | Minor errors were noted. |

## Amendment 1 (14 August 2019)

**Overall Rationale for the Amendment:** To update the protocol with a newly assigned EudraCT number to allow for re-submission of a request for the Voluntary Harmonisation Procedure (VHP) in the European Union.

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title page | Replacement of the previous EudraCT number (2018-000649-38) with a newly assigned EudraCT number (2019-003335-37). | To allow the re-submission of a request for the VHP for the assessment of the Clinical Trial Authorisation application in the European Union, following rejection of the initial VHP application for administrative reasons. |
| 10.7, Appendix 7 Protocol Amendment History | Update text to indicate that the Protocol Amendment Summary of Changes Table for this current amendment is located before the Table of Contents. | To update the amendment history to indicate that there are amendments for this protocol. |

# 11. REFERENCES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# INVESTIGATOR AGREEMENT

JNJ-67864238 Clinical Protocol 67864238PACRD2001 Amendment 5

## INVESTIGATOR AGREEMENT

I have read this protocol and agree that, in conjunction with the accompanying Master protocol, it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): PPD

Institution: Janssen Research & Development

PPD

Signature: _____ Date: 11 May 2021

(Day Month Year)

**Note:** If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.



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Approved, Date: 11 May 2021

**Janssen Research & Development ***

**Clinical Protocol**

**COVID-19 Appendix**

**Intervention Specific Appendix to Master Clinical Protocol PLATFORMPACRD2001**

# PRISM-SCARLET

**Protocol 67864238PACRD2001; Phase 2a**

**JNJ-67864238**

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

**EudraCT NUMBER:** 2019-003335-37

**Status:** Approved
**Date:** 20 May 2020
**Prepared by:** Janssen Research & Development, LLC;
**EDMS number:** EDMS-RIM-62480, 1.0

**THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL**

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

## COVID-19 APPENDIX

## GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

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

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

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

**ADDITIONAL ELEMENTS, WHERE APPLICABLE:**

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

    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures e.g. those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent)

    - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

    - other procedures, eg, imaging, may be conducted at an appropriate facility

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

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

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

- Exclusion: a potential participant with the following features will be excluded from participating in the study protocol:

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

        - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

        (i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, e.g. fever, cough, dyspnea)

AND

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

- NOTES on COVID-related exclusion:

  1. If a participant is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.

  2. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.

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

# INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-67864238 Clinical Protocol 67864238PACRD2001

## INVESTIGATOR AGREEMENT

I have read this protocol and agree that, in conjunction with the accompanying Master protocol PLATFORMPACRD2001, it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): PPD

Institution: Janssen Research & Development

PPD

Signature: _____ Date: 05-20-2020
(Day Month Year)

**Note:** If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.



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Status: Approved , Date: 20 May 2020