Janssen Research & Development *

Clinical Protocol

Protocol Title

A Randomized, Stratified, Double-blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of JNJ-55308942 in Bipolar Depression.

Short Title
A study to explore the efficacy of JNJ-55308942 in the treatment of bipolar depression

Protocol 55308942BIP2001; Phase 2a
Amendment 5

JNJ-55308942

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

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EudraCT NUMBER: 2021-004790-31

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Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	18 August 2023
Amendment 4	25 January2023
Amendment 3	27 July 2022
Amendment 2	4 July 2022
Amendment 1	01-February-2022
Original Protocol	02-September-2021

Amendment 5 (18 August 2023)

Overall Rationale for the Amendment: Antipsychotics approved for BD, however not effective for treating the current major depressive episode, whether taken alone or in combination with a mood stabilizer may be permitted. AiCure® services for medication compliance and meal intake are discontinued and replaced with Q1.6 for medication reminders. Vendor names are removed from the body of the protocol.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; Overall Design; 4.1 Overall Design; 4.2 Study Population; and throughout protocol	Modified text to include participantss taking an antipsychotic alone or taking an antipsychotic and a mood stabilizer. Participants taking an antipsychotic and mood stabilizer may be considered for eligibility upon investigator and sponsor assessment.	Updated concomitant medications to include antipsychotics approved for BD that are not effective for the participant's current major depressive episode, whether taken alone or in combination with a mood stabilizer.
1.1 Synopsis: Secondary Endpoints	Modified text to include participants with BD taking an antipsychotic alone or taking a combination of an antipsychotic and a mood stabilizer.	Efficacy evaluation of JNJ-55308942 compared to placebo to include antipsychotics.
1.1 Synopsis Overall Design; 4.1 Overall Design; 4.2 Blinding; Study Phase/Periods, Intervention Groups	Participants will enter the treatment period where they will be randomly assigned to daily dose administration with C mg JNJ-55308942 or placebo for 6 weeks, Day 1 up to and including the last treatment visit, Day 43 +/- 1 day.	Clarification to ensure the study drug is taken up to and including the last treatment visit.
Throughout the protocol,including Schedule of Activities and footnotes.	Vendor names (AiCure® and Q1.6) removed and replaced with Digital Health Asssessment app for the medication compliance and reminders. Footnotes (s) and (z) removed.	Applying best practice not to include vendor details in the protocol.
6.4.1 Medication Adherence and Reminder System; 8. Study Specific Materials; 8.1.3 Double-blind treatment phase (Visit 2 to Visit 6); 8.6 Digital Health Assessment; Schedule of Activities	AiCure® application removed throughout the protocol.	AiCure services discontinued. Meal intake is collected in the eCRF. The Digital Biomarker for US sites discontinued.

1.1 Synopsis Clinical Laboratory Tests; 9.4.3; Safety Analyses; Clinical Laboratory Tests	Removed summary of markedly abnormal results.	Summarizing clinical labs using the reference ranges is sufficient.
5.1 Inclusion Criteria	Inclusion Criterion 5 modified to include participants taking an antipsychotic alone or taking a combination of an antipsychotic and a mood stabilizer. Participants taking a mood stabilizer and an antipsychotic may be considered for eligibility upon investigator and sponsor assessment.	Updated critiera to include antipsychotics approved for BD that are not effective for the patient's current major depressive episode, whether taken alone or in combination with a mood stabilizer.
5.2 Exclusion Criteria; Other Exclusions	Added clinically stable as a status for participants successfully treated for HIV infection to be allowed in the study.	Clinically stable is acceptable for eligibility.
5.2 Exclusion Criteria; Other Exclusions	Added the status of clinically stable, removed the specifics of HCV and HCV RNA for infection treatment or recovery, added sponsor approval for eligibility if the participant is positive for hepatitis B surface antigen. Added the possibility of a confirmatory PCR test if the test results are ambiguous.	Clinically stable is acceptable for eligibility. Confirmatory PCR test will support ambiguous results for eligibility.
8. Study Assessments and Procedures	The PCRS, MADRS (SIGMA), CGI-S and participant self-rating baseline assessment is to be performed predose.	Explicitly stating the order of assessments for the study visits.
8. Study Assessments and Procedures; Schedule of Activities	Vital signs and 12-lead ECG, as well as C-SSRS and YMRS will be done pre-randomization on Day 1, and will be done predose on Day 8, 15, 29 and 43.	Clarifying the procedures and assessments to be done pre-randomization at the baseline visit versus pre-dose for treatment visits.
8. Study Assessments and Procedures; Study-Specific Materials	Added the Mood Stabilizer and Antipsychotic Eligibility Assessment form	Form added as a part of the investigator and sponsor assessment for Inclusion Criteria 5
6.7 Concomitant Therapy; 10.6 Appendix 6: Disallowed Concomitant Therapies	For concomitant medication, added the permitted antipsychotics lurasidone, cariprazine, quetiapine, lumateperone, and olanzapine for the treatment of bipolar disorder. Updated to 'Yes' for episodic use (PRN) and 'Yes' for Continuous Use.	Updated concomitant medications to include antipsychotics approved for BD that are not effective for the patient's current major depressive episode, whether taken alone or in combination with a mood stabilizer.
10.6 Appendix 6: Disallowed Concomitant Therapies	For concomitant medication, added fluticasone.	No interaction effect for fluticasone treatment.
Schedule of Activities	Footnote (ac) added to clarify only a non-confirmatory serology result for Hepatitis B, C and/or HIV may require a confirmatory test to be completed.	Clarify procedure for non-confirmatory serology result.

	Footnote (ad) added for the completion of the Mood Stabilizer and Antipsychotic Eligibility Assessment form. Added 'X' for Day 43 RNA. Added +/- 1 day window for telephone visits	Clinical judgement of the investigator and sponsor to document the eligibility outcome for each patient with a combination of an antipsychotic and a mood stabilizer regimen for trial participation. Day 43 missing. Window allowance applies to both in clinic and telephone visits.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Stratified, Double-blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of JNJ-55308942 in Bipolar Depression.

A study to explore the efficacy of JNJ-55308942 in the treatment of bipolar depression.

Bipolar disorders (BD) are chronic, serious mood disorders that affect 45 million people worldwide. In a publication by the National Institute of Mental Health (NIMH) in 2017, approximately 2.8% of adults in the United States had BD the past year (NIMH Statistics 2017). Characterized by episodes of mania and depression, it is often the depressive episodes that are most severe, common, and long-lasting. (Note, BD type I and II are distinguished by mania in type I and hypomania in type II).

Unfortunately, depressive episodes in BD are difficult to treat, with currently approved options limited to antipsychotics (e.g., lurasidone, cariprazine, lumateperone and quetiapine) or the olanzapine/fluoxetine combination treatment. Of note, only one medication—quetiapine—is US Food and Drug Administration (FDA) approved for bipolar II depression. It is estimated that patients with BD live 9 to 20 years less than those without BD (Crump 2013, Chesney 2014). The extent to which this is a consequence of the disease, the treatment, comorbidities, or all these factors combined, remains unclear. Nonetheless, there is a desperate need for novel, safe treatments for this population.

JNJ-55308942 is a potent, selective, and brain penetrant antagonist of the adenosine triphosphate (ATP) gated P2X7 receptor that is involved in the release of the proinflammatory cytokine, interleukin-1β (IL-1β) (Solle 2001). Within the brain, IL-1β is thought to contribute to a neuroinflammatory diathesis that is involved in the pathophysiology of neuropsychiatric and neurodegenerative disorders (Bhattacharya 2018; Chrovian 2014; Lord 2014; Sperlagh 2014). Therefore, JNJ-55308942 has potential for clinical application in mood disorders, including BD.

Given this potential mechanism, it can further be hypothesized that participants with a Gain of Function (GoF) single nucleotide polymorphism (SNP) mutation in the P2X7 receptor may be more likely to respond to treatment. Conversely, those participants with a Loss of Function (LoF) SNP mutation in the P2X7 receptor would be less likely to respond to treatment. Therefore, patient enrichment based on SNP profile may be a promising strategy for participant selection.

OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in participants with BD in a major depressive episode (MDE) at Week 6.	Change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline at Week 6.
Secondary Objectives of Special Interest	
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of anhedonia	Change in Snaith-Hamilton Pleasure Scale (SHAPS) total score from baseline at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in participants with BD who are heterozygous or	Change in MADRS total score from baseline at Week 6.

Objectives	Endpoints
homozygous for the CCCI P2RX7 GoF SNP (genetic subgroup analysis)	
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in participants with BD type I or BD type II (diagnosis subgroup analysis)	Change in MADRS total score from baseline at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in subgroups of patients with specific biomarker profiles (biomarker subgroup analysis).	Change in MADRS total score from baseline at Week 6.
Secondary	
To evaluate the overall safety and tolerability of treatment with JNJ-55308942 as compared to placebo in participants with symptomatic BD over a treatment period of 6 weeks.	Vital signs (pulse/heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP], respiratory rate), clinical labs (chemistry, hematology, urinalysis), Adverse Events, ECG, Young Mania Rating Scale (YMRS) score, Columbia Suicide Severity Rating Scale (C-SSRS) score.
To evaluate the effect of JNJ-55308942 compared to placebo on disease severity and improvement on the Clinical Global Impression-Severity scale (CGI-S)	CGI-S
To evaluate pharmacokinetics (PK) of JNJ-55308942 in participants with BD.	Plasma concentrations of JNJ-55308942.
To assess the effect of JNJ-55308942 on reduction of symptoms associated with depression compared to placebo as measured by self-rated outcomes.	PROMIS – Ability to Participate in Social Roles and Activities, Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder 7 (GAD-7) score.
To evaluate the impact of treatment with JNJ-55308942 compared with placebo on response (≥50% improvement in MADRS total score from baseline) and remission (MADRS total score ≤12) rates at Week 6.	Response (≥50% improvement in MADRS total score from baseline) and remission (MADRS total score ≤12) rates at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in a subgroup of patients with messenger ribonucleic acid (mRNA) transcript levels at baseline that exceed the median level for both P2RX7 and IL-1β.	Change in MADRS total score from baseline at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in subgroups of participants with BD not taking any mood stabilizer or antipsychotic, taking a	Change in MADRS total score from baseline at Week 6.

Objectives	Endpoints
mood stabilizer alone, taking an antipsychotic alone, and taking a combination of a mood stabilizer and an antipsychotic (concomitant medication subgroup analysis).	
Exploratory	
To explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship between plasma exposure of JNJ-55308942, and efficacy and safety parameters in patients with BD.	Exposure-response between exposure and MADRS and selected safety events, as appropriate.
To explore the effect of JNJ-55308942 on PD-related biomarkers.	Including, but not limited to, blood biomarkers related to immune, inflammatory, hormonal, metabolic, hypothalamic-pituitary-adrenal (HPA) axis, P2X7 receptor and monocyte activity.
To explore the effect of pharmacogenomic variations on the PK, efficacy, and safety of JNJ-55308942.	Influence of genetic polymorphisms (e.g., CCI [redacted]1) on plasma exposure, as well as on efficacy and safety measures.
To explore the effect of JNJ-55308942 compared to placebo on the well-being of participants.	Self-Assessment of Well-Being (SAWB) outcome.

Hypothesis

The primary hypothesis that will be tested in this study is that JNJ-55308942, compared to placebo, results in a significant improvement in the reduction of the symptoms of depression in participants with BD in a MDE as assessed by change in MADRS total score from baseline at Week 6.

OVERALL DESIGN

This is a double-blind, randomized, stratified, placebo-controlled, parallel group, multicenter study. A total of approximately 164 participants will be enrolled in this study to obtain approximately 132 completers.

The target study population includes participants of any gender, between 18 and 64 years of age inclusive, with a Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) diagnosis of BD (types I or II) without current psychotic features as confirmed by the Mini International Neuropsychiatric Interview (MINI) with Borderline Personality Disorder module. BD patients should be experiencing an MDE that does not require either hospitalization or antidepressant medication.

Each potential participant must satisfy one of the three criteria listed below in order meet eligibility for the study population.

- Participants who are currently unmedicated and have not received any mood stabilizers or antipsychotics for four weeks before screening.
- Participants who are on a stable monotherapy regimen of one of the following mood stabilizers (lithium, valproate forms [e.g., divalproex sodium], or lamotrigine) or one of the following antipsychotics (lurasidone, cariprazine, quetiapine, lumateperone, or olanzapine) for four weeks before screening.

- Participants who are on a stable adjunctive regimen of one of the following antipsychotics (lurasidone, quetiapine, lumateperone, or olanzapine) and one of the following mood stabilizers (lithium, or valproate forms [e.g., divalproex sodium]) may be considered for eligibility based on the approved therapies in each market with an eligibility assessment conducted between the investigator and sponsor. Assessment of the stable adjunctive regimen of an antipsychotic and a mood stabilizer will be conducted by the investigator and sponsor's clinical judgement and documented for each participant. This regimen must be in place 4 weeks before screening.

The participant must be symptomatic as assessed using the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$). Symptom intensity over the past week will be evaluated. Participants who are enrolled in the study will continue on their current medication regimen, if applicable, throughout the study. No dose changes are permitted from screening through the end of the study (until after the follow-up visit). No concurrent use of antidepressants will be allowed (until after the follow-up visit).

For each participant, the study will consist of 3 phases: a screening phase of up to 4 weeks, a double-blind treatment phase of 6 weeks, and a post-treatment follow-up phase of up to 2 weeks (Figure 1). Participants will enter the treatment period where they will be randomly assigned to daily dose administration with C mg JNJ-55308942 or placebo for 6 weeks, Day 1 up to and including the last treatment visit, Day 43 +/- 1 day. The study drug should be taken by the participant at every clinic visit during the treatment period. Between approximately 1 to 2 weeks after administration of the last dose, participants will return to the study site for a follow-up visit. The total study duration for each participant will be up to 12 weeks. There will be 7 scheduled visits to the study site during the study, including screening, and follow-up visit.

For study visits, a window of ±1 day will be allowed.

No study-specific screening procedures will be undertaken prior to finalization of the informed consent form (ICF) procedures and the provision of written informed consent by the participant.

Eligibility Screening Examination (for all study participants)

After giving written consent for screening, participants will be screened between 28 days and 1 day prior to the double-blind treatment phase to ascertain their eligibility for the study according to the inclusion and exclusion criteria. Although the screening period allows for up to 4 weeks, shorter screening periods are encouraged when possible. The assessments scheduled during the screening visit may be divided over multiple days, according to operational and/or site/country-specific needs.

To ensure that a participant is part of the target study population, specific assessments are prioritized during the screening period. These assessments must be administered on the first day of screening, and only if the participant qualifies will the remainder of the assessments be performed/scheduled. These assessments will be performed by a certified rater at the site. The priority screening procedures are as follows:

1. The MINI with Borderline Personality Disorder module.
    a. The participant must meet criteria for a diagnosis of either BD type I or II.
    b. The participant must not currently meet criteria for psychosis or psychotic disorder, borderline personality disorder, antisocial personality disorder, eating disorder, or suicide behavior disorder.
    c. The participant must not have ≥4 episodes of mood disturbances (e.g., mania, hypomania, or depression) within the past 12 months.
2. The Structured Interview Guide for the $HDRS_{17}$ (Structured Interview Guide for the $HDRS_{17}$ [SIGH-D]).
    a. The participant must be in a current MDE with a total score >20 and with a score >2 on the depressed mood item [question #1].

b. SIGH-D is based on the $HDRS_{17}$ and will be used in this study to perform the $HDRS_{17}$ at screening and at pre-randomization on Day 1, to confirm the participant continues to meet eligibility criteria.

3. The ATHF-SF: current and past antidepressant and antipsychotic treatments.

   a. The participant must not have taken any disallowed medications (per appendix 6) during the 4 weeks prior to the screening visit. Disallowed medications include antidepressants.

   b. Nonresponse to >4 treatments in the current episode is exclusionary. Of note, participants who have been nonresponsive or inadequately responsive to electroconvulsive therapy (ECT) or ketamine in the current episode will be excluded. Participants who received transcranial magnetic stimulation (TMS), any transcranial electrical stimulation, including transcranial direct current stimulation (tDCS), vagal nerve stimulation (VNS), and/or deep brain stimulation (DBS) within 6 weeks prior to randomization (assessed with the ATHF-SF at screening) will be excluded. Newly initiated psychotherapy (defined as psychotherapy that was started within 4 weeks of the screening visit and assessed with the ATHF-SF at screening) is also exclusionary.

If applicable, the Mood Stabilizer and Antipsychotic Eligibility Assessment form will be completed for participants who are on a stable adjunctive regimen of an antipsychotic and a mood stabilizer for 4 weeks before screening.

Once potential participants have met eligibility requirements for the MINI, SIGH-D, and ATHF-SF and the Mood Stabilizer and Antipsychotic Eligibility Assessment form (if applicable), the remaining screening procedures may be completed (see Sections 5.1 and 5.2 for details).

Participants will be screened to ascertain their eligibility for the study based on the presence of the GoF P2RX7 mutation (for inclusion, must be CC or CC at CCCI nucleotide CCI ; CCI) and the absence of the LoF P2RX7 mutations (must be CC or CCI at rsCCI /nucleotide CCI ; CCI and must be CC at rsCCI /nucleotide CCI ; CCI). In other words, participants will be excluded if they have the presence of two copies of the LoF C allele at rsCCI (i.e., exclude those with CCI at nucleotide CCI), and/or one or more copies of the LoF C allele at rsCCI (i.e., exclude those with CC or CC nucleotide CCI). This assessment will include the collection of a blood sample. In case participants need to be rescreened, this assessment does not need to be performed again.

Screening will also include assessment of study inclusion and exclusion criteria, medical history, demographics, physical examination, psychiatric and safety evaluations, and standard laboratory tests. The remaining assessments may be divided over multiple days, according to operational and/or site/country-specific needs and may take place before or after the P2RX7 genotyping results and other laboratory results become available.

Of note, although the SIGH-D will be used for study entry criteria, the MADRS will be used as the primary endpoint. The Structured Interview Guide for the MADRS (SIGMA) is based on the MADRS and will be used in this study to perform the MADRS. In order to protect against potential score inflation of the baseline MADRS score, the inclusion criteria are based on the SIGH-D instead of the primary efficacy endpoint (MADRS). Note, the first MADRS score will be obtained at randomization (pre-dose) in order to provide the baseline score prior to treatment.

Double-blind Treatment Phase

The duration of the double-blind treatment phase is 6 weeks. Participants will visit the study center for a baseline visit on Day 1 and receive the first dose of study intervention following randomization at the clinic.

On Day 1, after confirming the depressive state of the participant using the SIGH-D ($HDRS_{17}$ total score ≥20 and with a score ≥2 on the depressed mood item [question #1]), and completing all assessments as outlined in the schedule of activities (SoA), he/she will be randomly assigned to receive either treatment with C mg JNJ-55308942 or placebo once-daily in a 1:1 ratio for a 6-week treatment period. The SIGH-D

(screening and pre-randomization on Day 1) will ideally be completed by the same qualified rater for a given participant.

There will be 4 randomization stratification factors: BD type (I or II), country, P2RX7 GoF SNP genotype (homozygous or heterozygous), as well as concomitant medication use (no mood stabilizer or antipsychotic, a mood stabilizer alone, an antipsychotic alone, or a combination of a mood stabilizer and an antipsychotic). Investigators and participants will remain blinded to response criterion and study intervention treatment assignment for each participant.

During the double-blind treatment phase, the SIGMA (MADRS) and CGI-S will be completed by the same qualified rater for a given participant. Exceptions should be discussed with and approved by the sponsor. The sponsor can request a rater change based on quality concerns. The severity of depressive symptoms will be assessed using the SIGMA (MADRS) at randomization (pre-dose) in order to provide the baseline score prior to treatment and at subsequent visits to the study site.

Study intervention will be taken at home in the morning CC mg JNJ-55308942 or placebo) at approximately the same time (± 4 hours) each day, 30 minutes after the start of breakfast (maximum of 2 hours after the start of breakfast). There is an exception on Day 1 where participants will receive the study intervention at the study site after all baseline assessments have been completed.

On study visits 3, 4, 5, and 6, study intervention will be administered at the study site after the clinical lab and PK samples have been collected and at approximately the same time (± 4 hours). Study intervention will be dispensed at visits 2, 4, and 5 during this double-blind treatment period. When the participant returns to the site for visit 3, 4, 5 and 6, the participant will be administered the study intervention from the bottle dispensed from the previous visit.

Of note, on study site visits 3, 4, 5, and 6, participants will be instructed to eat breakfast at home and come to the site within 1 hour or less after completion of the meal. Inability to comply with these instructions would not constitute a protocol violation, but the participants are encouraged to comply with these instructions as closely as possible.

The well-being of the participant will be frequently tracked using an Digital Health Assessment app to monitor parameters such as, but not limited to, the pattern of sleep, energy level, and concentration level via the SAWB Questionnaire. Additionally, the Digital Health Assessment app will alert the investigator when a participant has indicated that their depression is ‘much worse’ or ‘very much worse’ when answering weekly questions on depression.

The SHAPS will be administered once at baseline (pre-dose) and once at the end of the double-blind treatment phase (after the final dose). Participants will complete the PROMIS - Ability to Participate in Social Roles and Activities and the PHQ-9 at baseline and once weekly, and the GAD-7 every two weeks. As per SoA, the self-rating instruments will be administered at clinic visits or at home. For self-rating instruments completed at home on paper, participants should complete these scales before the next clinic visit and participants will receive notifications from the Digital Health Assessment app on their mobile phones as reminders to complete these paper instruments.

Key safety assessments will include the monitoring of adverse events, physical examinations, vital signs (e.g., blood pressure, pulse/heart rate, body temperature), electrocardiogram (ECG), clinical laboratory tests, emergence of mania (YMRS), and suicidal ideation (C-SSRS).

In addition, blood samples for PK, biomarker assessment, hormones (males only), and pharmacogenomics (general SNPs and RNA) will be collected as per the SoA and use of concomitant medication will be recorded.

Follow-up Examination

Between 7 to 14 days after the last study visit, participants will return to the study site for a safety follow-up visit. The procedures to be completed during the follow-up visit are listed in the SoA.

NUMBER OF PARTICIPANTS

Approximately 164 participants will be enrolled in this study.

INTERVENTION GROUPS AND DURATION

Study intervention will be taken at home in the morning (C mg JNJ-55308942 or placebo) at approximately the same time (± 4 hours) each day 30 minutes after the start of breakfast (maximum of 2 hours after the start of breakfast). There is an exception on Day 1 where participants will receive the study intervention at the study site after all baseline assessments have been completed. On study visits 3, 4, 5 and 6, study intervention will be taken at the study site after the clinical lab and PK samples have been collected and at approximately the same time (± 4 hours). Study intervention will be dispensed at visits 2, 4 and 5 during this double-blind treatment period. When the participant returns to the site for visit 3, 4, 5 and 6, the participant will be administered the study intervention from the bottle dispensed from the previous visit.

The capsules must be swallowed whole and not chewed, divided, dissolved, or crushed.

The first dose of study intervention will be taken in the fed condition on Day 1 of the double-blind treatment phase when the participant is at the study site.

On days when participants visit the study site, they should not take the study intervention at home before arriving at the site. The participants will bring the study intervention with them at each study visit and will take study intervention—from the bottle dispensed at the previous study visit—at the site in the fed condition after completion of predose study assessments and blood collections. Dosing at the study site will be witnessed by the study staff.

Description of Interventions

Group/Arm Name	**Active study intervention group**	**Placebo group**
Intervention name:	JNJ-55308942	Placebo for JNJ-55308942
Dosage formulation	Capsule	Capsule
Unit dose strength(s)/ Dosage levels:	C mg	Not applicable
Dosage Level(s) and Frequency	C mg, 1 capsule once-daily	1 capsule once-daily
Route of Administration	☒ Oral ☐ IV infusion ☐ IV injection ☐ Intramuscular ☐ Other	☒ Oral ☐ IV infusion ☐ IV injection ☐ Intramuscular ☐ Other
Dosing instructions	One capsule daily, preferably at the same time, recommended to take each dose of study intervention in the morning with a glass of water 30 minutes after the start of breakfast (max. 2 hours).	One capsule daily, preferably at the same time, recommended to take each dose of study intervention in the morning with a glass of water 30 minutes after the start of breakfast (max. 2 hours).
Use	☒ Experimental ☐ Background intvn. ☐ Challenge agent	☐ Experimental ☒ Placebo comparator ☐ Active comparator

	☐ Diagnostic ☐ Other	☐ Sham comparator ☐ Rescue medication ☐ Background intvn. ☐ Challenge agent ☐ Diagnostic ☐ Other
Investigational Medicinal Product (IMP)	☒ Yes ☐ No	☒ Yes ☐ No
Non-Investigational Medicinal Product (NIMP)	☐ Yes ☒ No	☐ Yes ☒ No

ELIGIBILITY INSTRUMENTS

- MINI International Neuropsychiatric Interview (MINI) with Borderline Personality Disorder module
- The Antidepressant Treatment History Form-Short Form (ATHF-SF)
- 17-Item Hamilton Depression Rating Scale ($HDRS_{17}$) – administered via the Structured Interview Guide for the $HDRS_{17}$ (SIGH-D)
- Determination of the allele variant for P2RX7 for 1 GoF P2RX7 SNP and 2 LoF P2RX7 SNPs.
- If applicable, the Mood Stabilizer and Antipsychotic Eligibility Assessment form

EFFICACY EVALUATIONS

- Montgomery-Åsberg Depression Rating Scale (MADRS) – administered via the Structured Interview Guide for the MADRS (SIGMA)

OTHER CLINICIAN ADMINISTERED EVALUATIONS

- Clinical Global Impression - Severity scale (CGI-S)

SELF-RATING INSTRUMENTS

- Snaith-Hamilton Pleasure Scale (SHAPS)
- PROMIS – Ability to Participate in Social Roles and Activities
- Patient Health Questionnaire (PHQ-9)
- Generalized Anxiety Disorder 7 (GAD-7)
- Self-Assessment of Well-Being (SAWB)

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected for PK evaluation as indicated in SoA. Samples will be used to evaluate the plasma concentrations of JNJ-55308942 and metabolites (if required). In addition, some samples may be used to measure plasma concentrations of concomitant medications used by the participant. Participant confidentiality will be maintained.

BIOMARKER EVALUATIONS

Venous blood samples for the assessment of whole blood, serum, and plasma PD-related biomarkers potentially including, but not limited to, immune, inflammatory, hormonal, metabolic, and HPA axis activity will be collected as indicated in the SoA during the double-blind treatment phase. Samples may also be used to study markers of P2RX7 and monocyte activation. Blood samples will be collected as indicated in the SoA for gene expression analysis.

All PD-related biomarker data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between depression severity, phenotypes, and biomarkers, or to help explain interindividual variability in clinical outcomes or safety. Biomarker assays may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

GENETIC AND PHARMACOGENOMIC EVALUATIONS

A blood sample will be collected during the screening period to assess whether the participant:

1. is carrier of the [redacted] GoF P2RX7 mutation (must be [redacted] or [redacted] at [redacted] nucleotide [redacted] for inclusion).
2. is *not* a carrier of the [redacted] or [redacted] LoF P2RX7 mutations (must be [redacted] or [redacted] at rs[redacted]/nucleotide [redacted]; and must be [redacted] at rs[redacted]/nucleotide [redacted] In other words, participants will be excluded if they have the presence of two copies of the LoF C allele at rs[redacted] (i.e., exclude those with [redacted] at nucleotide [redacted]), and/or has one or more copies of the LoF [redacted] allele at rs[redacted] (i.e., exclude those with [redacted] or [redacted] nucleotide [redacted]

An additional optional pharmacogenomic blood sample will be collected from enrolled participants on Day 1 to identify genetic factors that may influence the PK, PD, efficacy, safety and/or tolerability of JNJ-55308942 and to identify genetic factors associated with BD. If collection on Day 1 is not feasible, it can be collected on any other visit during the double-blind treatment phase.

SAFETY EVALUATIONS

Adverse events (AEs) will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) from obtaining the screening informed consent through the day of last dose plus 30 days. There are no AEs of special interest.

The following safety assessments will be performed: physical examination, body weight, vital signs (including oral, tympanic or temporal temperature, blood pressure, pulse/heart rate and respiratory rate), 12-lead electrocardiogram (ECG), urine drug testing, alcohol breath test, pregnancy testing (female participants only), hormones, and clinical labs (hematology, chemistry panel and urinalysis) as per SoA. In addition, serology and hemoglobin A1c (HbA1c) assessments will be performed at screening only.

Emergence of mania will be assessed using the YMRS at each visit.

Emergence of suicidal ideation will be assessed using the C-SSRS at screening and during each visit. The Digital Health Assessment app will alert the investigator when a participant has indicated that the depression is 'much worse' or 'very much worse' when answering weekly questions on depression.

STATISTICAL METHODS

Sample Size

The estimated sample size of 164 participants (82 participants per group) was determined based on the assumption of an effect size of at least 0.45 for the MADRS total score (difference in mean change from baseline at Week 6 between the JNJ-55308942 and placebo groups of 3.9 units with a standard deviation of 8.6). This is considered to be a clinically relevant difference in a population with BD types I or II. The standard deviation of 8.6 in the change in MADRS total score from baseline is a reasonable assumption based on data in a published phase 3 study of quetiapine in BD type I and type II depression (Calabrese 2005). Power is set at 90%, with a 1-sided alpha of 0.10 and a 6-week drop-out rate of 20%. The estimated number of completers to be included in the primary analysis is 132.

Efficacy Analyses

The full analysis set (FAS) will include all randomized participants who receive at least 1 dose of study intervention and have both the baseline and at least 1 post-baseline MADRS measurement. Efficacy analyses will be based on the FAS.

The estimand for the primary efficacy analysis is defined with the following 5 attributes:

- Population: participants with BD types I or II in an MDE.
- Endpoint: change from baseline in the MADRS total score at Week 6.
- Treatment: JNJ-55308942 [redacted] mg once-daily versus placebo.

- Population-level summary: the difference in mean change from baseline in MADRS total score at Week 6 between JNJ-55308942 C mg once-daily and placebo.
- Intercurrent events (ICE) and corresponding strategy: The ICE to be considered is discontinuation of study intervention. The ICE will be addressed with a hypothetical strategy, targeting the effect of the initially randomized treatment that would have been observed had all participants remained on their treatment throughout the double-blind treatment phase.

The primary efficacy analysis will be performed utilizing the hypothetical estimand defined above. The change from baseline in MADRS total score will be compared between the JNJ-55308942 C mg once-daily group and the placebo group at Week 6 in a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo or JNJ-55308942), BD type (I or II), country, concomitant medication status (no mood stabilizer or antipsychotic, a mood stabilizer alone, an antipsychotic alone, or a combination of a mood stabilizer and an antipsychotic), P2RX7 GoF SNP genotype (homozygous or heterozygous) and time-by-treatment interaction as factors, with baseline MADRS total score as a continuous covariate. Data after treatment discontinuation is considered as missing. An unstructured variance-covariance matrix will be used. In case of convergence problems, alternative variance-covariance structures will be attempted in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and first order autoregressive. Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Sandwich estimator will be used to address the potential misspecification of the covariance matrix when a structured covariance matrix is used due to the convergence problem with the unstructured covariance matrix. The comparison of JNJ-55308942 C mg once-daily versus placebo will be performed using appropriate contrast.

To support the primary efficacy analysis, two sensitivity analyses will be performed:

- MMRM analysis with copy-reference multiple imputation where missing outcomes due to treatment discontinuation in the JNJ-55308942 C mg once-daily group is assumed to be similar to those in the placebo group.
- Tipping point analysis that imputes missing outcomes over a range of possible scenarios for the treatment effect and finds a 'tipping point' where the treatment effect in participants with missing data overturns the significant treatment effect. This analysis will be performed if the results from the primary analysis show a significantly greater improvement in the MADRS total score at Week 6 in the JNJ-55308942 C mg once-daily group compared to the placebo group.

Response and remission rates with respect to MADRS will be summarized by treatment group and by scheduled timepoint.

For the Secondary Objectives of Special Interest, change from baseline in SHAPS total score at Week 6 will be compared between JNJ-55308942 C mg once-daily and placebo in an ANCOVA model. The model will include intervention (placebo or JNJ-55308942), BD type (I or II), country, concomitant medication status (no mood stabilizer or antipsychotic, a mood stabilizer alone, an antipsychotic alone, or a combination of a mood stabilizer and an antipsychotic), P2RX7 GoF SNP genotype (homozygous or heterozygous) as factors, and baseline SHAPS total score as a covariate. Comparison between JNJ-55308942 C mg once-daily and placebo will be performed using appropriate contrasts. Change from baseline in MADRS total score at Week 6 will be assessed with confidence intervals in subgroups for BD type (I or II), P2RX7 GoF SNP genotype (heterozygous or homozygous), and patients with specific biomarker profiles (yes or no) using a similar MMRM as the one used for the primary endpoint analysis.

For other Secondary Objectives, similar MMRM analyses will be conducted for changes in T-score of PROMIS – Ability to Participant in Social Roles and Activities, the PHQ-9 total score, and the GAD-7 total score. Subgroup analyses by mRNA transcript (P2RX7 and IL-1β) level status at baseline (yes or no) and use of concomitant medication (no mood stabilizer or antipsychotic, a mood stabilizer alone, an

antipsychotic alone, or a combination of a mood stabilizer and an antipsychotic) will also be assessed with confidence intervals using a similar MMRM.

For the CGI-S efficacy endpoint, a frequency distribution of severity scores will be provided by treatment group from Week 1 to Week 6. In addition, frequency of shifting scale at Week 6 from baseline will be provided.

Descriptive statistics will be provided for the SAWB assessments.

Safety Analyses

Statistical analysis of the safety data will be done by the sponsor or under the authority of the sponsor. Specific details will be provided in the statistical analysis plan (SAP).

All safety analyses will be performed based on the safety analysis set, which will include all randomized participants who receive at least 1 dose of study intervention. Safety summaries will be provided by treatment, unless specified otherwise.

Adverse Events

The verbatim terms used in the case report form (CRF) by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be treatment emergent. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges).

Electrocardiogram (ECG)

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using [some or all of] the following correction methods: QT corrected according to Bazett's formula (QTcB) and QT corrected according to Fridericia's formula (QTcF).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 msec (males), >470 (females), >480 msec, or >500 msec will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 msec or >60 msec. Also, descriptive statistics of QTc will be provided by gender.

Vital Signs

Descriptive statistics of body temperature, pulse/heart rate, supine blood pressure, and respiratory rate values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values outside clinically relevant limits will be summarized.

Physical Examination

Abnormalities observed during the physical examination will be summarized and listed by treatment group at each scheduled time point.

Young Mania Rating Scale (YMRS)

Exploratory analyses will be performed for changes from baseline in YMRS total score and for changes from baseline in individual YMRS items by treatment group for all participants receiving at least 1 dose of study intervention. Details will be provided in the SAP.

Columbia Suicide Severity Rating Scale (C-SSRS)

Results from the C-SSRS will be tabulated by treatment group for all participants receiving at least 1 dose of study intervention.

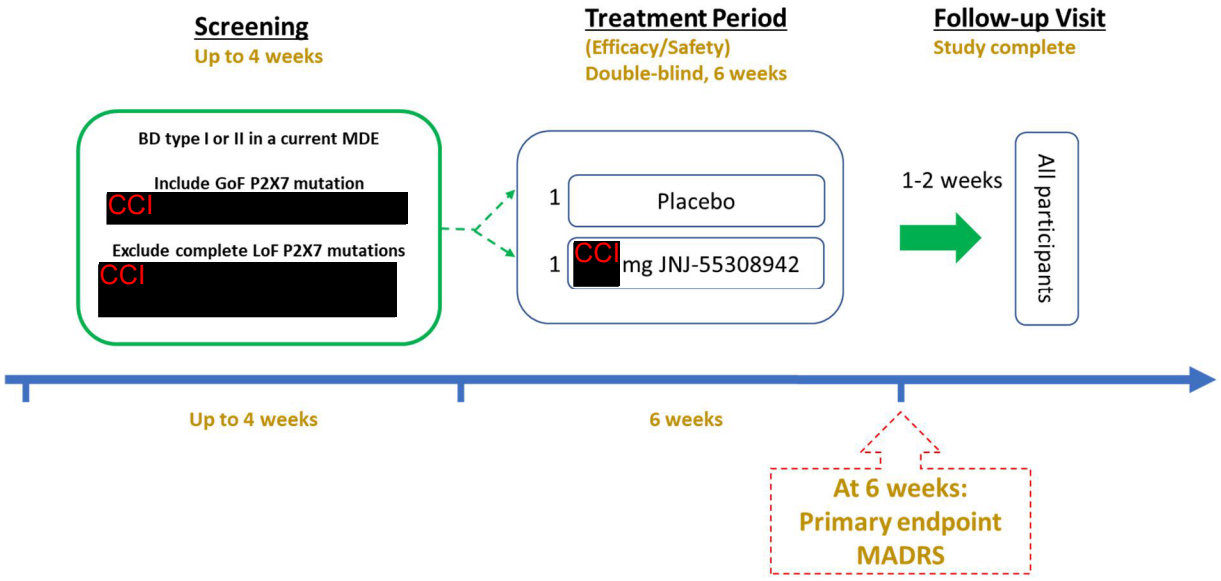
Interim analysis

No interim analysis is planned.

It may be recommended that an unblinded data review needs to be performed by an independent reviewer (e.g., data review committee) if deemed critical by the Janssen clinical team. Committee membership responsibilities, authorities, and procedures will be documented in a charter.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Phase	*Screening*	*Double-blind treatment phase*							*Follow-up or EW*[h] *(7 to 14 days after last study visit)*
Visit number[a]	1	2	3	4		5		6	7
Week (end of)	-4 to 0	0	1	2	3	4	5	6	7/8
Study Day	-28 to -1	1	8	15	22	29	36	43	49-56
Visit window			± 1 day	± 1 day	± 1 day	± 1 day	± 1 day	± 1 day	
Clinic Visit	C	C	C	C		C		C	C
Screening/Administrative									
Informed consent[b]	X								
MINI interview with Borderline Personality Disorder module	X								
ATHF-SF	X								
Inclusion/exclusion criteria	X	X[n ad]							
Prestudy therapies	X								
Medical history and demographics	X								
Download and install/register Digital Health Assessment app[q,r,c]	X	X							
Safety Assessments									
Physical examination	X	X						X	X
Height	X								
Body weight	X	X						X	X
Urine Drug Screen[ab]	X[m]	X	X	X		X		X	X
Alcohol Breath Test	X	X						X	
Pregnancy test[d]	X	X	X	X		X		X	X
Vital signs (supine blood pressure, heart rate, tympanic or oral temperature, respiratory rate)	X	X[n]	X[e]	X[e]		X[e]		X[e]	X
12-lead ECG[g]	X	X[n]	X[e]	X[e]		X[e]		X[e]	X
YMRS	X	X[w]	X[u]	X[u]		X[u]		X[u]	
C-SSRS[f]	X	X[w]	X[u]	X[u]		X[u]		X[u]	X
Study Intervention Administration									
Randomization		X							
Dispense study intervention		X		X		X			
Oral dose study intervention [i, j]		Day 1 up to and including Day 43[i] ± 1 day							
Study intervention accountability by the site		X		X		X		X	

Phase	*Screening*	*Double-blind treatment phase*							*Follow-up or EW*[h]
									(7 to 14 days after last study visit)
Visit number[a]	1	2	3	4		5		6	7
Week (end of)	-4 to 0	0	1	2	3	4	5	6	7/8
Study Day	-28 to -1	1	8	15	22	29	36	43	49-56
Visit window			± 1 day	± 1 day	± 1 day	± 1 day	± 1 day	± 1 day	
Clinic Visit	C	C	C	C		C		C	C
Blood and Urine Collection[m]									
Clinical Laboratory tests: Hematology, serum chemistry and urinalysis	X	X		X		X		X	X
Serology, HbA1c	X[ac]								
Blood sample collection for PK JNJ-55308942		X[l]	X[l]	X[l]		X[l]		X[l]	
Blood samples for other biomarkers[k]		X		X		X		X	
Blood for research samples (TruCulture)[x]		X						X	
Blood for research sample (PBMCs)[y]		X							
Blood samples for hormones (males only)[v]		X				X		X	X
Blood sample for Pharmacogenomics (general SNPs)[aa]		X							
Blood sample for GoF and LoF SNPs (P2X7)	X								
Blood sample for RNA		X[k]				X[k]		X[k]	
Clinician-Administered Assessments									
Structured Interview Guide for $HDRS_{17}$ (SIGH-D)	X	X[p]							
Placebo-control reminder script (PCRS)		X[t]	X	X		X		X	
Structured Interview Guide for MADRS (SIGMA)		X[t]	X	X		X		X	
CGI-S		X[t]	X	X		X		X	
Participant Self-Rating Assessments									
SHAPS		X[t]						X	
PROMIS-Ability to Participate in Social Roles and Activities		X[t]	X	X	X	X	X	X	
PHQ-9		X[t]	X	X	X	X	X	X	
GAD-7		X[t]		X		X		X	
SAWB[o]		X----------						----------X	
Ongoing Participant Review									
Concomitant therapy	Continuous								
Adverse events	Continuous								

Footnotes:
a) The procedures scheduled during the screening visit may be divided over multiple days, according to operational and/or site/country-specific needs. A ± 1 day window will be allowed for study days 8, 15, 22, 29, 36 and 43.
b) Must be signed before first study-related activity.
c) The use of the digital health assessment app is mandatory.
d) Performed for women of childbearing potential (WOCBP). Serum (β-hCG) pregnancy test performed at Screening. At all other time points, urine pregnancy test will be done. If positive, a serum β-hCG test will be performed. Investigators may perform additional pregnancy testing at their discretion as clinically needed.
e) 12-lead ECG and vital signs will be taken predose of study intervention.
f) There are 2 versions of the C-SSRS. A "baseline/screening" version will be conducted at screening. A "since your last visit" version will be conducted predose on visit 2, 3, 4, 5, and 6, at follow-up/early withdrawal.
g) 12-lead ECG should be performed in triplicate at screening.
h) If a participant discontinues study intervention before the end of the double-blind phase, early withdrawal (EW) visit should be completed.
i) Study intervention will be taken at home in the morning at approximately the same time (± 4 hours) each day, 30 minutes after the start of breakfast (maximum of 2 hours after the start of breakfast). Recommended to take each dose of study intervention with a glass of water.
j) On study visits3, 4, 5, and 6, study intervention will be administered at the study site. The participants are instructed to eat at home and come to the site within an hour or less after completion of the meal. Inability to comply with these instructions would not constitute a protocol violation but the patients are encouraged to comply with these instructions. Dosing should be witnessed by the study staff when study intervention is taken at the study site.
k) Collect biomarker samples at the same time as hormone and RNA samples. Collect the biomarker samples predose (i.e. before study intervention administration). Participants should avoid strenuous activity 24 hours prior to biomarker collection.
l) A PK sample will be taken predose and 1.5 (±0.5h) and 4 hours (range between 2-4 hours) postdose. **Note:** note that the blood is ideally drawn at 4 hours postdose. However, the ranges allow the PK measurement to be obtained while still maintaining flexibility (e.g., if the site cannot accommodate the participant for 4 hours, if the participant must go to work, etc.). If the participant is unable to complete a PK draw, electing to withdrawal participation in the study, the PK draw can be missed to avoid an early withdrawal due to blood collection burden.
m) Refer to study exclusion criteria for circumstances in which a repeat test during screening is permitted. This is not valid for the PK samples.
n) Pre-randomization
o) Daily follow-up questions will be asked to the participant by using the Digital Health Assessment app on the participant's smartphone from Day 1 (V2) onwards. Several items of interest may be covered: e.g., the pattern of sleep, energy level, concentration level.
p) $HDRS_{17}$ (SIGH-D) has to be administered pre-randomization to verify eligibility of the participant. Only if the participant qualifies (total score of ≥20 and a score ≥2 on the depression question [question #1]), the remainder of the assessments can be scheduled.
q) At screening (or if not feasible at Visit 2, Day 1) check if the phone is compatible and download and install the Digital Health Assessment app. Site staff will check to see if the participant's phone is compatible with the app. If the participant has a phone that is not compatible with the app, a compatible phone may be provided for use in the study.
r) In the Digital Health Assessment app, the date of Visit 2 (i.e., Baseline; Study Day 1) should be entered in the dashboard. This should be done to ensure that the participant starts receiving the questions from Study Day 1 onwards.
t) On Day 1, complete the assessments in the following order PCRS, MADRS (SIGMA), CGI-S. Both the Clinican rated assessments and participant self-rating baseline assessment have to be performed predose.
u) Will be taken/performed predose.
v) On Day 1, the baseline hormone sample should be collected before dosing (predose). At all visits, hormone samples should be collected in the morning (7AM-11AM local time).
w) On Day 1, C-SSRS and YMRS have to be performed pre-randomization to verify eligibility of the participant.
x) These research samples (TruCulture) will be collected only at certain sites and collected only for sites in the US, Canada, Spain, and Poland.
y) This research sample (PBMC) may be collected only at certain sites and collected only for sites in the US.
aa) The general pharmacogenomics sample will be optional and, if not feasible on Day 1, can be collected on any day of the double-blind treatment phase.
ab) At screening: a urine sample will be analysed by the central lab. All other visits: a dipstick test and only in case of a positive result the urine sample will be analysed by the central lab for confirmation of the positive result.
ac) In the case of a non confirmatory serology result for Hepatitis B, C and/or HIV, a confirmatory PCR test may be done. Decisions regarding eligibility will be made by the investigator in consultation with the medical monitor on a case by case basis.
ad) Mood Stabilizer and Antipsychotic Eligibility Assessment form to be completed for patients on a stable adjuctive regimen of an antipsychotic and mood stabilizer.

2. INTRODUCTION

Bipolar disorders (BD) are chronic, serious mood disorders that affect 45 million people worldwide. In a publication by the National Institute of Mental Health (NIMH) in 2017, approximately 2.8% of adults in the United States had BD the past year (NIMH Statistics 2017). Characterized by episodes of mania and depression, it is often the depressive episodes that are most severe, common, and long-lasting. (Note, BD type I and II are distinguished by mania in type I and hypomania in type II).

Unfortunately, depressive episodes in BD are difficult to treat, with currently approved options limited to antipsychotics (e.g., lurasidone, cariprazine, lumateperone, and quetiapine) or the olanzapine/fluoxetine combination treatment. Of note, only one medication—quetiapine—is US Food and Drug Administration (FDA) approved for bipolar II depression.

It is estimated that patients with BD live 9 to 20 years less than those without BD (Crump 2013, Chesney 2014). The extent to which this is a consequence of the disease, the treatment, comorbidities, or all these factors combined, remains unclear. Nonetheless, there is a desperate need for novel, safe treatments for this population.

JNJ-55308942 is a potent, selective, and brain penetrant antagonist of the adenosine triphosphate (ATP) gated P2X7 receptor that is involved in the release of the proinflammatory cytokine, interleukin-1β (IL-1β) (Solle 2001). Within the brain, IL-1β is thought to contribute to a neuroinflammatory diathesis that is involved in the pathophysiology of neuropsychiatric and neurodegenerative disorders (Bhattacharya 2018; Chrovian 2014; Lord 2014; Sperlagh 2014). Therefore, JNJ-55308942 has potential for clinical application in mood disorders, including BD.

Given this potential mechanism, it can further be hypothesized that participants with a Gain of Function (GoF) single-nucleotide polymorphism (SNP) in the *P2RX7* gene may be more likely to respond to treatment. Conversely, those patients with Loss of Function (LoF) SNPs in the *P2RX7* gene would be unlikely to respond to treatment.

For the most comprehensive nonclinical and clinical information regarding JNJ-55308942, refer to the latest version of the Investigator's Brochure (IB) for JNJ-55308942.

The term "study intervention" throughout the protocol, refers to study drug as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

JNJ-55308942 is a selective, brain penetrant P2RX7 receptor antagonist. Nonclinical and clinical literature suggest that P2RX7 receptor antagonism may have clinical utility in the treatment of BD. In this study, we will investigate the effect of JNJ-55308942 in outpatients with BD Types I or II who are in a current major depressive episode (MDE). This study is being performed to collect

initial efficacy and safety signals in this patient population, which will guide the further development of JNJ-55308942.

2.2. Background

Nonclinical Studies

Pharmacologic Profile

A calcium flux assay showed JNJ-55308942 to be a potent antagonist at the human, rat, mouse, dog, and monkey P2X7 receptor orthologues. In human blood and monocytes, the compound attenuated IL-1β release with potencies (pIC_{50}) of 7.7±0.2 and 7.2±0.1, respectively.

Ex vivo P2X7 receptor occupancy (RO) studies of JNJ-55308942 after oral 10 mg/kg dose administration in rats indicated that maximal levels of brain P2X7 receptor occupancy occurred at C minutes (94%±4%) and that high occupancy levels (>80%) were maintained up to C hours after compound administration. The concentration of JNJ-55308942 producing 50% (EC_{50}) and 90% (EC_{90}) of maximal effect in rats are CC ng/mL, and CCI ng/mL, respectively.

Clear functional inhibition of central P2X7 receptors was demonstrated in an in vivo brain microdialysis assay in freely moving rats. Orally administered JNJ-55308942, significantly suppressed brain IL-1β release resulting from challenge with the P2X7 receptor agonist benzoyl-ATP (BzATP).

JNJ-55308942 dampened microglial activation in a mouse model of lipopolysaccharide (LPS)-induced neuroinflammation. In a model of chronic mild stress in rats, anhedonic-like behavior (i.e., reduction in sucrose intake) observed in stressed animals was reversed by JNJ-55308942. JNJ-55308942 was also efficacious in a mouse model of neuroinflammation associated depressive behaviors. The active doses in both models would result in high (>80%) occupancy of P2X7 receptors in the brain.

JNJ-55308942 is highly selective for the P2X7 receptor: no relevant binding at a broad panel of ion channels, enzymes, and receptors (at 10 µM) and no activity was seen when against tested kinases (at 1 µM). In addition, no activity was seen at other human P2X receptor subtypes when tested at concentrations of up to 100 µM.

Safety Pharmacology

The cardiovascular safety of JNJ-55308942 was extensively tested in several in-vitro and in-vivo models. In human Ether-à-go-go-Related Gene (hERG)-transfected human embryonic kidney cells 293 (HEK293) cells, expressing hERG potassium channels, the IC_{50} for potassium current inhibition was CCI µM, indicating a very low risk for electrocardiogram (ECG) effects or arrhythmogenic events. This was confirmed in perfused rabbit ventricular wedge preparations, an anesthetized guinea pig model, and in anesthetized and conscious dog studies, in which no ECG abnormalities were identified up to the highest concentrations/doses tested. Cardiovascular effects observed in these models were hemodynamic in nature. In the anesthetized guinea pig, increases in mean arterial blood pressure were seen at plasma concentrations >CC µg/mL and in the freely

moving telemetered dog, systolic blood pressure increased, and heart rate decreased transiently at doses of C mg/kg (mean $C_{6.5h}$ = CCI µg/mL) and higher. Mild hemodynamic changes were also seen in anesthetized dogs at plasma exposures >CCI µg/mL. In rats, single oral dosing up to CCI mg/kg did not affect respiratory parameters, however, in combination with isoflurane anesthesia 2-4 hours the maximal tolerated dose was C mg/kg (plasma exposures [C_{plasma}] = CC µg/mL at 2 hours and CCI µg/mL at 4 hours).

A neurobehavioral safety assessment in rats showed a transient effect on defecation frequency and body temperature at plasma exposures of CCI µg/mL. At plasma exposures >CCI µg/mL, more pronounced adverse effects on motor-affective, sensory motor, and autonomic responses were identified and at the highest dose tested of 500 mg/kg (C_{plasma} =CCI µg/mL), 1 rat was euthanized because of clonic convulsions. In all other animals, all observations were reversible.

Toxicology

In single oral dose experiments in dogs, doses up to CCI mg/kg were tested and no mortality was observed. In rat studies, doses as high as CCI mg/kg were given, but mortality occurred at ≥CCI mg/kg. In the Irwin's test, 1 rat dosed with CCI mg/kg was euthanized after showing clonic convulsions. In mice, doses ≥CCI mg/kg were associated with mortality.

The toxicity profile after chronic, oral administration of JNJ-55308942 was further assessed in repeated dose (RD) GLP toxicity studies with a maximum treatment duration of 9 months in dogs and 6 months in rats.

In the dog studies, organ changes were mostly seen at the CCI These changes were mainly histological in nature. Microscopic examination showed CCI and CCI in all dose groups, indicating the CCI CCI The CCI sometimes resulted in increased CCI At dose levels considered non-adverse, these CCI changes were sometimes accompanied by minimal to mild and reversible increases in CCI and CCI]). Furthermore, CCI) inclusions were observed in the CCI of several treated animals. The ultrastructural characteristics of these inclusions strongly suggest that they are composed of CCI . It can be assumed that the CCI , the CCI appearance, and the CCI are all part of the same adaptive process. Dose levels where the CCI changes were limited to the above description, were considered non adverse.

At higher dose levels, these adaptive, non-adverse CCI findings evolved to changes that were considered adverse because they were associated with more pronounced increases in CCI CCI and/or resulted on adverse effects on CCI and CCI . In the 1-month dog study doses >C mg/kg/day led to severe toxicity with CCI CCI evidence of CCI and CCI and CCI In the 9-month dog study, the no observed adverse effect level (NOAEL) was C mg/kg/day. At the NOAEL, the mean C_{max} and AUC_{0-24h} values for males were CCI µg/mL and CCI µg.h/mL

In rats, the main organs of toxicity were the CCI in females and the CCI in males.

At the CCI of female rats dosed for 6 months at CCI mg/kg/day, CCI CCI and hyperplasia of the CCI were found. These findings showed an ongoing recovery after 3 months (presence of CCI in the region affected by the CCI, representing CCI from a previous CCI No CCI changes were seen in male rats, probably because of the difference in high dose between female and male rats CCI mg/kg/day in females and C mg/kg/day in males). It is possible that these changes represent a localized effect of the test item and dosing procedure (i.e., deposition of the test item in the stomach by gavage). The NOAEL for the adverse CCI changes in female rats was C mg/kg/day ($AUC_{0\text{-}24h}$ = CCI µg.h/mL; ie. CC fold the AUC at the anticipated clinically efficacious exposure).

CCI toxicity was seen in the Sprague-Dawley male rat during the 1-, 3- and 6-month toxicity studies (lowest observed effect level [LOEL] of C mg/kg/day), but not in the 1-, 3-, or 9-month toxicity studies in dogs (while exposures were higher than the LOEL in rats). In short: 1-month dosing ≥CC mg/kg/day resulted in a dose-related increased incidence of CCI with secondary findings of lower numbers of CCI and CCI morphology in the CCI. This bilateral finding showed full recovery after 1 month. The no observed effect level (NOEL) for the finding in the 1-month study was CC mg/kg/day. In the follow-up 3- and 6-month studies, CCI changes comprised CCI CCI, and marked to severe CCI. Concurrently, there were secondary changes at the CCI of affected animals. As in the 1-month study, the NOEL for CCI changes was CC mg/kg/day; the LOEL in the 6-month study was C mg/kg/day. Following the 3-month recovery period, there was no reversibility of the findings in the CCI and CCI in males. There were no effects on CCI (CCI and CCI in males or on female CCI

Pharmacokinetic and Metabolism Profile

Following a single intravenous (IV) administration, plasma clearance in mice, rats, dogs, and monkeys was CCI relative to hepatic blood flow (C % to C%), with a CCI volume of distribution. Elimination and clearance were approximately C fold reduced in dogs compared to mice, rats, and monkeys.

Following single oral dosing, CCI absorption was observed in rats, dogs, and monkeys (time to reach the maximum plasma concentration [T_{max}] C hours). The absolute bioavailability was CCI (C % to C %).

After 6 months dosing in the rat GLP study, exposure (maximum plasma concentration [C_{max}] and area under the concentration time curve from 0 to 24 hours [$AUC_{0\text{-}24h}$]) generally increased close to dose proportionally from CC to CC mg/kg in males, and less than dose proportionally from CC to CCI mg/kg in females. No relevant change in exposure was seen after repeated dosing at all dose levels in males, whereas in females, exposure increased at all dose levels after repeated

administration. After 9 months of dosing in the dog GLP study, exposure generally increased dose proportionally from [redacted] to [redacted] mg/kg and more than dose proportionally from [redacted] to [redacted] mg/kg. No clear sex differences were observed.

In a 14-day mouse study, exposure (C_{max} and AUC_{0-24h}) increased in a generally dose proportional manner from [redacted] to [redacted] mg/kg/day following a single dose and after repeat dosing for 14 days in males. Females were only dosed at [redacted] mg/kg/day. On Day 14, exposure was slightly higher in females than in males at that dose.

In vitro plasma protein binding was [redacted] in all species (unbound fraction: [redacted] % in mouse, [redacted] % in monkey, [redacted] % in dog, [redacted] % in human, and [redacted] % in rat).

In vivo tissue distribution in rat after single oral administration of [redacted] mg/kg showed differential distribution, with tissue to plasma ratios ranging from [redacted] (brain) to [redacted] (liver). Quantitative whole-body autoradiography (QWBA) in rat confirmed wide distribution of radioactivity throughout the body [redacted]-hour postdose, which was mostly eliminated within [redacted]-hour postdose. There was no specific affinity to melanin.

The main metabolic pathway in human hepatocytes was the ring opening of the pyridine with formation of the carboxylic acid (major metabolite) and the primary alcohol. Acyl glucuronide isomers were also observed. Formation of a glutathione conjugate was also observed, as well as multiple additional minor metabolites.

All human in vitro metabolites were observed in rat and/or dog hepatocytes or in vivo in rat with the exception of 2 minor in vitro metabolites.

In rats and dogs, JNJ-55308942 clearance was mainly mediated by metabolism.

In human hepatocytes in vitro, the oxidative metabolism of JNJ-55308942 was mediated mainly by cytochrome P450 (CYP)3A4; [redacted]-P1-1 was also involved, the relative contribution of [redacted] vs [redacted] is unclear.

In vitro, moderate inhibition of CYP[redacted] was seen (IC_{50} = [redacted] µM in human liver microsomes) with no inhibition of other isoforms (IC_{50} values >100 µM). No time-dependent inhibition of CYP[redacted] (IC_{50} >10 µM) was observed. In human liver microsomes, JNJ-55308942 was not an inducer of CYP[redacted] or CYP[redacted] activity but was an inducer of CYP[redacted] and CYP[redacted] messenger ribonucleic acid (mRNA) at concentrations of ≥10 µM in human hepatocytes in vitro.

JNJ-55308942 is not a substrate of [redacted], and [redacted]. JNJ-55308942 shows limited inhibitory potential towards [redacted] ([redacted] µM< IC_{50} [redacted] µM), [redacted] ([redacted] µM< IC_{50} <[redacted] µM), [redacted] (IC_{50} = [redacted] µM), [redacted] ([redacted] µM <IC_{50} <[redacted] µM), [redacted] (IC_{50} >[redacted] µM), [redacted] (IC_{50} = [redacted] µM), [redacted] ([redacted] µM< IC_{50} <[redacted] µM), [redacted]

(IC_{50} = [redacted] µM), [redacted] (IC_{50} >[redacted] µM). Based on this, no transporter mediated interaction is expected at a dose of [redacted] mg once-daily.

Clinical Studies

To date, JNJ-55308942 has been tested in 3 Phase 1 clinical studies: 55308942EDI1001 (part 1 [SAD]: n=62; part 2 [MAD]: n=36), 55308942EDI1002 (part 1: n=9; part 2: n=3), and 55308942EDI1003 (n=14).

Study 55308942EDI1001 consisted of 2 parts: a single ascending dose (SAD) and food effect part (Part 1), followed by a multiple ascending dose (MAD) part (Part 2) in healthy male and female participants.

Study 55308942EDI1002 was an open-label positron emission tomography (PET) study in healthy male participants to investigate P2X7 receptor occupancy (RO) by JNJ-55308942 using [^{18}F]-JNJ-64413739. Part 1 investigated the occupancy of P2X7 receptors in the human brain and gut at T_{max} after a single dose of JNJ-55308942 solution using [^{18}F]-JNJ-64413739. Part 2 investigated receptor occupancy of JNJ-55308942 over time by measuring the brain P2X7 receptor occupancy at both T_{max} and at 24 hours after a single dose of JNJ-55308942 solution using [^{18}F]-JNJ-64413739.

Study 55308942EDI1003 was an open-label drug interaction study in healthy male and female participants to evaluate the effects of multiple doses of JNJ-55308942 on CYP3A4, CYP2D6, and CYP2C19 activity.

Human Pharmacokinetics and Product Metabolism

Following single oral doses of JNJ-55308942 solution in study 55308942EDI1001 [redacted] to [redacted] mg) under fasted conditions, the T_{max} was within [redacted] to [redacted] hours and the half-life ($T_{1/2}$) ranged from [redacted] to [redacted] hours across doses.

Mean exposure parameters (C_{max}, $AUC_{0\text{-}24h}$, AUC from time zero to the time of the last quantifiable concentration [AUC_{last}], and AUC from time zero to infinite time [AUC_{∞}]) increased generally in a dose proportional manner.

After a single dose administration of [redacted] mg JNJ-55308942 in the presence of food, C_{max} and AUC_{∞} were decreased by 28% and 18%, respectively, compared to when dosed in the fasted state.

After once-daily dosing with [redacted] to [redacted] mg JNJ-55308942 for 10 consecutive days in healthy male and female participants, the mean $T_{1/2}$ values after steady-state administration were similar to the mean $T_{1/2}$ values after a single dose, suggesting no time-dependent mechanisms are involved in the metabolism of JNJ-55308942. The average Day 10 to Day 1 accumulation ratio ranged between 1.98 and 2.51 after once-daily dosing. Mean $T_{1/2}$ values at steady-state were similar among the different doses.

At [redacted] mg once-daily for 10 days, JNJ-55308942 was the major circulating entity in plasma. Major metabolites M9 and M5 (hydrolysis of 5-fluropyrimidine- triazole bond and subsequent

glucuronidation) were estimated as 5.9% and 4.2% of unchanged drug and were deemed as the most important metabolites, but none of the metabolites reached 10% of JNJ-55308942 concentrations.

A drug-drug interaction study (55308942EDI1003) showed that JNJ-55308942, at steady-state after once-daily administration of[redacted] mg dose (solution), is a weak inducer of CYP[redacted] and a moderate inhibitor of CYP[redacted]. There was no clinically significant inhibition observed for CYP[redacted].

Efficacy/Safety Studies

JNJ-55308942 was generally safe and well tolerated. Overall, there were no safety concerns observed in healthy adult participants after the repeated dosing of JNJ-55308942 either alone or in combination with a drug cocktail consisting of[redacted]

There were no deaths, SAEs, or treatment emergent adverse events (TEAEs) leading to discontinuation during any of the studies.

There were no consistent treatment-related effects in clinical laboratory parameters (hematology, biochemistry, coagulation, and urinalysis), vital signs, or ECG measurements and no treatment-related, clinically significant abnormalities were observed during physical examination in any of the clinical studies.

55308942EDI1001 (part 1: [redacted] mg; part 2: [redacted] mg): In the 70 participants dosed with JNJ-55308942, the most common TEAEs for all doses of JNJ-55308942 in all parts of the study were: headache (n=20); viral respiratory tract infection (n=4); and cough, abdominal pain, and skin irritation (n=3 each). Most TEAEs were mild in severity. The following TEAEs of moderate severity were reported during the study: headache (n=2), fibromyalgia (n=1), paresthesia (n=1), dry eye (n=1), and viral upper respiratory tract infection (n=1).

55308942EDI1002 ([redacted] mg): In the 12 participants dosed with JNJ-55308942 and/or the tracer [^{18}F]-JNJ-64413739, the most commonly reported (≥20% of participants) TEAEs under system organ class (SOC) were general disorders and administration site conditions (3 participants, 33.3%) infections and infestations (3 participants, 33.3%) and psychiatric disorders (2 participants, 22.2%) in Part 1 and nervous system disorders (reported term: headache) in Part 2.

55308942EDI1003 ([redacted] mg): The overall incidence of TEAEs was higher in participants when the drug cocktail (midazolam, dextromethorphan, and omeprazole) was administered alone (8 [57.1%] of 14 participants) compared to when JNJ-55308942 [redacted] mg (solution) was administered once-daily on Days 3 to 11 (5 [35.7%] of 14 participants) and on Day 13 (1 [7.1%] of 14 participants). Only 1 [7.1%] of 14 participants had TEAEs when taking the drug cocktail in combination with JNJ-55308942 80 mg on Day 12.

The most frequently reported TEAEs by SOC were seen in nervous system disorders SOC (6 [42.9%] of 14 participants who received drug cocktail alone, 3 [21.4%] of 14 participants who received JNJ-55308942 [redacted] mg alone [on Days 3-11], and 1 [7.1%] of 14 participants who received

JNJ-55308942 C mg and drug cocktail; none was reported on Days 13 or 14 when JNJ-55308942 was administered alone following the combined dosing).

The small number of TEAEs that were considered possibly related to JNJ-55308942 C mg included dizziness (n=2), hyperacusis (n=1), photosensitivity reaction (n=1), and headache (n=1).

Pharmacodynamics

In the SAD part of Study 55308942EDI1001, the release of IL-1β was measured from ex vivo LPS-primed/BzATP-stimulated peripheral blood cells and showed a dose responsive inhibition of the ex vivo LPS stimulated release of IL-1β. The estimated IC_{50} and IC_{90} (JNJ-55308942 plasma exposures) were CCI ng/mL and CCI ng/mL, respectively.

In the MAD part at steady-state, at the Day 10 predose (trough) timepoint, based on group means, no inhibition was seen up to C mg, approximately half maximal inhibition was seen at C mg, near maximal inhibition was evident at CC mg, and maximal inhibition was seen at CC mg.

In study 55308942EDI1002, the PD evaluation of P2X7 RO in human brain showed that P2X7 RO in general increased with increasing JNJ-55308942 doses. At the lower dose range, the increase in RO with dose appeared more pronounced, i.e., 7.44% (after C mg JNJ-55308942) to 59.58% (after C mg JNJ-55308942). Receptor occupancy appeared to reach a plateau at the higher doses (C mg and C mg JNJ-55308942).

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of JNJ-55308942 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**
Emerging safety and tolerability profile in human participants	JNJ-55308942 has not been dosed in humans for >10 days and patients with bipolar depression have not previously been exposed to JNJ-55308942.	Participants in this study will have to attend scheduled visits to the study site, where the safety and tolerability of the study intervention will be evaluated along with efficacy evaluations. Patients will be regularly evaluated for symptom changes.
Risks Due to Study Intervention(s) [JNJ-55308942]		
Testicular toxicity (males only)	CCI toxicity was seen in the 1-, 3-, and 6-month toxicity studies in Sprague Dawley rats with JNJ-55308942. No CCI toxicity was observed in similar studies in dogs with up to 9 months of dosing.	Male participants in this study will have regular CCI measurements at defined timepoints. The dose of C mg once-daily has a predicted >12-fold safety margin.

Drug-Drug Interactions	JNJ-55308942 is a weak inducer of CYP[redacted] and a moderate inhibitor of CYP[redacted] JNJ-55308942 is mainly metabolized by CYP[redacted].	The use of concomitant medications that are metabolized solely by CYP[redacted] should preferably be avoided, or participants should be carefully monitored. Co-administration with moderate or strong inhibitors/inducers of CYP[redacted] should be avoided. A list of disallowed concomitant therapies is provided in Section 10.6

2.3.2. Benefit-Risk Assessment for Study Participation

JNJ-55308942 is in the early stages of clinical development. Patients with BD typically require lifelong treatment. Therefore, benefits of study participation in a 6-week trial may be limited (even though participants may experience short-term symptom relief). If the results from this study support the continued development of JNJ-55308942 for the treatment of bipolar depression/disorder, study participation may enhance future treatment options. Although study participation is associated with specified risks (see 2.3.1 above), the sponsor aims to minimize such risk both by protocol design (schedule and nature of assessments) and by thorough evaluation of the nonclinical safety of JNJ-55308942 at high dose levels.

Prior studies in humans have established a firm understanding of the pharmacokinetic/pharmacodynamic (PK/PD) relationship of JNJ-55308942 and established reproducible PD activity at safe and tolerable dose levels, including the [redacted] mg/day dose level selected for this study. Thus, participants will be exposed to a dose level that is characterized by PD activity with a benign risk profile.

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with JNJ-55308942 are justified by the potential benefits that may be afforded to participants with BD.

3. OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in participants with BD in an MDE at Week 6.	Change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline at Week 6.

Objectives	Endpoints
Secondary Objectives of Special Interest	
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of anhedonia	Change in Snaith-Hamilton Pleasure Scale (SHAPS) total score from baseline at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in participants with BD. Who are heterozygous or homozygous for the C/CC[redacted] P2RX7 GoF SNP (genetic subgroup analysis)	Change in MADRS total score from baseline at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in participants with BD type I or BD type II (diagnosis subgroup analysis)	Change in MADRS total score from baseline at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in subgroups of patients with specific biomarker profiles (biomarker subgroup analysis).	Change in MADRS total score from baseline at Week 6.
Secondary	
To evaluate the overall safety and tolerability of treatment with JNJ-55308942 as compared to placebo in participants with symptomatic BD over a treatment period of 6 weeks.	Vital signs (pulse/heart rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], respiratory rate), clinical labs (chemistry, hematology, urinalysis), adverse events (AEs), ECG, Young Mania Rating Scale (YMRS) score, Columbia Suicide Severity Rating Scale (C-SSRS) score.
To evaluate the effect of JNJ-55308942 compared to placebo on disease severity and improvement on the Clinical Global Impression-Severity Scale (CGI-S)	CGI-S
To evaluate the pharmacokinetics (PK) of JNJ-55308942 in participants with BD.	Plasma concentrations of JNJ-55308942.
To assess the effect of JNJ-55308942 on reduction of symptoms associated with	PROMIS – Ability to Participate in Social Roles and Activities, Patient Health

Objectives	Endpoints
depression compared to placebo as measured by self-rated outcomes.	Questionnaire (PHQ-9), Generalized Anxiety Disorder 7 (GAD-7) score.
To evaluate the impact of treatment with JNJ-55308942 compared with placebo on response (≥50% improvement in MADRS total score from baseline) and remission (MADRS total score ≤12) rates at Week 6.	Response (≥50% improvement in MADRS total score from baseline) and remission (MADRS total score ≤12) rates at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in a subgroup of patients with messenger ribonucleic acid (mRNA) transcript levels at baseline that exceed the median level for both P2RX7 and IL-1β.	Change in MADRS total score from baseline at Week 6.
To evaluate the efficacy of JNJ-55308942 compared to placebo on symptoms of depression in subgroups of participants with BD not taking any mood stabilizer or antipsychotic, taking a mood stabilizer alone, taking an antipsychotic alone, and taking a combination of a mood stabilizer and an antipsychotic (concomitant medication subgroup analysis).	Change in MADRS total score from baseline at Week 6.
Exploratory	
To explore the PK / PD (pharmcodynamic) relationship between plasma exposure of JNJ-55308942, and efficacy and safety parameters in patients with BD.	Exposure-response between exposure and MADRS and selected safety events, as appropriate.
To explore the effect of JNJ-55308942 on PD-related biomarkers.	Including, but not limited to, blood biomarkers related to immune, inflammatory, hormonal, metabolic, hypothalamic-pituitary-adrenal (HPA) axis, P2X7 receptor and monocyte activity.
To explore the effect of pharmacogenomic variations on the PK, efficacy, and safety of JNJ-55308942.	Influence of genetic polymorphisms (e.g., CCI -1) on plasma exposure, as well as on efficacy and safety measures.

Objectives	Endpoints
To explore the effect of JNJ-55308942 compared to placebo on the well-being of participants.	Self-Assessment of Well-Being (SAWB) outcome.

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

HYPOTHESIS

The primary hypothesis that will be tested in this study is that JNJ-55308942, compared to placebo, results in a significant improvement in the reduction of the symptoms of depression in participants with BD in an MDE as assessed by change in MADRS total score from baseline at Week 6.

Further details on the statistical consideration can be found under Section 9.

4. STUDY DESIGN

4.1. Overall Design

This is a double-blind, randomized, stratified, placebo-controlled, parallel group, multicenter study. A total of approximately 164 participants will be enrolled in this study to obtain approximately 132 completers.

The target study population includes participants of any gender, between 18 and 64 years of age inclusive, with a Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) diagnosis of BD (types I or II) without current psychotic features as confirmed by the Mini International Neuropsychiatric Interview (MINI) with Borderline Personality Disorder module. BD participants should be experiencing an MDE that does not require either hospitalization or antidepressant medication.

Each potential participant must satisfy one of the three criteria listed below in order meet eligibility for the study population.

- Participants who are currently unmedicated and have not received any mood stabilizers or antipsychotics for four weeks before screening.

- Participants who are on a stable monotherapy regimen of one of the following mood stabilizers (lithium, valproate forms [e.g., divalproex sodium], or lamotrigine) or one of the following antipsychotics (lurasidone, cariprazine, quetiapine, lumateperone, or olanzapine) for four weeks before screening.

- Participants who are on a stable adjunctive regimen of one of the following antipsychotics (lurasidone, quetiapine, lumateperone, or olanzapine) and one of the following mood stabilizers (lithium, or valproate forms [e.g., divalproex sodium]) may be considered for eligibility based on the approved therapies in each market with an eligibility assessment conducted between the investigator and sponsor. Assessment of the stable adjunctive regimen of an antipsychotic and a mood stabilizer will be conducted by the investigator

and sponsor's clinical judgement and documented for each participant. This regimen must be in place 4 weeks before screening.

The participant must be symptomatic as assessed using the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$). Symptom intensity over the past week will be evaluated. Participants who are enrolled in the study will continue on their current medication regimen, if applicable, throughout the study. No dose changes are permitted from screening through the end of the study (until after the follow-up visit). No concurrent use of antidepressants will be allowed (until after the follow-up visit).

For each participant, the study will consist of 3 phases: a screening phase of up to 4 weeks, a double-blind treatment phase of 6 weeks, and a post-treatment follow-up phase of up to 2 weeks (Figure 1). Participants will enter the treatment period where they will be randomly assigned to daily dose administration with C mg JNJ-55308942 or placebo for 6 weeks, Day 1 up to and including the last treatment visit, Day 43 +/- 1 day. The study drug should be taken by the participant at every clinic visit during the treatment period. Between approximately 1 to 2 weeks after administration of the last dose, participants will return to the study site for a follow-up visit. The total study duration for each participant will be up to 12 weeks. There will be 7 scheduled visits to the study site during the study, including screening, and follow-up visit

For study site visits, a window of ±1 day will be allowed.

No study-specific screening procedures will be undertaken prior to finalization of the informed consent form (ICF) procedures and the provision of written informed consent by the participant.

Eligibility Screening Examination (for all study participants)

After giving written consent for screening, participants will be screened between 28 days and 1 day prior to the double-blind treatment phase to ascertain their eligibility for the study according to the inclusion and exclusion criteria. Although the screening period allows for up to 4 weeks, shorter screening periods are encouraged, when possible. The assessments scheduled during the screening visit may be divided over multiple days, according to operational and/or site/country-specific needs.

To ensure that a participant is part of the target study population, specific assessments are prioritized during the screening period. These assessments must be administered on the first day of screening, and only if the participant qualifies will the remainder of the assessments be performed/scheduled. These assessments will be performed by a certified rater at the site. The priority screening procedures are as follows:

1. The MINI with Borderline Personality Disorder module.
    a. The participant must meet criteria for a diagnosis of either BD type I or II.
    b. The participant must not currently meet criteria for psychosis or psychotic disorder, borderline personality disorder, antisocial personality disorder, eating disorder, or suicide behavior disorder.

c. The participant must not have ≥4 episodes of mood disturbances (e.g., mania, hypomania, or depression) within the past 12 months.

2. The Structured Interview Guide for the $HDRS_{17}$ (Structured Interview Guide for the $HDRS_{17}$ [SIGH-D]).

   a. The participant must be in a current MDE with a total score >20 and with a score >2 on the depressed mood item [question #1].

   b. SIGH-D is based on the $HDRS_{17}$ and will be used in this study to perform the $HDRS_{17}$ at screening and at pre-randomization on Day 1, to confirm the participant continues to meet eligibility criteria.

3. The ATHF-SF: current and past antidepressant treatments.

   a. The participant must not have taken any disallowed medications (per appendix 6) during the 4 weeks prior to the screening period. Disallowed medications include antidepressants. Nonresponse to >4 treatments in the current episode is exclusionary. Of note, participants who have been nonresponsive or inadequately responsive to electroconvulsive therapy (ECT) or ketamine in the current episode will be excluded. Participants who received transcranial magnetic stimulation (TMS), any transcranial electrical stimulation, including transcranial direct current stimulation (tDCS), vagal nerve stimulation (VNS), and/or deep brain stimulation (DBS) within 6 weeks prior to randomization (assessed with the ATHF-SF at screening) will be excluded. Newly initiated psychotherapy (defined as psychotherapy that was started within 4 weeks of the screening visit and assessed with the ATHF-SF at screening) is also exclusionary.

If applicable, the Mood Stabilizer and Antipsychotic Eligibility Assessment form will be completed for participants who are on a stable adjunctive regimen of an antipsychotic and a mood stabilizer for 4 weeks before screening.

Once potential participants have met eligibility requirements for the MINI, SIGH-D and ATHF-SF and the Mood Stabilizer and Antipsychotic Eligibility Assessment form (if applicable), the remaining screening procedures may be completed (see Sections 5.1 and 5.2 for details).

Participants will be screened to ascertain their eligibility for the study based on the presence of the GoF P2RX7 mutation (for inclusion, must be [redacted] or [redacted] at [redacted] nucleotide [redacted]; [redacted]) and the absence of the LoF P2RX7 mutations (must be [redacted] or [redacted] at rs[redacted]/nucleotide [redacted] [redacted] and must be [redacted] at rs[redacted]/nucleotide [redacted]; [redacted]). In other words, participants will be excluded if they have the presence of two copies of the LoF C allele at rs[redacted] (i.e., exclude those with [redacted] at nucleotide [redacted]), and/or one or more copies of the LoF [redacted] allele at rs[redacted] (i.e., exclude those with [redacted] or [redacted] nucleotide [redacted]). This assessment will include the collection of a blood sample. In case participant needs to be rescreened, this is the only assessment that does not need to be performed again.

Screening will also include assessment of study inclusion and exclusion criteria, medical history, demographics, physical examination, psychiatric and safety evaluations, and standard laboratory tests. The remaining assessments may be divided over multiple days, according to operational and/or site/country-specific needs and may take place before or after the P2RX7 genotyping results and other laboratory results become available.

Of note, although the SIGH-D will be used for study entry criteria, the MADRS will be used as the primary endpoint. The Structured Interview Guide for the MADRS (SIGMA) is based on the MADRS and will be used in this study to perform the MADRS. In order to protect against potential score inflation of the baseline MADRS score, the inclusion criteria are based on the SIGH-D instead of the primary efficacy endpoint (MADRS). Note, the first MADRS score will be obtained at randomization (pre-dose) in order to provide the baseline score prior to treatment.

Double-blind Treatment Phase

The duration of the double-blind treatment phase is 6 weeks. Participants will visit the study center for a baseline visit on Day 1 and receive the first dose of study intervention following randomization at the clinic.

On Day 1, after confirming the depressive state of the participant using the SIGH-D ($HDRS_{17}$ total score ≥20 and with a score ≥2 on the depressed mood item [question #1]), and completing all assessments as outlined in the Schedule of Assessments (SoA), he/she will be randomly assigned to receive either treatment with CC mg JNJ-55308942 or placebo once-daily in a 1:1 ratio for a 6-week treatment period. The SIGH-D (screening and pre-randomization on Day 1) will ideally be completed by the same qualified rater for a given participant.

There will be 4 randomization stratification factors: BD type (I or II), country, P2RX7 GoF SNP genotype (homozygous or heterozygous), as well as concomitant medication status (no mood stabilizer or antipsychotic, a mood stabilizer alone, an antipsychotic alone, or a combination of a mood stabilizer and an antipsychotic). Investigators and participants will remain blinded to response criterion and study intervention treatment assignment for each participant.

During the double-blind treatment phase, the SIGMA (MADRS) and CGI-S will be completed by the same qualified rater for a given participant. Exceptions should be discussed with and approved by the sponsor. The sponsor can request a rater change based on quality concerns. The severity of depressive symptoms will be assessed using the SIGMA (MADRS) at randomization (pre-dose) in order to provide the baseline score prior to treatment and at subsequent visits to the study site.

Study intervention will be taken at home in the morning (C mg JNJ-55308942 or placebo) at approximately the same time (± 4 hours) each day, 30 minutes after the start of breakfast (maximum of 2 hours after the start of breakfast). There is an exception on Day 1 where participants will receive the study intervention at the study site after all baseline assessments have been completed.

On study visits 3, 4, 5 and 6, study intervention will be administered at the study site after the clinical lab and PK samples have been collected and at approximately the same time (± 4 hours). Study intervention will be dispensed at visits 2, 4, and 5 during this double-blind treatment period.

Of note, on study site visits 3, 4, 5 and 6, participants will be instructed to eat breakfast at home and come to the site within 1 hour or less after completion of the meal. Inability to comply with

these instructions would not constitute a protocol violation, but the participants are encouraged to comply with these instructions as closely as possible.

The well being of the participant will be frequently tracked using a Digital Health Assessment app to monitor parameters such as, but not limited to, the pattern of sleep, energy level, and concentration level via the SAWB Questionnaire. Additionally, the Ditigal Health Assessment app will alert the investigator when a participant has indicated that their depression is 'much worse' or 'very much worse' when answering weekly questions on depression.

The SHAPS will be administered once at baseline (pre-dose) and once at the end of the double-blind treatment phase (after the final dose). Participants will complete the PROMIS – Ability to Participate in Social Roles and Activities and the PHQ-9 at baseline and once weekly, and the GAD-7 every two weeks. As per SoA, the self-rating instruments will be administered at clinic visits or at home. For self-rating instruments completed at home on paper, participants should complete these scales before the next clinic visit and participants will receive notifications from the Digital Health Assessment app on their mobile phones as reminders to complete these paper instruments.

Key safety assessments will include the monitoring of adverse events, physical examinations, vital signs (e.g., blood pressure, pulse/heart rate, body temperature), electrocardiogram (ECG), clinical laboratory tests, emerging of mania (YMRS), and suicidal ideation (C-SSRS).

In addition, blood samples for PK, biomarker assessment, hormones (males only), and pharmacogenomics (general SNPs and ribonucleic acid [RNA]) will be collected as per the SoA and use of concomitant medication will be recorded.

Follow-up Examination

Between 7 to 14 days after the last study visit, participants will return to the study site for a safety follow-up visit. The procedures to be completed during the follow-up visit are listed in the SoA.

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

4.2. Scientific Rationale for Study Design

Blinding, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active study intervention.

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (e.g., demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

For each participant, the study will consist of 3 phases:

1. a screening phase of up to 4 weeks
2. a double-blind treatment phase of 6 weeks. Participants will enter the treatment period where they will be randomly assigned to daily dose administration with C mg JNJ-55308942 or placebo for 6 weeks, Day 1 up to and including the last treatment visit, Day 43 +/- 1 day. The study drug should be taken by the participant at every clinic visit during the treatment period. This is considered an acceptable duration of treatment in a study with an antidepressant medication and is supported by available nonclinical data.
3. a post-treatment follow-up phase of up to 2 weeks

The total study duration for each participant will be up to 12 weeks. There will be 7 scheduled visits to the study site during the study, including the screening and follow-up visits.

Study population

The target study population includes participants of any gender, between 18 and 64 years of age inclusive, with a DSM-5 diagnosis of BD (type I or II) without current psychotic features as confirmed by the MINI with Borderline Personality Disorder module. BD participants should be experiencing an MDE that does not require hospitalization or antidepressant medication.

Each potential participant must satisfy one of the three criteria listed below in order meet eligibility for the study population.

- Participants who are currently unmedicated and have not received any mood stabilizers or antipsychotics for four weeks before screening.

- Participants who are on a stable monotherapy regimen of one of the following mood stabilizers (lithium, valproate forms [e.g., divalproex sodium], or lamotrigine) or one of the following antipsychotics (lurasidone, cariprazine, quetiapine, lumateperone, or olanzapine) for four weeks before screening.

- Participants who are on a stable adjunctive regimen of one of the following antipsychotics (lurasidone, quetiapine, lumateperone, or olanzapine) and one of the following mood stabilizers (lithium, or valproate forms [e.g., divalproex sodium] may be considered for eligibility based on the approved therapies in each market with an eligibility assessment conducted between the investigator and sponsor. Assessment of the stable adjunctive regimen of an antipsychotic and a mood stabilizer will be conducted by the investigator and sponsor's clinical judgement and documented for each participant. This regimen must be in place 4 weeks before screening.

No concurrent use of antidepressants will be allowed. This is to avoid a possible switch to a hypomanic or manic episode due to treatment with antidepressants, to decrease the risk of drug-drug interactions from polypharmacy, to decrease treatment heterogeneity in the sample, and to maximize the chance to identify possible signals from JNJ-55308942. Despite stable use of mood

stabilizers in some patients, eligible participants must be symptomatic, as assessed using the $HDRS_{17}$.

Past and current history of antidepressant drug treatment and response to treatment (per the structured ATHF-SF) should be used retrospectively to determine antidepressant therapies used in this current episode. A failed trial of electroconvulsive therapy (ECT) or ketamine will be considered exclusionary. Participants who received transcranial magnetic stimulation (TMS), any transcranial electrical stimulation, including transcranial direct current stimulation (tDCS), vagal nerve stimulation (VNS), and/or deep brain stimulation (DBS) within 6 weeks prior to randomization (assessed with the ATHF-SF at screening) will be excluded. Newly initiated psychotherapy (defined as psychotherapy that was started within 4 weeks of the screening visit and assessed with the ATHF-SF at screening) is also exclusionary.

Men, women of non-childbearing potential (WONCBP), and women of childbearing potential (WOCBP) will be recruited to participate in this study. The inclusion of WOCBP is enabled by embryofetal development studies in rats and rabbits. Pregnancy and pregnancy risks will be evaluated at each visit for WOCBP. Refer to the latest version of the IB for JNJ-55308942.

Placebo as the control

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active study intervention. Participants will be randomly assigned to receive placebo or [redacted] mg JNJ-55308942 once-daily for 6 consecutive weeks during the double-blind treatment period.

Similar to participants randomized to receive JNJ-55309842, participants with BD randomized to receive placebo must continue on their current medication regimen, that was present at least 4 weeks before screening. As needed, medications for anxiety and insomnia will be allowed, per protocol guidelines.

At each in-person study visit, a placebo-control reminder script (PCRS) (Cohen 2021) will be completed prior to completing the primary outcome measure, the MADRS. The PCRS was designed to educate clinical trial participants about commonly cited factors that impact placebo responses and the importance to attending to these factors when reporting on symptoms and potential side effects. The entire procedure takes about 3 minutes.

Genetic and Pharmacogenomic and Biomarker Collection

A blood sample will be collected during screening to allow for the analysis of 3 SNPs in the *P2RX7* gene to determine participant eligibility for the study. These polymorphisms have been shown to alter P2X7 receptor function in vitro and be associated with altered IL-1β release from peripheral blood mononuclear cells (Stokes 2010, Gu 2001, Wiley 2003). It is hypothesized that P2X7 receptor inhibition would be most effective in participants with increased P2X7 receptor functionality. Participants are eligible if they carry the GoF *P2RX7* mutation (must be [redacted] or [redacted] at [redacted] nucleotide [redacted]: [redacted]). Participants will be excluded if two copies of the LoF [redacted] allele are present at rs[redacted] (i.e., exclude those with [redacted] at nucleotide [redacted]), and/or one or

more copies of the LoF C allele is present at rsCCI (i.e., exclude those with CCI or CC nucleotide CCI). It is expected that participants that lack functional P2X7 receptors would not respond to a P2X7 receptor antagonist such as JNJ-55308942, and therefore would not be anticipated to derive potential benefit and also may not provide safety and tolerability data that results from on-target pharmacology.

An additional optional blood sample will be collected on Day 1 from enrolled participants for pharmacogenomic research. If collection on Day 1 is not feasible, it can be collected on any other visit during the double-blind treatment phase. It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect Deoxyribonucleic acid (DNA) to allow the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of JNJ-55308942 and to identify genetic factors associated with BD.

Blood samples for measuring biomarkers will be collected to evaluate the mechanism of action and/or target engagement (PD effect) of JNJ-55308942, help to explain inter-individual variability in clinical outcomes, or to identify population subgroups that respond differently to an intervention and/or for exploratory analyses. The goal of the biomarker analyses is to evaluate the PD of JNJ-55308942 and aid in evaluating the intervention-clinical response relationship.

DNA, RNA, and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies. Biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity and phenotypes and biomarkers.

Clinical Assessments

Assessment of Depression

17-Item Hamilton Depression Rating Scale ($HDRS_{17}$)

The $HDRS_{17}$ is a clinician-administered rating scale designed to assess the severity of symptoms in participants diagnosed with depression with a total score range of 0 to 52, with higher scores indicating greater severity of depressive symptoms. It is the most widely used symptom severity measure for depression. The $HDRS_{17}$ will be performed at screening and Day 1 pre-randomization, by an appropriately trained staff member, using the SIGH-D.

Montgomery–Åsberg Depression Rating Scale (MADRS)

The 10-item clinician-administered MADRS was designed to be used in persons with major depressive disorder (MDD) to measure the overall severity of depressive symptoms with a total score range of 0 to 60, with higher scores indicating greater severity of depressive symptoms. The MADRS scale has been selected as the primary efficacy measure for this study because it is

validated, reliable, and acceptable to regulatory health authorities as a primary scale to determine efficacy for depression. The MADRS will be administered during the double-blind treatment phase using the SIGMA.

The primary efficacy endpoint is the change from the baseline (Day 1) MADRS total score at the end of the 6-week treatment period.

Clinical Global Impression – Severity (CGI-S)

The CGI-S is included to rate the severity of the participant's illness at the time of assessment, relative to the clinician's experience with participants who have the same diagnosis and improvement with treatment (Guy 1976). The CGI-S evaluates the severity of illness on a scale from 1 to 7.

Patient Health Questionnaire (PHQ-9)

The 9-item PHQ-9 scale scores each of the 9 symptom domains of the DSM-5 MDD criteria, and it has been used both as a screening tool and a measure of response to treatment for depression (Kroenke 2001). Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The participant's item responses are summed to provide a total score (range 0 to 27), with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks.

Self-Assessment of Well-Being (SAWB)

During the double-blind treatment phase, participants will answer a 1- or 2-item self-report scale designed to provide the participant's subjective experience with relation to their depression while taking the treatment. This is an internal Janssen questionnaire, and the questions will be asked to the participant weekly by the Digital Health Assessment app. The Digital Health Assessment app will send an alert to the investigator when the participant replies that her/his depression is 'much worse' or 'very much worse'.

Assessment of Social Isolation

PROMIS - Ability to Participate in Social Roles and Activities

The PROMIS - Ability to Participate in Social Roles and Activities item bank assesses the perceived ability to perform one's usual social roles and activities. The item bank does not use a time frame (e.g., over the past seven days) when assessing ability to participate in social roles and activities. The Short Form 4a includes 4 items that represent this concept. Each question has 5 response options ranging in value from 1 to 5. The total raw score for the short form is calculated by summing the values of the response to each question, so for the 4-item form, the lowest possible raw score is 4; the highest possible raw score is 20. Raw scores can also be converted to a T score with mean of 50 and standard deviation of 10.

Assessment of Anxiety

Generalized Anxiety Disorder-7 (GAD-7)

The GAD-7 is a self-reported questionnaire for screening for and measuring the severity of GAD. The GAD-7 has 7 items, which measure the severity of various signs of GAD according to reported response categories with assigned points. Assessment is indicated by the total score (0 to 21), which is calculated by adding together the scores for all 7 items. For each item, as well as for the total score, a higher score represents a more severe condition.

Assessment of Anhedonia

Snaith-Hamilton Pleasure Scale (SHAPS)

An instrument developed for the assessment of hedonic capacity is the 14-item, self-report, Snaith–Hamilton Pleasure Scale (Snaith et al., 1995). The SHAPS was developed to minimize cultural, gender, and age biases in the evaluation of hedonic capacity. It not only measures hedonic tone, but also its absence, i.e. anhedonia. Anhedonia can be a core symptom of depression. Four major domains are covered in the scale, namely interest/pastimes, social interaction, sensory experience, and food/drink.

Assessment of Disease Progression at Home

Self-Assessment of Well-Being (SAWB)

The SAWB questionnaire is a multiple-item self-report questionnaire designed to provide additional information regarding the participant's subjective experience while taking study intervention. This is an internal Janssen questionnaire, and the questions will be asked to the participant daily by the Digital Health Assessment app during the double-blind treatment phase. Several items of interest can be covered: such as, but not limited to, the pattern of sleep, energy level, and concentration level.

Safety Assessments

Standard safety assessments including physical examination, body weight, vital signs (including oral, tympanic or temporal body temperature, pulse/heart rate, and respiratory rate), 12-lead ECG, urine drug testing, alcohol breath test, pregnancy testing (female participants only), and clinical labs (hematology, chemistry panel, hormones [male participants only], and urinalysis) will be performed as per SoA. In addition, serology and hemoglobin A1C (HbA1C) assessments will be performed at screening only.

Additionally, emergence of suicidal ideation will be assessed using the C-SSRS at screening and during each visit.

4.2.1. Participant Input Into Design

To gather the insights of patients suffering from BD, a live Patient Advisory Committee was organized with clinical and operations study team members in attendance. The patient advocates were invited to share their insight into how they experience the disease and aspects related to the

disease (e.g., medication, impact on family life or professional life). Study participants were also asked for their opinion on several design aspects of this clinical study (e.g., placebo, the use of apps). All information was collected and evaluated, and, if relevant, implemented in the protocol (e.g., kept number of assessments to a minimum; added a follow-up visit based on patient feedback about needing continuity of care) or in operational aspects (e.g., development of recruitment/retention and site engagement strategy, use bright colors for pamphlets or posters).

4.2.2. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study and provide their consent voluntarily will be enrolled.

Although some of the BD participants in this study may benefit from the 6-week treatment period, participants will not be allowed to continue the treatment after completion of the study. The results of the investigation of JNJ-55308942 may help future patients.

The primary ethical concern is the use of placebo (in addition to the ongoing treatment with a mood stabilizer, if applicable) during the double-blind treatment phase of 6 weeks, while symptoms of at least moderate depression are present. The rationale for this placebo treatment and the impact on the study population has been described in Section 4.2, 'Placebo as the control'. Although placebo treatment may not harm most of the participants, participants who deteriorate in a clinically significant manner during the double-blind treatment phase will be withdrawn from the study (see Section 7.3) and will be referred to treatment according to local standards. The status of depressive symptoms will be assessed and documented weekly or every 2 weeks. Furthermore, the well-being of the participant will be tracked using an Digital Health Assessment app to monitor parameters such as, but not limited to, the pattern of sleep, energy level, and concentration level via the SAWB. The Digital Health Assessment app will alert the investigator when a participant has indicated that their depression is 'much worse' or 'very much worse' when answering weekly questions on depression.

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 standard of a Red Cross blood donation. For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 450 mL.

4.3. Justification for Dose

The PK/PD models developed based on concentration and PD responses (% inhibition of IL-1β release or % receptor occupancy) were used for dose selection simulations. The [redacted] mg once-daily dose proposed for this study is expected to provide maximal target engagement based on the results of the receptor occupancy study (55308942EDI1002) where a plateau in receptor occupancy was reached after participants received doses of [redacted] and [redacted] mg JNJ-55308942 (ranging from 54% to

80% receptor occupancy after a single dose). In addition, the proposed [redacted] mg dose is predicted to provide near maximal inhibition of P2X7-mediated peripheral release of IL-1β.

The proposed dose for this proof-of-concept study is [redacted] mg once-daily. The steady-state exposure margin (based on area under the curve [AUC]) between the exposures calculated for humans receiving a daily dose of [redacted] mg JNJ-55308942 and the exposures in rats at the no observed effect level (NOEL) for [redacted] toxicity is 12-fold, which is above the 10-fold safety margin outlined in the FDA guidance (FDA Guidance 2018; ICH Guidance 2021). Additionally, comparing the exposures at [redacted] mg daily with the rat exposure at the lowest observed effect level (LOEL) for [redacted] toxicity, there is a 16-fold difference. Based on these data, the once-daily dose of [redacted] mg JNJ-55308942 demonstrates a 12-fold safety margin to [redacted] toxicity NOEL in rats and supports inclusion of men in the study. Further, the results from the Phase 1 clinical program have shown JNJ-55308942 to be safe and well-tolerated at repeated doses of up to [redacted] mg daily for 10 days, with no severe or serious adverse events observed. This further supports the use of the proposed [redacted] mg daily dose of JNJ-55308942. Additionally, the proposed duration of treatment of 6 weeks for this study is supported by data from the nonclinical toxicology studies.

JNJ-55308942 showed delayed T_{max} and decreased exposures (C_{max} by [redacted]% and AUC by [redacted]%) in the presence of a high-fat diet. So, to reduce the overall PK variability to facilitate establishing PK/PD relationship, a regular diet of standard breakfast will be administered first and then JNJ-55308942 should be administered 30 minutes to 2 hours after breakfast.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit (Visit 7) for the last participant in the study. The final data from the study site will be sent to the sponsor after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 6 of the double-blind treatment phase.

Participants who prematurely discontinue study intervention for any reason before completion of the double-blind treatment phase will not be considered to have completed the study. Any participant who withdraws after receiving the study intervention will have an early withdrawal evaluation as described in Section 8.1.4.

5. STUDY POPULATION

The inclusion and exclusion criteria for enrolling participants in this study 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 criteria to be enrolled in the study:

Age

1. Criterion modified per Amendment 2

1.1. Any gender, 18 to 64 years of age, inclusive.

Participants should be at least 18 years of age or older as per the legal age of consent in the jurisdiction in which the study is taking place.

Type of Participant and Disease Characteristic

2. Presence of one or two copies of the GoF A allele at CCCI (must be CCI or CCI at nucleotide CCI CCI) in the *P2RX7* gene.

3. Criterion modified per Amendment 4

3.1. Have a primary DSM-5 diagnosis of BD (Type I or II) without current psychotic features, as confirmed by the MINI.

4. Must be experiencing an MDE (current episode must be of ≥4 weeks but <24 months in duration), meeting the following criteria at screening and baseline (Day 1, pre-randomization):

- Have a $HDRS_{17}$ total score ≥20 and with a score ≥2 on the depression question (question #1).

5. Criterion modified per Amendment 5

5.1A

Must meet one of the following criteria regarding current medication regimen.

- Currently unmedicated and has not received any mood stabilizers or antipsychotics for four weeks before screening.

OR

- Currently on a stable monotherapy regimen of one of the following mood stabilizers (lithium, valproate forms [e.g., divalproex sodium], or lamotrigine) or one of the following antipsychotics (lurasidone, cariprazine, quetiapine, lumateperone, or olanzapine) for four weeks before screening.

OR

- Currently on a stable adjunctive regimen of one of the following antipsychotics (lurasidone, quetiapine, lumateperone, or olanzapine) and one of the following mood stabilizers (lithium, or valproate forms [e.g., divalproex sodium])

5.1B

- Participants on adjunctive regimens as described above may be considered for eligibility based on the approved therapies in each market with an eligibility assessment conducted between the investigator and sponsor. Assessment of the stable adjunctive regimen of an antipsychotic and a mood stabilizer will be conducted by the investigator and sponsor's clinical judgement and documented for each participant. This regimen must be in place 4 weeks before screening. Participants on a stable adjunctive regimen of an antipsychotic and a mood stabilizer who do not qualify per the assessment will not be eligible for the study.

6. Medically stable on the basis of physical examination, medical history, and vital signs performed at screening. Any abnormalities must be consistent with the underlying illness in the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.

7. Medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

Weight

8. Have a Body Mass Index (BMI) between 18.0 and 35.0 kg/m^2 inclusive (BMI = weight/height^2).

Sex and Contraceptive/Barrier Requirements (also see section 10.5)

9. A woman of childbearing potential (WOCBP) must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine pregnancy test before the first dose of study intervention.

10. A woman using oral contraceptives must use an additional contraceptive method (see Inclusion Criterion 11).

11. Criterion modified per Amendment 2

11.1. Before randomization, a woman must be either:

- Not of childbearing potential defined as:
  - Postmenopausal (amenorrhea for at least 12 months without an alternative medical cause. A serum follicle stimulating hormone (FSH) level at screening >40 IU/L in women not using hormonal contraception or hormonal replacement therapy may be used for confirmation, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient), or
  - Permanently sterilized (including hysterectomy, bilateral salpingectomy,bilateral oophorectomy and bilateral tubal occlusion/ligation), or
  - Otherwise, be incapable of pregnancy.

- Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for participants in clinical studies (i.e., one that results in a less than 1% per year failure rate when used consistently and correctly). This may include:
  - Established and ongoing use of oral hormonal methods of contraception in combination with barrier methods.
  - Established and ongoing use of patch, injected or implanted hormonal methods of contraception.
  - Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).

    Accepted barrier methods as indicated above include:
    - condom with spermicidal foam/gel/film/cream/suppository
    - occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

    Note that a barrier method on its own is not sufficient.

  - Male partner sterilization (the vasectomized partner should be the sole partner for that participant).
  - True abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the participant).

  Women must agree to continue using these methods of contraception throughout the study and for at least 1 month after receiving the last dose of study intervention.

  - Note: If a woman of childbearing potential who is not heterosexually active becomes active after the start of the study, she must begin a highly effective method of birth control, as described above.

12. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 1 month after receiving the last dose of study intervention.

13. Men who are sexually active with a woman of childbearing potential and have not had a vasectomy must agree to use a barrier method of birth control (i.e., a condom with spermicidal foam/gel/film/cream/suppository) for the duration of the study plus 3 months after receiving the last dose of study intervention, and all men must not donate sperm during the study and for 3 months after receiving the last dose of study intervention. In addition, their female partners should also use an additional method of birth control (which may include a hormonal method, an intrauterine device [IUD] or an intrauterine system [IUS]) for at least the same duration.

Informed Consent

14. Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

5.2. Exclusion Criteria

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

Medical Conditions

1. Presence of two copies of the LoF C allele at rsCCI (i.e., exclude those with CC at nucleotide CCI), and/or has one or more copies of the LoF C allele at rsCCI (i.e., exclude those withCCI or CC nucleotide CCI in the *P2RX7* gene.

2. Criterion modified per Amendment 4:

2.1. Based on the MINI (with Borderline Personality Disorder module) and clinical discretion, has a *current* DSM-5 diagnosis of:
   - borderline personality disorder
   - antisocial personality disorder
   - eating disorder
   - suicide behavior disorder
   - ≥4 episodes of mood disturbances (e.g., mania, hypomania, or depression) within the past 12 months
   - any psychotic disorder

3. Currently meets the DSM-5 criteria for Manic Episode (ME) on the MINI.

4. A YMRS of >12.

5. Received transcranial magnetic stimulation (TMS), any transcranial electrical stimulation, including transcranial direct current stimulation (tDCS), vagal nerve stimulation (VNS) and/or deep brain stimulation (DBS) within 6 weeks prior to randomization (assessed with the ATHF-SF at screening).

6. Criterion modified per Amendment 4:

6.1 Nonresponse or inadequate response to ECT (assessed with the ATHF-SF at screening) or ketamine in the current episode.

7. Nonresponse to >4 treatments in the current episode (assessed with the ATHF-SF at screening).

8. History of alcohol misuse according to DSM-5 criteria within 6 months before screening.

9. History of substance misuse disorder (aside from mild cannabis misuse disorder), according to the DSM-5 criteria, within 6 months before screening, or has a positive urine drug screen for opioids (including methadone), cocaine, barbiturates or amphetamine/methamphetamine at screening. In the case of a positive drug screen for prohibited substances, a one-time repeat urine drug screen may be performed at the discretion of the investigator, provided the participant is willing to abstain from all prohibited substances during the study.

10. History of moderate to severe cannabis misuse according to DSM-5 criteria within 6 months before screening.

11. Has a current or recent (within the past 3 months) history of clinically significant suicidal ideation (corresponding to a score of ≥3 for ideation on the C-SSRS) or any suicidal behavior within the last 6 months, as validated on the C-SSRS at screening. Participants with a prior suicide attempt, or history of prior serious suicidal ideation/plan should be carefully screened for current suicidal ideation and only included at the discretion of the investigator.

12. Participant is currently in need of hospitalization.

13. History of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator is considered cured with minimal risk of recurrence).

14. Known allergies, hypersensitivity, or intolerance to JNJ-55308942, placebo, or its excipients.

15. Had major surgery (e.g., involving a major body cavity or significant blood loss) within 12 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

16. Evidence of clinically severe or active disease, or a clinical finding that is unstable or that, in the opinion of the investigator, would be negatively affected by the study intervention or that would affect the study intervention.

Prior/Concomitant Therapy

17. Taken any disallowed therapies (as noted in Section 6.7, Concomitant Therapy) within the past 4 weeks (5 weeks for fluoxetine) prior to screening.

18. Criterion modified per Amendment 4:

18.1. Newly initiated psychotherapy (defined as psychotherapy that was started within 4 weeks of the screening visit and assessed with the ATHF-SF at screening).

Prior/Concurrent Clinical Study Experience

19. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 60 days or 5 half-lives, whichever is longer, before the planned first dose of study intervention.

20. Is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 1 month after the last dose of study intervention.

21. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Other Exclusions

22. 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.

23. Positive test for hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) at Screening, or other clinically active liver disease (in SoA). If participants are clinically stable, or have been successfully treated for infection, or have spontaneously recovered from infection, they may be allowed in the study with sponsor approval. Confirmatory PCR testing may be required in the case of ambiguous serology results.

24. History of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening. If participants have been successfully treated for HIV infection and are HIV RNA negative, or are clinically stable, they will be allowed in the study.

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 the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once using an unscheduled visit during the screening period (to reassess eligibility). The required source documentation to support meeting the enrollment criteria is noted in Section 10.3, (Appendix 3: 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 study to be eligible for participation:

1. Refer to Section 6.7, Concomitant Therapy for details regarding prohibited and restricted therapy.

2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (e.g., contraceptive requirements).

3. Avoid donating blood for at least 90 days after completion (i.e., final follow-up visit) of the study.

4. Avoid strenuous exercise/activity for 24 hours prior to Visits 2, 4, 5, 6, and 7.

5.3.1. Meals and Dietary Restrictions

1. May not consume any food or beverages containing grapefruit, grapefruit juice, Seville oranges (including any orange marmalade), or quinine (e.g., tonic water) from 72 hours before first dose of study intervention to the end of study visit.

5.3.2. Caffeine and Alcohol

1. Must avoid excessive use of caffeine (e.g., no more than approximately 500 mg/day, as contained in 5 cups of tea or coffee or 8 cans of cola), during the entire study (from screening to end of study)

2. The use of limited amounts of alcohol (up to 2 standard drink consumptions daily) will be allowed, but not within 24 hours before any study visit. A standard drink is defined as: a 350 mL/12 oz glass of 5% alcohol-by-volume (ABV) beer (1.7 units), a 150 mL/5 oz glass of 12% ABV wine (2 units), or a 45 mL/1.5 oz glass of a 40% ABV (80 proof) spirit (1.7 units).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

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

For the "Screening" period, rescreening will be permitted when the time between the first screening visit and the baseline visit has passed. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. In the event of a rescreen the blood sample for the GoF and LoF P2RX7 SNPs should not be redrawn. If participants were found ineligible for the SNP analysis outcome (5.2 Exclusion Criteria: exclusion criteria 1) they cannot be rescreened.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Description of Interventions

All participants will take 1 capsule once-daily in the morning (JNJ-55308942 or matching placebo) from Day 1 up to and including the last treatment visit, Day 43 ± 1 day (at home and when at the study site unless otherwise specified in the protocol) in a fed condition (30 minutes after the start of breakfast [maximum of 2 hours after the start of breakfast]) with some water. The first dose of study intervention will be taken in the fed condition on Day 1 of the double-blind treatment phase when the participant is at the study site after all baseline assessments have been completed. On study visits 3, 4, 5 and 6, study intervention will be taken at the study site after the clinical lab and PK samples have been collected and at approximately the same time (± 4 hours).

The capsules must be swallowed whole and not chewed, divided, dissolved, or crushed.

On days when participants visit the study site, they will take the dose of the study intervention at the study site. Specifically, they should eat a meal before coming to the site. They will bring all study intervention, including the study intervention for that day, to the study site in the bottles dispensed at the previous visit. They will take the study medication at the study site, after completion of the predose study assessments and blood collections. Dosing at the study site will be witnessed by the study staff.

Group/Arm Name	Active study intervention group	Placebo group
Intervention Name	JNJ-55308942	Placebo for JNJ-55308942
Type	Drug	Placebo
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	C mg	Not applicable
Dosage Level(s)	C mg, 1 capsule once-daily	1 capsule once-daily
Route of Administration	Oral	Oral
Use	Experimental	Experimental
Investigational Medicinal Product (IMP)	Yes	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No	No
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements)	Study intervention (JNJ-55308942) will be provided in bottles. Each bottle package will be identified by a unique kit number.	Study intervention (placebo) will be provided in bottles. Each bottle package will be identified by a unique kit number.
	Child resistant	Child resistant
Delivery Instructions	One capsule daily, preferably at the same time point, recommended to take each dose of study intervention in the morning with a glass of water	One capsule daily, preferably at the same time point, recommended to take each dose of study intervention in the morning with a glass of water
Food/Fasting Requirement	30 minutes after the start of breakfast (max. 2 hours)	30 minutes after the start of breakfast (max. 2 hours)

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

JNJ-55308942 and placebo will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention at the study site will be stored in a secure area with restricted access. Capsules must be stored at controlled room temperatures as indicated on the product specific

labeling. All study intervention must be stored at controlled temperatures ranging from 59 °F to 86 °F (15 °C to 30 °C).

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, must be documented on the intervention accountability form. Participants must be instructed to return all original bottles, whether empty or containing study intervention.

Study intervention must be handled in strict accordance with the protocol and the bottle label. 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 intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 groups (JNJ-55308942 or placebo) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by 4 factors: BD type (I or II), country, P2RX7 GoF SNP genotype (homozygous or heterozygous), as well as concomitant medication status (no mood stabilizer or antipsychotic, a mood stabilizer alone, an antipsychotic alone, or a combination of a mood stabilizer and an antipsychotic). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. Sites will be given instructions and training on the number of study intervention kits expected to be assigned by IWRS per patient visit. 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

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

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

Data that may potentially unblind the intervention assignment (e.g., study intervention plasma concentrations, plasma biomarkers) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. Also, the site staff should not discuss insights on unblinding of randomization with the participants.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized/locked. The investigator may, in an emergency, determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed/locked.

6.4. Study Intervention Compliance

Study intervention will be taken at home by the participant, unless otherwise indicated below. The first dose will be taken by the participant on Day 1 of the study at the site.

6.4.1. Medication Adherence and Reminder System

The administration of study medication will be witnessed by the investigator or a properly trained designee. The date and time of study administration during clinic visits will be recorded in the eCRF. Daily study medication reminder(s) will be provided by the Digital Health Asessment app

on the participant's smartphone, or on a smartphone provided to the participant for use in the study if they are unable to use their own.

The investigator or designated study personnel will maintain a log of all study intervention dispensed and returned. Study intervention supplies will be inventoried and accounted for throughout the study.

If appropriate, additional details may be provided in a pharmacy manual/study site investigational product manual that is provided separately and noted in Section 8, Study-Specific Materials.

6.5. Continued Access to 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 Section 10.3, Appendix 3: 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 study intervention and that they should return to their primary physician to determine standard of care.

It is recommended participants continue taking their mood stabilizer or antipsychotic, if they were using them during the study, until such time as changes are recommended by their treating physician. If the participant has persistent symptoms of depression at the completion of the study and has no access to a primary physician or psychiatrist, the investigator should ensure appropriate medical care for the participant after completion of the study.

6.6. Treatment of Overdose

For this study, any dose of JNJ-55308942 greater than CCI mg within a 24-hour time period will be considered an overdose.

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

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted.
- Closely monitor the participant for AE/serious adverse event (SAE) and laboratory abnormalities until JNJ-55308942 can no longer be detected systemically (at least 8 days).
- Obtain a plasma sample for PK analysis within 8 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- 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.

6.7. Concomitant Therapy

All prestudy therapies administered up to 4 weeks before the intial screening visit must be recorded at screening.

Any administration of concomitant therapy throughout the study, from signing of the screening informed consent to final follow-up visit, must be recorded in the eCRF.

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, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

One of the following regimens will be followed for the concomitant medication status:

- Participants who are currently unmedicated and have not received any mood stabilizers or antipsychotics for four weeks before screening.

- Participants who are on a stable monotherapy regimen of one of the following mood stabilizers (lithium, valproate forms [e.g., divalproex sodium], or lamotrigine) or one of the following antipsychotics (lurasidone, cariprazine, quetiapine, lumateperone, or olanzapine) for four weeks before screening.

- Participants who are on a stable adjunctive regimen of one of the following antipsychotics (lurasidone, quetiapine, lumateperone, or olanzapine) and one of the following mood stabilizers (lithium, or valproate forms [e.g., divalproex sodium]) may be considered for eligibility based on the approved therapies in each market with an eligibility assessment conducted between the investigator and sponsor. Assessment of the stable adjunctive regimen of an antipsychotic and a mood stabilizer will be conducted by the investigator and sponsor's clinical judgement and documented for each participants. This regimen must be in place 4 weeks before screening.

Participants will continue to take their current medication regimen, if applicable, throughout the study at an adequate and tolerated dose. No dose changes are permitted from screening through the end of the study (until after the follow-up visit). Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study. Newly initiated psychotherapy (defined as psychotherapy that was started within 4 weeks of the screening visit) is prohibited. Regular ongoing psychotherapy that was initiated prior to 4 weeks before the screening visit will be permitted.

JNJ-55308942 is a weak inducer of CYP[redacted], and a moderate inhibitor of CYP[redacted]. It is preferred that the use of co-medications that are metabolized solely by CYP[redacted] is avoided, or participants should be carefully monitored.

JNJ-55308942 is mainly metabolized by CYP[redacted] Therefore, co-administration with moderate or strong inhibitors/inducers of CYP[redacted] should be avoided.

See section 10.6, (Appendix 6: Disallowed Concomitant Therapies) for an important list of prohibited concomitant medications from 4 weeks prior to the screening visit until 7 days after last dose of study intervention. Of special note, treatment with antidepressants is not allowed in the study.

Following any administration of any disallowed concomitant medication during the study, the sponsor and investigator will evaluate whether a participant should be discontinued or remain in the study.

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

See Section 10.6 for more information on disallowed concomitant therapies.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant discontinues study medication or withdraws from the study before the end of the double-blind treatment phase, the early withdrawal assessments should be obtained.

7.1. Safety Data Review

Continuous or periodic blinded safety reviews will be done by the study responsible physician (SRP). An unblinded review of the data (on the individual participant level) will be conducted if there are safety concerns from this blinded review as a result of severe, serious, or unexpected AEs that are at least possibly related to the study intervention or if the frequency of discontinuations due to TEAEs exceeds 10% of the participants.

7.2. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- Serious violation of protocol procedures after discussion with and agreement of the medical monitor
- The participant withdraws consent to receive study intervention
- The investigator or sponsor believes that for safety reasons or tolerability reasons (e.g., an SAE at least possibly related to the study intervention) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant
- Non-adherence to take the study medication. Non-adherence will be decided on a case-by-case basis depending on the number of missed capsules and the interval between missed doses.
- Aspartate aminotransferase (AST) and/or ALT exceeds 5x the upper limit of normal (ULN) (confirmed by repeat testing)

- AST and/or ALT exceeds 3x the ULN and total bilirubin exceeds 1.5x ULN (confirmed by repeat testing)

If a participant discontinues study intervention for any reason before the end of the double-blind treatment phase, then the early withdrawal assessments should be obtained, and scheduled assessments of study intervention should be continued.

7.3. Protocol stopping criteria

BD is a serious mental condition with significant morbidity and mortality. In this study, participants with at least moderate depression ($HDRS_{17}$ total score ≥20 and with a score ≥2 on the depression question [question #1]) will be included.

For this reason, stopping criteria have been established in this study which will ensure participants who experience any harmful worsening of their symptoms are withdrawn from the study to permit transfer onto alternative active treatment and referral to a psychiatrist when required. Participants will be seen weekly or every 2 weeks and will be monitored with the Digital Health Assessment app for worsening symptoms daily. Therefore, any deterioration is anticipated to be detected quickly.

Blinded medical monitoring by the sponsor will occur on a continuous basis including AEs, laboratory and ECG data. Any concerning safety data will be reviewed with the Safety Management Team (SMT). Issues may be escalated to an internal Janssen Medical Safety Council (MSC). The study will be stopped at any time if significant safety concerns are related to JNJ-55308942 as per the Safety Council's decision.

The principal investigator (PI) may decide to stop study participation at any time when he/she estimates there is an acute risk for participants in study.

7.4. Participant Discontinuation/Withdrawal From the Study

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

- If the participant experiences clinically significant worsening of major depression that requires any new intervention based on clinician judgment or participant preference.
- A participant who shows signals of clinically meaningful acute suicidal ideation at any time during the study should be withdrawn from the study and referred for appropriate medical/psychiatric care.

Also, a participant will be automatically withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Discontinuation of the study treatment for any reason, including those outlined in Section 7.2, (Discontinuation of Study Intervention)
- Death

Additional participants may be enrolled if a relatively large number of participants discontinue or are withdrawn from the study before the end of the double-blind treatment phase and the number of participants completing the study will be below 132.

These additional participants will receive a new participant ID number and will be assigned to a new randomization code in the IWRS.

Study intervention assigned to the withdrawn participant may not be assigned to another participant.

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.4.1. Withdrawal From the Use of Research Samples

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.5. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, e.g., home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, and to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls,

emails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, e.g., for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA summarizes the frequency and timing of efficacy, safety, PK, PD, and biomarker measurements applicable to this study.

Information regarding collection, handling, shipment, and labeling of biological samples (including safety labs) will be provided in a separate lab manual.

Any changes to the lab manual will not result in a protocol amendment.

It is preferred that the self-rating scales and other clinical assessments (except blood collection, if applicable) are done in the fed condition. Participants will be asked to eat a meal before their in-person study site visits, ideally within 1 hour of the study visit. During the site visits it is recommended that:

On Visit 2, Day 1:

- A $HDRS_{17}$ (SIGH-D) has to be administered pre-randomization to verify eligibility of the participant.
- A PCRS, MADRS (SIGMA), CGI-S and participant self-rating baseline assessment has to be performed predose.
- All baseline blood collections should be completed predose.

On Visit 3, 4, 5, and 6 (Weeks 1, 2, 4, and 6 respectively):

- Blood sampling will be performed predose.
- A PK sample will be taken predose and 1.5 (± 0.5 hour) and 4 hours (range between 2 to 4 hours) postdose. Note: note that the blood is ideally drawn at 4 hours postdose. However, the ranges allow the PK measurement to be obtained while still maintaining flexibility (e.g., if the site cannot accommodate the participant for 4 hours, if the participant must go to work, etc.). If the participant is unable to complete a PK draw, electing to withdrawal participation in the study, the PK draw can be missed to avoid an early withdrawal due to blood collection burden.

All study visits:

The primary outcome MADRS (SIGMA) should be admistered as early in the study visit as possible to reduce confounding effects of the subsequent study assessments on mood. The PCRS must be administered before the MADRS.

The order of assessments for study visits on Day 8, 15, 29 and 43 is PCRS followed by the MADRS followed by the CGI-S.

Vital signs and 12-lead ECG, as well as C-SSRS and YMRS will be done pre-randomization on Day 1, and will be done predose on Day 8, 15, 29 and 43.

It is recommended that the order of multiple assessments within 1 protocol time point are the same throughout the study. Additional blood collections for PK and PD assessments need to be kept as close to the specified time as possible. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Additional blood sampling or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation. The time points for individual measures may be changed (with or without affecting the overall frequency of these investigations) prior to and during the study based on newly obtained data to allow for optimal fit to the actual safety or PK/PD profile of the study intervention. This modification may result in a change in the overall frequency of the individual measures (e.g., safety measures, blood samplings) provided the defined maximal total blood volume collected per participant is not be exceeded. Such modifications, where performed only to allow optimal fit to the actual safety or PK/PD profile of the study intervention, will not be an (substantial) amendment to the protocol.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 450 mL.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the SoA for the timing and frequency of all sample collections. During screening, the blood sample for the SNP analysis can be collected along with the other screening clinical laboratory samples.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples

must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for JNJ-55308942
- Sample ICF
- Paper forms for MINI
- Paper documents for the completion of YMRS, C-SSRS, CGI-S, SIGH-D and SIGMA
- Paper documents and instrument completion guidelines for self-rating instruments for the completion of SHAPS, PROMIS - Ability to Participate in Social Roles and Activities, PHQ-9 and GAD-7
- PCRS
- IWRS manual
- Electronic data capture (eDC) manual
- Pharmacy manual/study site investigational product manual or equivalent document e.g., Investigational Product Preparation Instructions
- Laboratory manual, tubes, and labels
- Manuals for investigator and participant for the Digital Health Assessment app to complete the follow-up on self-assessment of treatment experience. The Digital Health Assessment app will be downloaded on the participant's own smartphone, or a smartphone with the app installed will be provided to the participant for use in the study. The Digital Health Assessment app will ask the pre-programmed study-related questions after opening/unlocking the smartphone by the participant. A privacy statement will be provided by the Digital Health Assessment provider. The Digital Health Assessemnt app will report non-adherence of the participant to the investigator.
- Mood Stabilizer and Antipsychotic Eligibility Assessment Form

8.1. Study Procedures

8.1.1. Screening (Visit 1)

Participants will report to the study site for the eligibility screening assessment within 28 to 1 day prior to Day 1 (Baseline). Although the screening period allows for up to 4 weeks, shorter screening periods are encouraged, when possible. The procedures scheduled during the screening visit may be divided over multiple days, according to operational and/or site/country-specific needs. Before any study specific procedures are conducted and following an explanation of the purpose and risks of the study, participants will sign a screening ICF. The collection of AEs and concomitant medications will start after the screening ICF has been signed through the day of last dose plus 30 days.

To ensure that a participant is part of the target study population, specific assessments are prioritized during the screening period. These assessments must be administered on the first day of screening, and only if the participant qualifies will the remainder of the assessments be performed/scheduled. The priority screening procedures are as follows:

1) The MINI with Borderline Personality Disorder module.

    a) The participant must meet criteria for a diagnosis of either Bipolar Depression type I or II.

    b) The participant must not currently meet criteria for psychosis or psychotic disorder, borderline personality disorder, antisocial personality disorder, eating disorder, or suicide behavior disorder.

    c) The participant must not have ≥4 episodes of mood disturbances (e.g., mania, hypomania, depression, or hypomania) within the past 12 months.

2) The Structured Interview Guide for the HDRS17 (Structured Interview Guide for the HDRS$_{17}$ [SIGH-D]).

    a) The participant must be in a current MDE with a total score >20 and with a score >2 on the depressed mood item [question #1].

3) The ATHF-SF.

    a) The participant must not have taken any disallowed medications (per appendix 6) during the 4 weeks prior to the initial screening visit. Disallowed medications include antidepressents.

If applicable, the Mood Stabilizer and Antipsychotic Eligibility Assessment form will be completed for participants who are on a stable regimen of an antipsychotic and a mood stabilizer for four weeks before screening.

Once potential participants have met eligilibity requirements for the MINI, SIGH-D, and ATHF-SF, and the Mood Stabilizer and Antipsychotic Eligibility Assessment form (if applicable) the remaining screening procedures may be completed (see Sections 5.1 and 5.2 for details). Participants will be screened (collection of a blood sample) to ascertain their eligibility for the study, based on the presence of GoF P2RX7 mutation and the absence of the LoF P2RX7 mutations. Further screening will include the full assessment of study inclusion and exclusion criteria, medical history, demographics, physical examination, psychiatric and safety evaluations, and standard laboratory tests. The remaining assessments may be divided over multiple days, according to operational and/or site/country-specific needs and may take place before or after the P2RX7 genotyping results and other laboratory results become available.

After all inclusion and exclusion criteria have been met and confirmed, the participant will be invited to return to the study center for Day 1 of the double-blind treatment study period.

It is recommended that during screening (Visit 1), the Digital Health Assessment app will be downloaded but, if this is not feasible, it is allowed to be performed at Visit 2 instead. Site staff will check to see if the participant's phone is compatible with the app. If the participant has a phone that is not compatible with the app, a compatible phone may be provided for use in the study. In the Digital Health Assessment app, the date of Visit 2 (i.e., Baseline; Study Day 1) should be entered in the dashboard. It is important that the latter is done to ensure that the participant starts receiving the questions from Study Day 1 onwards.

After all inclusion and exclusion criteria have been met and confirmed, the participant will be invited to return to the study center for Day 1 of the double-blind treatment study period.

8.1.2. Baseline Visit (Visit 2; Study Day 1)

The study participant will be asked to come to the study site in fed condition (i.e., to eat a meal before coming to the study site). During the study visit, all assessments will be completed per the SoA. For the "Study Assessments and Procedures" see Section 8.

If the participant is still eligible based on the inclusion and exclusion criteria, the participant will be randomized and supplied with study intervention. The first dose of study intervention will be taken in the fed condition on Day 1 when the participant is at the study site. All baseline study assessments must be completed before taking the study intervention.

8.1.3. Double-blind Treatment Phase (Visit 2 to Visit 6)

The double-blind treatment phase will start on the day of first study intervention administration - the baseline visit (i.e., Visit 2; Study Day 1).

From Day 2 onwards, the participant will take the study intervention at home in the fed condition.

During this phase, the participant will visit the study site weekly or every 2 weeks. At each study visit, the participant should come to the study site in the fed condition and will take his/her dose at the study site after predose blood collections. Study intervention administration should be witnessed by the study staff. At each study visit, participants should bring their study medication with them and return used and partly used bottles.

During the study visits, all assessments will be completed per the SoA. For the "Study Assessments and Procedures" see Section 8.

Between visits, the Digital Health Assessment app will ask the participant about their current depressive state and they will receive questions about their well-being (SAWB). Additionally, they will also need to complete self-rating instruments on paper (see SoA and Section 8.5 for an overview of the self-rating instruments). For self-rating instruments completed at home on paper, participants will receive notifications from the Digital Health Assessment app on their mobile phones as reminders to complete these paper instruments.

8.1.4. Follow-up or Early Withdrawal Visit (Visit 7)

All participants will have to complete Visit 7 (final follow-up visit or early withdrawal visit). Participants who prematurely withdraw from the study are encouraged to complete Visit 7. During Visit 7, all assessments will be completed per the SoA.

8.2. Screening Instruments

8.2.1. MINI International Neuropsychiatric Interview with Borderline Personality Disorder module

The MINI (Sheehan 1998) to assess DSM-5 depressive features in manic and hypomanic episodes is a short structured diagnostic interview which can be administered by clinicians including research nurses and research assistants. The MINI will be completed with a Borderline Personality Disorder module. An appropriately trained staff member at the investigational site will perform the MINI interview once during the screening phase.

8.2.2. P2RX7 GoF and LoF SNP Analysis

Pharmacogenomic blood samples will be collected to assess whether the participant is a carrier of the allele variants for a GoF P2RX7 SNP (≥1 copy of the C allele for CCI [CCCI needed for inclusion) and 2 LoF P2RX7 SNPs (2 copies of the C allele for CCI [rsCCI] and/or ≥1 copy of the C allele for CCI [rsCCI] needed for exclusion). In other words, participants will be excluded if they have the presence of two copies of the LoF C allele at rsCCI (exclude those with CC at nucleotide CCI), and/or has one or more copies of the LoF C allele at rsCCI (exclude those with CCI or CCI nucleotide CCI).

This assessment will include the collection of a blood sample that can be collected along with the other screening clinical laboratory tests. In case participants need to be rescreened, this is the only assessment that does not need to be performed again.

8.2.3. Antidepressant Treatment History Form-Short Form (ATHF-SF)

The ATHF-SF consists of scoring instructions and ratings for most antidepressants / augmentation / and ECT trials. The ATHF-SF documents the administration of common depressantsants, as well as brain/nerve stimulation interventions (ECT, TMS, and VNS), and provides explicit criteria to assess the adequacy of these interventions with established efficacy.

8.2.4. 17-Item Hamilton Depression Rating Scale ($HDRS_{17}$)

The $HDRS_{17}$ is a clinician-administered rating scale designed to assess the severity of symptoms in participants diagnosed with depression (Hamilton 1960) with a total score range of 0 to 52, with higher scores indicating greater severity of depressive symptoms. It is the most widely used symptom severity measure for depression. The $HDRS_{17}$ will be administered at screening and at baseline, by an appropriately trained staff member, using the SIGH-D.

8.3. Efficacy Assessments

8.3.1. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment (Montgomery 1979). The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability. The MADRS will be administered by an appropriately trained staff member, using the SIGMA.

8.4. Secondary Assessments

8.4.1. Clinical Global Impression—Severity scale (CGI-S)

The CGI-S provides an overall clinician-determined summary measure of the severity of the participant's illness that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function (Guy 1976). The CGI-S evaluates the severity of psychopathology on a scale of 0 to 7. Considering total clinical experience, a participant is assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. The CGI-S permits a global evaluation of the participant's condition at a given time.

8.5. Self-Rating Instruments

- The patient reported outcome (PRO) instrument will be provided in the local language in accordance with local guidelines.
- The PRO instrument must be available for regulators and for IRB/ERC submissions, therefore the PRO instrument or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol.
- Non completion of the PRO instrument will not be considered a protocol deviation if the scale has not been approved by the IRB/ERC.
- The PRO and AE data will not be reconciled with one another.

8.5.1. Snaith-Hamilton Pleasure Scale (SHAPS)

An instrument developed for the assessment of hedonic capacity is the 14-item, self-report, Snaith-Hamilton Pleasure Scale (Snaith et al., 1995). The SHAPS was developed to minimize cultural, gender, and age biases in the evaluation of hedonic capacity. It not only measures hedonic tone, but also its absence, i.e. anhedonia. Anhedonia can be a core symptom of depression. Four major domains are covered in the scale, namely interest/pastimes, social interaction, sensory experience, and food/drink.

8.5.2. PROMIS—Ability to Participate in Social Roles and Activities

The PROMIS—Ability to Participate in Social Roles and Activities item bank assesses the perceived ability to perform one's usual social roles and activities. The item bank does not use a time frame (e.g., over the past 7 days) when assessing ability to participate in social roles and activities. The Short Form 4a includes 4 items that represent this concept. Each question has 5 response options ranging in value from 1 to 5. The total raw score for the short form is calculated by summing the values of the response to each question, so for the 4-item form, the lowest possible raw score is 4; the highest possible raw score is 20.

8.5.3. Patient Health Questionnaire-9 (PHQ-9)

The 9-item PHQ-9 scale scores each of the 9 symptom domains of the DSM-5 MDD criteria, and it has been used both as a screening tool and a measure of response to treatment for depression (Kroenke 2001). Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The participant's item responses are summed to provide a total score (range 0 to 27), with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks.

8.5.4. Generalized Anxiety Disorder-7 (GAD-7)

The GAD-7 is a self-reported questionnaire for screening for and measuring the severity of GAD. The GAD-7 has 7 items, which measure the severity of various signs of GAD according to reported response categories with assigned points. Assessment is indicated by the total score (0 to 21), which is calculated by adding together the scores for all 7 items. For each item, as well as for the total score, a higher score represents a more severe condition.

8.6. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 7, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached. After completion of the study, a safety follow-up visit may be scheduled if deemed necessary by the study responsible safety physician or the investigator (e.g., for the collection af additional blood or urine samples).

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA.

8.6.1. Physical Examinations

The study investigator, or other authorized and appropriately qualified designee, will perform the physical examinations.

Height and weight will be measured as indicated in the SoA.

8.6.2. Vital Signs

Body temperature (oral, tympanic, or temporal), pulse/heart rate, respiratory rate, blood pressure will be assessed.

Blood pressure and pulse/heart rate measurements will be assessed after being in supine position for at least 5 minutes with a completely automated device, at the timepoints indicated in the SoA. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements have to be preceded by at least 5 minutes of rest in a quiet setting without distractions (e.g., television, cell phones).

8.6.3. Electrocardiograms

Twelve-lead ECGs, intended for safety monitoring, will be recorded in supine position (following 5 minutes of rest) so that the different ECG intervals (pulse/heart rate [BPM], PR [msec], QRS duration [msec], QT interval, and QTc [msec]) can be measured at multiple timepoints at screening and during the study as indicated in the SoA.

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

At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings will be obtained as closely as possible in succession. The full set of triplicates will be completed in less than 8 minutes.

Clinically relevant abnormalities occurring during the study should be recorded in the AE Section of the eCRF.

8.6.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, hormone levels (if applicable), and pregnancy testing (if applicable) and urine samples for urinalysis and pregnancy testing (if applicable) will be collected as noted in Appendix 2: 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 AE section of the electronic case report form (eCRF). In addition, serology

and HbA1C assessments will be performed at screening only. The laboratory reports must be filed with the source documents.

A urine drug screen (UDS) and an alcohol breath test will be performed at the timepoints indicated in the SoA.

8.6.5. Pregnancy Testing

For WOCBP, a negative screening serum pregnancy test must be obtained at screening. Urine pregnancy testing will be performed before the first dose of study intervention on Day 1 and at all subsequent visits to the study site.

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.

8.6.6. Suicidal Ideation and Behavior Risk Monitoring

8.6.6.1. Young Mania Rating Scale (YMRS)

The YMRS is one of the most frequently utilized rating scales to assess manic symptoms (Young 1978). The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Additional information is based upon clinical observations made during the clinical interview. The items are selected based upon published descriptions of the core symptoms of mania. There are 4 items (irritability, speech, thought content, and disruptive/aggressive behavior) that are graded on a 0 to 8 scale, while the remaining 7 items are graded on a 0 to 4 scale. These 4 items are given twice the weight of the others to compensate for poor cooperation from severely ill patients. There are well described anchor points for each grade of severity. The YMRS total score, with range of 0 to 60, is the sum of each of the 11 individual scores, with higher total YMRS scores reflecting greater symptom severity.

The scale is generally performed by a qualified clinician or other qualified trained rater with expertise with manic patients and takes 15 to 30 minutes to complete.

8.6.6.2. Columbia Suicide Severity Rating Scale (C-SSRS)

An interview to assess the risk of suicidal ideation and behavior will be conducted at regular timepoints during the study from screening through the follow-up visit, as indicated in the SoA.

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. The C-SSRS is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the occurrence and intensity of suicidal thoughts and suicidal behaviors. It can also be used during treatment to monitor for clinical worsening.

If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

8.6.6.3. Follow-up of Well-Being and Depression

The SAWB questionnaire is a multiple-item self-report questionnaire designed to provide additional information regarding the participant's subjective experience while taking study intervention. This is an internal Janssen questionnaire, and the questions will be asked to the participant daily by the Digital Health Assessment app during the double-blind treatment phase. Several items of interest can be covered: such as, but not limited to, the pattern of sleep, energy level, and concentration level. The Digital Health Assessment app will also alert the investigator when a participant has indicated that their depression is 'much worse' or 'very much worse' when answering weekly questions on depression.

8.7. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaints (PQCs), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study and for 30 days after the last dose of study intervention.

AEs of special interest (AESI) have not yet been defined in this study. If observations of AEs during the study require inclusion of AESI, a protocol amendment will be issued.

Further details on AEs, SAEs, and PQCs can be found in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated screening ICF through the day of last dose plus 30 days, which may include contact for follow-up of safety.

Serious Adverse Events

All SAEs, as well as PQCs, 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.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported. The sponsor will evaluate any safety

information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.7.2. Method of Detecting Adverse Events and Serious Adverse Events

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

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

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.7.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated 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 intervention under investigation. For the purposes of this study, the following SAEs will be considered anticipated events:

- Depression
- Mania
- Suicidal ideation/thinking/behavior
- Suicide attempt

- Bipolar disorder (bipolar I/bipolar II)
- Depression suicidal
- Overdose
- Intentional self-injury
- Anxiety
- Panic attacks
- Substance abuse
- Alcohol abuse
- Intoxication
- Aggression

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 intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the study intervention 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.

8.7.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

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

8.8. Pharmacokinetics

Venous blood samples will be collected for PK evaluation as indicated in SoA. Samples will be used to evaluate the plasma concentrations of JNJ-55308942 and metabolites (if required). In addition, some samples may be used to measure plasma concentrations of concomitant medications used by the participant. Participant confidentiality will be maintained.

8.8.1. Evaluations

Venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of JNJ-55308942 as per SoA. The exact dates and times of blood sampling must be recorded in the eCRF.

8.8.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of JNJ-55308942 using a validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method 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 the metabolite profile.

8.8.3. Pharmacokinetic Parameters and Evaluations

Pharmacokinetic and statistical analyses will be done by the sponsor or under the authority of the sponsor. A general description of the methods to be used to analyze the PK data is outlined below. Specific details will be provided in the PK Analysis Plan. Data will be listed for all participants with available JNJ-55308942 plasma concentrations by intervention. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g., non-adherence to study intervention administration; missing PK draws; or early discontinuation from the study). All concentrations below the lowest quantifiable (BLQ) concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the BLQ concentration will be treated as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented in the study report.

For all participants, based on the individual plasma concentration-time data, using the binned nominal sampling times, the following JNJ-55308942 concentrations will be summarized at Visits 2, 3, 4, 5, and 6.

$C_{pre\text{-}dose}$: observed plasma concentration measured before study intervention intake.

$C_{1.5h}$: observed plasma concentration at approximately 1.5 hours after study intervention intake (sampling window of +/- 0.5 hours).

C_{4h}: observed plasma concentration at approximately 4 hours after study intervention intake (sampling window will be 2 to 4 hours post-dose, to allow flexibility, but with the preferred time point being 4 hours postdose).

Other PK parameters may be calculated as needed to characterize the PK of JNJ-55308942.

Population PK analysis of plasma concentration-time data of JNJ-55308942 may be performed if deemed useful using nonlinear mixed-effects modeling. If performed, details may be given in a

population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Evaluations

The exposure-response between JNJ-55308942 and MADRS may be explored. The exposure-response between exposure and adverse events may also be explored. When applicable, details of this PK/PD analysis may be given in a separate analysis plan and the results will be presented in a separate report.

8.9. Genetics and Pharmacogenomics

A blood sample will be collected during screening to assess whether the participant:

- is carrier of the CCI GoF P2RX7 mutation (must be CCI or CCI at CCCI nucleotide CCI for inclusion).
- is *not* a carrier of the CCI or CCI LoF P2RX7 mutations (must be CCI or CCI at rsCCI /nucleotide CCI ; and must be CC at rsCCI /nucleotide CCI). In other words, participants will be excluded if they have the presence of two copies of the LoF C allele at rsCCI (exclude those with CC at nucleotide CCI), and/or has one or more copies of the LoF C allele at rsCCI (exclude those with CCI or CCI nucleotide CCI).

A second pharmacogenomic optional blood sample will be collected from enrolled participants on Day 1 to identify genetic factors that may influence the PK, PD, efficacy, safety, and/or tolerability of JNJ-55308942 and to identify genetic factors associated with BD. If collection on Day 1 is not feasible, it can be collected on any other visit during the double-blind treatment phase.

8.10. Biomarkers

Venous blood samples for the assessment of whole blood, serum, and plasma PD related biomarkers will be collected as indicated in the SoA during the double-blind treatment phase. Biomarker measurements may include cytokine levels, such as TNF-α, IL-1β, IL-6, IL-10 and inflammatory markers, such as IL-6 receptor, CRP, and other exploratory markers. Samples may also be used to study markers of P2X7 and monocyte activation via IL-1β release, shed P2X7 receptor and TREM2 ectodomains, and RNA expression of P2RX7, IL-1β, and other genes related to immune and HPA axis activity. Treatment effects will be analyzed in patients with specific biomarker profiles using statistical modeling.

Biomarker blood samples that may be collected for the research assays measuring functional inhibition of P2X7 receptor in whole blood (TruCulture) may be collected at certain sites in the US, Canada, Spain, and Poland, and those collected for peripheral blood mononuclear cells (PBMCs) inflammatory profiles is taken in the US. The list of countries for these 2 biomarker assays may be updated if countries are added or removed throughout the study. This change will not be considered a protocol deviation.

All biomarker data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between depression severity, phenotypes, and biomarkers, or to help explain interindividual variability in clinical outcomes or safety. Biomarker assays may be added

or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analyses may be deferred or not performed, if during or at the end of the study, it becomes clear that the analyses will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments may not be performed.

8.11. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

JNJ-55308942, compared to placebo, results in a significant improvement in the severity of the symptoms of depression in participants with BD in an MDE, as evaluated by change in MADRS total score from baseline at Week 6.

Hypotheses will be tested at 1-sided alpha 0.10. Multiplicity adjustment will not be carried out.

9.2. Sample Size Determination

The estimated sample size of 164 participants (82 participants per group) was determined based on the assumption of an effect size of at least 0.45 for the MADRS total score (difference in mean change from baseline at Week 6 between the JNJ-55308942 and placebo groups of 3.9 units with a standard deviation of 8.6). This is considered to be a clinically relevant difference in a population with BD types I or II. The standard deviation of 8.6 in the change in MADRS total score from baseline is a reasonable assumption based on data in a published phase 3 study of quetiapine in BD type I and type II depression (Calabrese 2005). Power is set at 90%, with a 1-sided alpha of 0.10 and a 6-week drop-out rate of 20%. The estimated number of completers to be included in the primary analysis is 132.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed the ICF at screening

Randomized	All participants who were randomized in the study
Safety	All randomized participants who received at least 1 dose of study intervention
Full analysis set (FAS)	All randomized participants who received at least 1 dose of study intervention and have both the baseline and at least 1 post-baseline MADRS measurement

9.4. Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary objectives of special interest.

9.4.1. Primary Endpoint(s)

Efficacy analyses will be based on the full analysis set.

The estimand for the primary efficacy analysis is defined with the following 5 attributes:

- Population: participants with BD types I or II and in an MDE.
- Endpoint: change from baseline in the MADRS total score at Week 6.
- Treatment: JNJ-55308942 C mg once-daily versus placebo.
- Population-level summary: the difference in mean change from baseline in MADRS total score at Week 6 between JNJ-55308942 C mg once-daily and placebo.
- Intervention events (ICE) and corresponding strategy: The ICE to be considered is discontinuation of study intervention. The ICE will be addressed with a hypothetical strategy, targeting the effect of the initially randomized treatment that would have been observed had all participants remained on their treatment throughout the double-blind treatment phase.

The primary efficacy analysis will be performed utilizing the hypothetical estimand defined above. The change from baseline in MADRS total score will be compared between the JNJ-55308942 C mg once-daily group and the placebo group at Week 6 in a mixed-effects model using repeated measures (MMRM), with time, treatment (placebo or JNJ-55308942), BD type (I or II), country, concomitant medication status (no mood stabilizer or antipsychotic, a mood stabilizer alone, an antipsychotic alone, a combination of a mood stabilizer and an antipsychotic), P2RX7 GoF SNP genotype (homozygous or heterozygous) and time-by-treatment interaction as factors, with baseline MADRS total score as a continuous covariate. Data after treatment discontinuation will be considered as missing. An unstructured variance-covariance matrix will be used. In case of convergence problems, alternative variance-covariance structures will be attempted in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and first order autoregressive. Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Sandwich estimator will be used to address the potential misspecification of the covariance matrix when a structured covariance matrix is used due to the convergence problem with the unstructured covariance matrix. The comparison of JNJ-55308942 versus placebo will be performed using the appropriate contrast.

To support the primary efficacy analysis, 2 sensitivity analyses will be performed:

- MMRM analysis with copy-reference multiple imputation where missing outcomes due to treatment discontinuation in the JNJ-55308942 C mg once-daily group are assumed to be similar to those in the placebo group.
- Tipping point analysis that imputes missing outcomes over a range of possible scenarios for the treatment effect and finds a 'tipping point' where the treatment effect in participants with missing data overturns the significant treatment effect. This analysis will be performed if the results from the primary analysis show a significantly greater improvement in the MADRS total score at Week 6 in the JNJ-55308942 C mg once-daily group compared to the placebo group.

Response and remission rates with respect to MADRS will be summarized by treatment group and by scheduled timepoint.

9.4.2. Secondary Endpoint(s)

For the secondary objectives of special interest, changes from baseline in SHAPS total score at Week 6 will be compared between JNJ-55308942CC mg once-daily and placebo in an ANCOVA model. The model will include intervention (placebo or JNJ-55308942), BD type (I or II), country, concomitant medication status (no mood stabilizer or antipsychotic, a mood stabilizer alone, an antipsychotic alone, a combination of a mood stabilizer and an antipsychotic), P2RX7 GoF SNP genotype (homozygous or heterozygous) as factors, and baseline SHAPS total score as a covariate. Comparison between JNJ-55308942 C mg once-daily and placebo will be performed using appropriate contrasts. Change from baseline in MADRS total score will be assessed with confidence intervals in subgroups for BD type (I or II), P2RX7 GoF SNP genotype (heterozygous or homozygous), and patients with specific biomarker profiles (yes or no) using a similar MMRM as the one used for the primary endpoint analysis.

For the other secondary objectives, similar MMRM analyses will be conducted for changes in the T-score of PROMIS – Ability to Participant in Social Roles and Activities, the PHQ-9 total score, and the GAD-7 total score. Subgroup analyses by mRNA transcript (P2RX7 and IL-1β) level status at baseline (yes or no) and use of concomitant medication (no mood stabilizer or antipsychotic, a mood stabilizer alone, an antipsychotic alone, a combination of a mood stabilizer and an antipsychotic) will also be conducted for the change from baseline in MADRS total score using a similar MMRM.

For the CGI-S efficacy endpoint, a frequency distribution of severity scores will be provided by treatment group from Week 1 to Week 6. In addition, frequency of shifting scale at Week 6 from baseline will be provided.

Descriptive statistics will be provided for the SAWB assessments.

9.4.3. Safety Analyses

All safety analyses will be performed on the Safety population.

Statistical analysis of the safety data will be done by the sponsor or under the authority of the sponsor. Specific details will be provided in the SAP.

Safety summaries will be provided by treatment, unless specified otherwise.

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class, by severity and relationship to study intervention and will be presented by intervention. SAEs will be summarized separately.

The safety analysis will include the incidence of AEs, actual data and changes in blood pressure, pulse/heart rate, oral, tympanic, or temporal body temperature, laboratory safety data, 12-lead ECG, and physical examination data from Day 1 predose to all postdose assessments.

Results from the C-SSRS will be tabulated by treatment group for all participants receiving at least 1 dose of study intervention.

Exploratory analyses for changes in YMRS total score, as well as for individual YMRS items, from baseline will be performed. Details will be provided in the SAP.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be treatment emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study intervention group. In addition, comparisons between study intervention groups will be provided, if appropriate.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline (Day 1 predose) and at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges).

Electrocardiogram

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are pulse/heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using [some or all of] the following correction methods: QT corrected according to Bazett's formula (QTcB) and QT corrected according to Fridericia's formula (QTcF).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 msec (males), >470 (females), >480 msec, or >500 msec will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 msec or >60 msec. Also, descriptive statistics of QTc will be provided by gender.

Vital Signs

Descriptive statistics of body temperature, pulse/heart rate, supine blood pressure values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examinations

Abnormalities observed during the physical examination will be summarized and listed by treatment group at each scheduled time point.

9.4.4. Other Analyses

Pharmacokinetic Analyses

Descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation, geometric mean, median, minimum, and maximum will be calculated for the JNJ-55308942 plasma concentrations at each sampling time. For other demographic covariates, as specified in the PK analysis plan, descriptive statistics will also be calculated.

Mean and/or median plasma JNJ-55308942 concentration-time profiles will be plotted. Individual plasma concentration-time profiles may also be plotted.

Population PK analysis of plasma concentration-time data of JNJ-55308942 may be performed if deemed useful using nonlinear mixed-effects modeling. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Biomarkers Analyses

Biomarker data will be tabulated for each time point and summary statistics will be calculated. Post-treatment changes in each assay will be assessed.

The remaining exploratory biomarkers will be tabulated by intervention and summary statistics will be calculated. Post-treatment changes in exploratory biomarkers will be summarized by intervention group. Associations between baseline biomarker levels and clinical endpoints may be explored. Also, exploratory analyses on P2RX7 and IL-1β mRNA signatures may be performed. Planned biomarker analyses may not be performed if emerging study data show no likelihood of providing useful scientific information. Results may be presented in a separate biomarkers report.

Pharmacokinetic/Pharmacodynamic Analysis

The exposure-response between JNJ-55308942 and MADRS may be explored. The exposure-response between JNJ-55308942 exposure and selected AEs may also be explored. When

applicable, details of this PK/PD analysis may be given in a separate analysis plan and the results will be presented in a separate report.

Genetic and Pharmacogenomic Analyses

DNA samples will be analyzed to assess whether the participant is a carrier of allele variants for P2RX7 in order to determine eligibility for the study, and to identify genetic factors that may influence the PK, PD, safety, and/or tolerability of JNJ-55308942. As part of the exploratory analysis, mutations of the CCI enzyme (CCI [rsCCI and CCI [rsCCI]) will be measured and may be compared to PK data. 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 JNJ-55308942 and/or BD. They may also be used to develop tests/assays related to JNJ-55308942 and/or BD. Pharmacogenomic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate) in relation to JNJ-55308942 and/or BD clinical endpoints.

Results will be presented in a separate report.

9.5. Interim Analysis

No interim analysis is foreseen.

It may be recommended that a data review needs to be performed by an independent reviewer (e.g., safety review committee), if deemed critical by the Janssen clinical team. Committee membership responsibilities, authorities, and procedures will be documented in a charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ABV	alcohol-by-volume
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATHF-SF	antidepressant treatment history form-short form
ATP	adenosine triphosphate
AUC	area under the curve
BCRP	breast cancer resistance protein
BD	bipolar disorder
BMI	body mass index
BUN	blood urea nitrogen
BzATP	benzoyl-ATP
CGI	Clinical Global Impression
CGI-S	Clinical Global Impression-Severity scale
CNS	central nervous system
CPK	creatine phosphokinase
C_{plasma}	plasma concentration
CRF	case report form(s) (paper or electronic as appropriate for this study)
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DBP	diastolic blood pressure
DBS	deep brain stimulation
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
DTP	direct-to-patient
ECT	electroconvulsive therapy
ECG	Electrocardiogram
eCRF	electronic data capture system
eDC	electronic data capture
EW	early withdrawal
FDA	US Food and Drug Administration
FSH	follicle stimulating hormone
GAD-7	Generalized Anxiety Disorder 7
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GoF	Gain of Function
GST	glutathione S-transferase
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
$HDRS_{17}$	17-item Hamilton Depression Rating Scale
HEK293	human embryonic kidney cells
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL	Interleukin

IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDH	lactic acid dehydrogenase
LDL	low density lipoprotein
LH	luteinizing hormone
LOEL	lowest observed effect level
LoF	loss of function
LPS	Lipopolysaccharide
LTM	local trial manager
MAD	multiple ascending dose
MADRS	Montgomery-Åsberg Depression Rating Scale
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDD	major depressive disorder
MDE	major depressive episode
MDR1	multidrug resistance protein 1
ME	manic episode
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed-effects model for repeated measures
mRNA	messenger ribonucleic acid
NIMH	National Institute of Mental Health
NIMP	Non-Investigational Medicinal Product
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OAT	organic anion transporter
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
PBMC	peripheral blood mononuclear cells
PCRS	placebo-control reminder script
PD	pharmacodynamic(s)
PET	positron emission tomography
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient reported outcome
QTc	corrected QT
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
QWBA	quantitative whole-body autoradiography
RBC	red blood cell
RD	repeated dose
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAD	single ascending dose
SAP	statistical analysis plan
SAWB	Self-Assessment of Well-Being questionnaire
SBP	systolic blood pressure
SD	standard deviation
SHAPS	Snaith-Hamilton Pleasure Scale

SIGH-D	Structured Interview Guide for the $HDRS_{17}$
SIGMA	Structured Interview Guide for the MADRS
SNP	single-nucleotide polymorphism
SoA	Schedule of Activities
SRP	study responsible physician
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
Tbili	total bilirubin
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
UDS	urine drug screen
VNS	vagal nerve stimulation
WBC	white blood cell
WHO	World Health Organization
WMH	World Mental Health
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential
YMRS	Young Mania Rating Scale
β-hCG	β-human chorionic gonadotropin

Definitions of Terms

C_{max}	maximum plasma concentration
EC_{50}	The concentration of JNJ-55308942 producing 50% of maximal effect
EC_{90}	The concentration of JNJ-55308942 producing 90% of maximal effect
ED_{50}	median effective dose
Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.
IC_{50}	50% inhibitory concentration
pIC_{50}	-log of 50% inhibitory concentration
pKi	the negative logarithm of the molar concentration of an antagonist that would produce a 2-fold shift in the concentration response curve for an agonist
T_{max}	time to reach the maximum plasma concentration
$T_{1/2}$	time required for a quantity to reduce to half of its initial value.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	RBC Indices: MCV MCH % Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT)	Total bilirubin (Tbili) and Direct bilirubin Alkaline phosphatase Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Cholesterol Triglycerides Magnesium	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria	
	If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment.		
Hormones	Women only: Follicle Stimulating Hormone (FSH) (at screening) Males only: Inhibin B Luteinizing hormone (LH) Prolactin Total Testosterone (low sensitivity = LC/MS-MS) Total Testosterone (high sensitivity = ELISA) Free Testosterone		

	Sex Hormone Binding Globulin (SHBG)
Other Screening Tests	• Serum β-hCG pregnancy test performed at Screening (WOCBP only). At all other time points, if the urine pregnancy test is positive, a serum β-hCG test will be performed. Investigators may perform additional serum or urine pregnancy testing at their discretion as clinically needed. • Serology (human immunodeficiency virus [HIV] antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus [HCV] antibody) • HbA1c at screening • Urine drug screen (UDS) (opiates [including methadone], cocaine, barbiturates, cannabinoids, and amphetamine/methamphetamine). At screening: a urine sample will be analysed by the central lab. At all other visits: a dipstick test will be used and only in case of a positive result will the urine sample be analysed by the central lab for confirmation of the positive result. • Alcohol breath test

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) Document may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC Document explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and

agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICFs, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (e.g., Form FDA 1572), if applicable
- Documentation of investigator qualifications (e.g., curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (e.g., curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICFs (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

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

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.2.

10.3.2. Financial Disclosure

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

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

10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail.

Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. The physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

The participant will be given sufficient time to read the ICF(s) and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 35 days from the previous ICF signature date.

Where local regulations require, a separate ICF may be used for the required DNA and RNA components of the study.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

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

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-55308942, to understand differential intervention responders, and to develop tests/assays related to JNJ-55308942 and/or any indication for which this compound is developed. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.4.1, Withdrawal From the Use of Research Samples).

10.3.6. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding JNJ-55308942 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-55308942, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of e.g., pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright

protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.7. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

The sponsor may review the CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After uploading the data into the study database, they will be verified for accuracy and consistency with the data sources.

10.3.8. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (e.g., clinician-administered scales or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.3.9. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination
- Investigator-completed scales and assessments
- PROs

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (e.g., electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. These data are electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

10.3.10. Monitoring

The sponsor will use a combination of monitoring techniques; central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the CRF with the source documents (e.g.,

hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

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

10.3.11. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.12. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications

in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.13. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.7.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

  *Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-55308942, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort, and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

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

- Overdose of a sponsor study intervention

- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product [e.g., product name confusion, product label confusion, intercepted prescribing or dispensing errors])
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

10.4.5. Procedures

All Adverse Events

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

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study within 30 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.7.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: 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. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.

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

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

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 **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)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(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 **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] –oral –intravaginal –transdermal –injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] –oral –injectable
• Sexual abstinence *(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.

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

10.6. Appendix 6: Disallowed Concomitant Therapies

The pharmacotherapies listed below are permitted (Y) or excluded (N) due to potential impact on efficacy evaluation and/or participant safety, or because they are indicated for exclusionary conditions.

Except where specifically noted in the protocol, the prohibited therapies listed in this table are prohibited from 4 weeks prior to the initial screening visit until 7 days after the last dose of study medication.

The table below is intended for GENERAL GUIDANCE and is not exhaustive. Please contact the study team to discuss any questions or concerns regarding any specific concomitant therapies for a participant.

Of note, if any concomitant medication that is not listed below has the potential to be a strong or moderate CYP[redacted] inhibitor or inducer, please check with the study team.

Drug Class	Episodic Use (PRN)	Continuous Use	Comments
ADHD Medications	N	N	See also "Psychostimulants" row.
Amantadine	N	N	
Anorexiants (e.g., phenteramine)	N	N	
Antibiotics: Macrolides	N	N	
Antibiotics: Nafcillin	N	N	
Antibiotics: Quinolones	N	N	
Anticonvulsants	N	N	Lithium, valproic acid, and lamotrigine products are permitted, per protocol guidelines, for the indication of bipolar disorder. Gabapentin and pregabalin are allowed if not prescribed for use as an anticonvulsant.
Antidepressants	N	N	
Antifungals	N	N	Topical terbinafine is allowed.
Antipsychotics	Y	Y- if on a stable dose for 4 weeks prior to screening	lurasidone, cariprazine, quetiapine, lumateperone, olanzapine are allowed.
Antivirals: non-nucleoside reverse transcriptase inhibitor (NNRTIs)	N	N	

Antivirals: Protease Inhibitors	N	N	
Aprepitant	N	N	
Avasimibe	N	N	
Benzodiazepines (at doses equal to or less than the equivalent of 2 mg/day of lorazepam)	Y – maximum of 3 consecutive days PRN	Y – if on a stable dose for 4 weeks prior to screening	The ONLY permitted benzodiazepines are as follows: clonazepam, lorazepam, oxazepam, temazepam. All other benzodiazepines are prohibited.
Bosentan	N	N	
Calcium Channel Blockers	N	N	
Chloral hydrate	N	N	
Caffeine	Y	N	Caffeine supplements and pills are prohibited. Certain caffeine-containing drinks (soda, tea, and coffee) are allowed, but cannot exceed 500 mg/day.
Conivaptan	N	N	
Corticosteroids	N	N	Fluticasone permitted.
Cough/Cold/Allergy Preparations	Y	Y	Dextromethorphan- and diphenhydramine-containing products are not allowed.
Crizotinib	N	N	
Hypnotics (Non-Benzodiazepine)	Y	Y	
Fluticasone	Y	Y	
Imatinib	N	N	
Methyldopa	N	N	
Opioids	N	N	
St. John’s wort	N	N	
Proton Pump Inhibitors (PPI)	Y	Y	PPI levels may be increased. Maximum doses of PPI medications are not recommended.
Psychostimulants (e.g., amphetamine, methylphenidate, modafinil, armodafinil)	N	N	
Scopolamine	N	N	

10.7. Appendix 7: Study Conduct During the COVID-19 Pandemic

10.7.1. 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 unavailable, isolated or reassigned to critical tasks.

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 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 travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the COVID-19 pandemic , scheduled visits cannot be conducted in person at the study site, they 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 with the participant, investigator, and the sponsor. 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).

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 tests positive for COVID-19 during the study, the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing study assessments, 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.

10.7.2. Guidance Specific to this Protocol Related to the COVID-19 Pandemic

Scheduled Visits

In the event that a participant is unable to come to the site due to COVID-19-related restrictions for a protocol-required visit, the visit should be conducted by phone. The date of the phone call should be recorded as the visit date. If a visit is conducted by phone, at a minimum data should be recorded for the following in the eCRF:

- Adverse event (AE)
- Serious AE
- Concomitant therapy
- Pregnancy test results (as applicable for women of childbearing potential)
    - For participants in the double-blind treatment period, the urine pregnancy tests provided to the site by the central lab for on-site visits may be shipped to the patient for use at home under guidance from the site.

Additionally, all clinician reported measures may be administered by phone (at a minimum the MADRS) if applicable to the scheduled visit

- **EFFICACY EVALUATIONS**
    - MADRS – administered via the Structured Interview Guide for the MADRS (SIGMA)
- **OTHER CLINICIAN ADMINISTERED EVALUATIONS**
    - CGI-S

Site personnel may not conduct any self-rating instruments over the telephone.

- **SELF-RATING INSTRUMENTS**
    - SHAPS
    - PROMIS – Ability to Participate in Social Roles and Activities
    - PHQ-9
    - GAD-7

In the event that a participant cannot come to the site due to COVID-19-related restrictions for laboratory safety tests, required tests may be conducted at a certified local laboratory. The use of local laboratories must be done in accordance with local regulations.

If samples are analyzed by a local laboratory, results, including units and normal ranges, must be recorded in the eCRF. The investigator must review all safety assessments to confirm the participant can continue his/her study treatment. If the safety assessments cannot be performed and reviewed by the investigator in a timely manner, the investigator may decide to interrupt or permanently discontinue study intervention, if it is in the best interests of the participant.

If assessments are done at a time other than at a scheduled visit, an unscheduled visit should be created in the eCRF to record the results.

Modifications to any assessment due to COVID-19-related restrictions (e.g., assessments done over the phone instead of in-person) must be documented in the participant's source documents.

Missed visits and/or assessments

If a visit is missed entirely due to COVID-19-related restrictions (i.e., no site visit or phone visit performed), it will be captured as a protocol deviation in the clinical trial management system with the prefix "COVID-19-RELATED".

Missed assessments or assessments done out of window due to COVID-19-related restrictions will be captured in the clinical trial management system as protocol deviations with the prefix "COVID-19-RELATED".

Laboratory tests that are missed or delayed due to the COVID-19 pandemic will be identified in the clinical trial management system as "COVID-19-RELATED".

Premature discontinuations due to the COVID-19 pandemic will be documented in the eCRF with the reason "COVID-19-RELATED".

Investigational medical product (IMP)

Direct-to-patient (DTP) shipment of study intervention from the site may be considered with prior approval from the sponsor. Site staff need to obtain permission from the participant and record this in the participant source record for DTP shipments. DTP shipments must be done in accordance with local regulations.

Used, partially used, and unused study treatment bottles, including empty study treatment bottles must be returned to the site for treatment accountability.

Statistical Analysis

The sponsor will evaluate the totality of impact of COVID-19 on collection or missingness of key study data, and additional data analyses will be outlined in the study statistical analysis plan(s).

10.7.3. Study Conduct Related to COVID-19 Vaccine Deployment for NonCOVID-19 Clinical Trials.

- Study participants can undergo a COVID-19 vaccination procedure in compliance with applicable local governmental regulations.
- No pharmacokinetic interactions between the study intervention and currently available COVID-19 vaccines are expected. In addition, based on the mechanism of action of the study intervention and COVID-19 vaccines, no relevant interaction is expected.
- Any COVID-19 vaccine administered to a study participant is considered a concomitant medication and should be reported in the eCRF.
- For SAEs reported after COVID-19 vaccination, the investigator should provide narrative details on the SAE form to allow adequate assessment of causality relationship between the reported SAE and vaccination. This is particularly relevant in cases where the reported SAE is an expected event with the study intervention and the COVID-19 vaccine. If the event is serious and considered to be related to both the COVID-19 vaccine and the study intervention,

it is a serious adverse reaction and expectedness must be assessed. SUSAR reporting will be performed if the serious adverse reaction is unexpected as per applicable reference safety document.

- Study participants do not require unblinding of the study intervention to receive a COVID-19 vaccine.

10.8. Appendix 8: Protocol Amendment History

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

Amendment 4 (25 January 2023)

Overall Rationale for the Amendment: To allow for operational efficiency the prescreening visit will be removed from the study and the prescreening assessment, a blood sample for P2RX7 genotyping, will be part of the screening phase.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis; 1.3. Schedule of Activities; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 5.4. Screen Failures; 8.1. Study Procedures	The prescreening visit is not a separate visit anymore. All assessments (a blood sample for P2RX7 genotyping) will be performed during the screening visit. Visit numbers are updated to reflect this throughout the protocol.	To allow for operational efficiency.
1.1. Synopsis; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 5.4. Screen Failures; 8.1. Study Procedures	It has been clarified that before the blood sample collection for P2RX7 genotyping it is important to evaluate if participants meet the criteria of the target study population (bipolar disorder [BD] type I or II in a major depressive episode [MDE]). This will be done by using the International Neuropsychiatric Interview (MINI) with Borderline Personality Disorder module and the antidepressant treatment history form-short form (ATHF-SF).	To allow the sites to make a better assessment of potential participants for the study.
1.1. Synopsis; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 5.4. Screen Failures; 8.1. Study Procedures	It has been clarified that the remainder of the screening assessments can be performed at any time in the screening period after the P2RX7 genotyping blood sample has been collected. No changes have been made to the single nucleotide polymorphism (SNP) genotyping test itself.	To allow flexibility to the sites and the patients to plan the remainder of the screening assessments.
1.1. Synopsis; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design	It has been clarified that a mood stabilizer is only allowable when taken as a monotherapy.	Patients on more than one mood stabilizer will not be allowed into the study.
1.3. Schedule of Activities;	It has been clarified that the Digital Health Assessment will only be performed in the US.	Clarification.
5.2. Exclusion Criteria	Serology exclusion criteria were added.	These were missing from the protocol and added to ensure the safety of the participant.
1.3. Schedule of Activities; 8.Study Assessments and Procedures	The text has been updated to reflect the correct timing for pharmacokinetic (PK) sampling.	Correction.

1.1. Synopsis; 8.1.1. Screening (Visit 1); 8.8.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	It has been clarified that the collection period for AEs is from the screening informed consent through the day of last dose plus 30 days.	Clarification.
1.1. Synopsis; 8.2.3. Antidepressant Treatment History Form-Short Form (ATHF-SF)	The ATHF-SF has been added as a screening instrument.	It has been added for completeness.
8.7. Safety Assessments	Language was added to clarify that an additional safety visit can be scheduled if this is deemed necessary (e.g., for an additional safety blood sample).	Clarification.
1.1. Synopis; 8.7.2. Vital Signs; 9.4.3. Safety Analysis	In addition to oral and tympanic body temperature measurement, temporal body temperature measurement is allowed.	To allow sites to use devices to take temporal temperature.
8.7.6.3. Follow-up of Well-Being and depression	It has been clarified that the Q1.6 app is also used for safety follow-up more specifically for depression status.	To clarify that the Q1.6 can be used by the site/investigator to monitor the safety, related to depression, of the participant.
1.1. Synopsis; 9.3. Populations for Analysis Sets; 9.4.1. Primary Endpoint(s)	The name of the primary efficacy analysis population is changed from modified Intent-to-Treat (mITT) to Full Analysis Set (FAS) and the reference to the inclusion/exclusion criteria in the Population attribute of the estimand for primary efficacy endpoint is removed.	To clarify the efficacy analysis population will include the maximum possible set of participants.
1.1. Synopsis; 3. Objectives and Endpoints; 9.4.2. Secondary Endpoint(s)	Subgroup analyses by messenger ribonucleic acid (mRNA) transcript (P2RX7 and interleukin-1β [IL-1β]) level status at baseline (yes or no) is changed from a secondary objective of special interest to a secondary objective.	P2RX7 and IL-1β mRNA transcript levels are considered as exploratory biomarkers.
1.1. Synopsis; 9.4.1. Primary Endpoint(s); 9.4.2. Secondary Endpoint(s)	Biomarker profile status (yes or no) and mRNA transcript (P2RX7 and IL-1β) level status (yes or no) are removed from the list of covariates to be included in analyses of primary and secondary endpoints.	Using these biomarkers as covariates in the analysis is considered exploratory. The effect of these biomarkers on the efficacy of JNJ-55308942 will be examined in the corresponding subgroup analyses.
1.1. Synopsis; 9.4.1. Primary Endpoint(s)	Changed the sensitivity analyses for the primary estimand to mixed-effects model using repeated measures (MMRM) analysis with copy-reference multiple imputation and tipping point analysis.	To use more sophisticated sensitivity analysis approaches, such as multiple imputation and tipping point analysis, based on regulatory feedback.
1.3. Schedule of Activities; 10.2. Appendix 1: Clinical Laboratory Tests	It was clarified that at screening a urine sample will be analysed by the central lab for urine drug screening. At all other visits a dipstick test will be used and only in case of a positive result will the sample be analysed by the central lab for confirmation of the positive result.	To give better operational guidance to the sites on how to manage the urine drug screen.

1.1. Synopsis; 4.1. Overall Design; 8.1.1. Screening (Visit 1)	Dysthemia was removed as an example of a mood disturbance that the participant must not have ≥4 of within the past 12 months.	Dysthymia by definition is depressed mood for 2 years. It does not make clinical sense to ask if the patient had an episode of dysthymia that lasted less than a year.
6.6. Treatment of Overdose	The text has been updated to reflect that any dose of JNJ-55308942 greater than CC mg within a 24-hour time period will be considered an overdose.	This is a more relevant representation of the time period.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (27 July 2022)

Overall Rationale for the Amendment: To change the definition of a treatment emergent AE on regulatory request.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 9.4.3. Safety Analyses	Changed: Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 6 days is considered to be treatment emergent. Into Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be treatment emergent.	On regulatory request.

Amendment 2 (4 July 2022)

Overall Rationale for the Amendment: To add clarifications on timing of self-rating assessments, downloading of apps, prohibited concomitant therapy. To add recommendations on order of events and when the second pharmacogenomics sample can be taken. To add Canada as a new country where TruCulture sampling will be performed, provide flexibility on the country list where TruCulture assay or determination of peripheral blood mononuclear cells (PBMCs) inflammatory profiles can be perfomed and to remove Russia where we were provisioning phones to all participants.

The changes made to the clinical protocol 55308942BIP2001 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.8 Appendix 8: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 3. Objectives and Endpoints	SHAPS was removed as secondary outcome.	SHAPS is already analyzed as an endpoint for secondary objectives of special interest.
1.1 Synopsis; 4.1. Overall Design;	The prescreening Phase has been extended from up to 3 weeks to up to 4 weeks and the total study duration was therefore updated to 15 weeks.	To allow the sites more time to schedule the screening visit.

1.1 Synopsis; 4.1. Overall Design; 8.1.4. Double-blind Treatment Phase (Visit 3 to Visit 7)	The timing of the self-rating instruments assessments has been clarified and language was added on the reminders from Q1.6 that will occur when self-rating assessments are performed at home.	This is a clarification.
1.1 Synopsis; 4.2. Scientific Rationale for Study Design; 8.11. Genetics and Pharmacogenomics	If the second pharmacogenomics sample cannot be taken on Day 1, it is allowed to collect this sample during any other visit of the double-blind treatment phase.	The collection of this sample is not time sensitive.
1.1 Synopsis; 9.4. Statistical Analyses	The statistical analysis section is updated.	To better align with the Objectives and Endpoints (Section 3).
1.1 Synopsis; 10.2. Appendix 2: Clinical Laboratory Tests	Added language to clarify that FSH is for women only and at screening only. All other hormones are for males only.	This is a clarification.
1.3. Schedule of Activities	Study medication will not be dispensed on Visit 7.	This had been added to the schedule of Activities (SoA) in error and is therefore now removed.
1.3. Schedule of Activities	“Paxgene tubes” has been replaced by “RNA samples”.	To be consistent throughout the protocol and avoid confusion.
1.3. Schedule of Activities; 8. Study Assessments and Procedures	The recommendation on order of events has been clarified.	This is a clarification.
1.3. Schedule of Activities; 8.1.2. Screening (Visit 2)	Added language to explain that downloading the Q1.6 app can happen at Visit 3 if it is not feasible to be done at Visit 2.	Operational flexibility to the sites.
1.3. Schedule of Activities; 8.12 Biomarkers	Canada was added as a country where the TruCulture sampling will be performed. We also added language to allow updates to the country list for the TruCulture assay and determination of peripheral blood mononuclear cells (PBMCs) inflammatory profiles without it being considered a protocol deviation	Canada is a new country and it was decided TruCulture sampling can be performed there. In addition we wanted to add flexibility on the country list where TruCulture assay or determination of peripheral blood mononuclear cells (PBMCs) inflammatory profiles can be perfomed.
4.2. Scientific Rationale for Study Design	Added language to clarify the use of mood stabilizers in both JNJ-55308942 and placebo treatment groups.	To clarify that the approach for mood stabilizers is the same for both treatment groups (JNJ-55308942 and placebo).
6.3. Measures to Minimize Bias: Randomization and Blinding	Added language to clarify that sites will be given instructions and training on the number of study intervention kits expected to be assigned by IWRS per patient visit.	This is a clarification.
6.4.1. Medication Adherence and Reminder System	Language on agreement for participants in Russia has been removed.	Russia is no longer participating in the study.
6.7. Concomitant Therapy; 10.6. Appendix 6:	Added language to clarify that “prohibited concomitant medications from 4 weeks prior to	To be in line with inclusion criteria 17.

Disallowed Concomitant Therapies	screening until 5 half-lives after last dose of study intervention."	
8. Study Assessments and Procedures	ECG manual was removed.	This ECG manual is not provided and therefore removed from the list.
8.1.2. Screening (Visit 2)	Added language to explain that the AiCure app will be downloaded to same phone as used for Q1.6 App which can be done at screening or Visit 3 (baseline visit, Day 1).	This is a clarification and to allow operational flexibility to the sites.
8.1.3. Baseline Visit (Visit 3; Study Day 1)	To allow consistency, for the order of assessments we refer to section 8 and the SoA.	This is a clarification and to allow operational flexibility to the sites.
8.8.4. Electrocardiogram	Updated language: "If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, it is recommended the procedures be performed in the following order: ECG(s), vital signs, blood draw."	Operationally more feasible.
9.3. Populations for Analysis Sets; 9.4.1. Primary Endpoints	Updated name of analysis population for primary endpoint from ITT (Intent-To-Treat) to mITT (Modified Intent-To-Treat)	The analysis population defined for primary endpoint is different from the standard definition for ITT. It is typically called mITT.
10.7. Appendix 7: Guidance on Study Conduct During the COVID-19	The language in this appendix was updated.	To be aligned with the most recent updated internal template language.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 1 (01 February 2022)

Overall Rationale for the Amendment: To remove the Safety, Tolerability, and Efficacy Preview (STEP) interview, PROMIS - social isolation and Patient and Global Impression of Severity for Depression (PGI-S), to add clarification on the antidepressant treatment history-short form (ATHF-SF), to replace the DARS with the SHAPS, to replace the SMDDS with the PHQ-9, and the use of the AiCure application, to add the digital health assessment by the AiCure app, and to add the urine drug screen (UDS) to every visit.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis Objectives, Overall Design; 1.3 Schedule of Activities; 3 Objectives and Endpoints; 4.1 Overall Design; 8.6 Self-Rating Instruments	The STEP interview was removed from the protocol.	It was decided not to implement this exit interview for this study.
1.1 Synopsis Objectives, Overall Design; 1.3 Schedule of Activities; 3 Objectives and Endpoints; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 8. Study Assessments and Procedures; 8.6 Self-Rating Instruments; 9.4.2 Secondary Endpoints	The PROMIS - social isolation and PGI-S are removed from the protocol.	It was decided not to implement these self-rating scales for this study.
1.1 Synopsis Objectives, Overall Design; 1.3 Schedule of Activities; 3 Objectives and Endpoints; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 8. Study Assessments and Procedures; 8.6 Self-Rating Instruments; 9.4.2 Secondary Endpoints	For the self-rating assessment: the DARS was replaced by the SHAPS and the SMDDS was replaced by the PHQ-9.	It was decided these self-ratings assessments are considered better suited for this study.
8.6 Self-Rating Instruments	Added language to describe flexibility on the incorporation/removal of the PROs in the study.	To increase study feasibility.
5.2 Exclusion Criteria	Exclusion criteria 5, 6 and 18 were further clarified by adding that the ATHF-SF was used at screening.	Exclusion criteria 5, 6 and 18 were further clarified by adding that the ATHF-SF will be used at screening to determine the antidepressant treatment history.
5.2 Exclusion Criteria	Vagal nerve stimulation (VNS) and deep brain stimulation (DBS) were added to exclusion criterion 5.	These two treatments were added for completeness.
1.3 Schedule of Activities	Meal intake status on the day of PK sampling, prior to dosing, will be captured in the AiCure® app. This is now also updated in the SoA.	This is a clarification.
6.4 Study Intervention Compliance	Language was added to further clarify the use of the AiCure® application. Russia was added	This is a clarification.

Section Number and Name	Description of Change	Brief Rationale
	as a country where all participants will receive a provisioned device. It was clarified that the application is compliant with all applicable privacy and data security laws.	
8.7 Digital Health Assessment; 8. Study Assessments and Procedures	Digital health assessment (AiCure®) was added to the protocol.	New assessment.
8.12 Biomarkers	Language was added that the P2X7 monocyte activation status assay and PBMC inflammatory profile may only be performed in certain countries.	These two assays will not be performed in all countries participating in this study.
1.3 Schedule of Activities; 8.11. Genetics and Pharmacogenomics	The general pharmacogenomics sample will be optional.	It was decided to make this an optional sample.
1.3 Schedule of Activities	UDS was added to each in-person visit.	UDS added to provide additional protection of participant safety and to minimize confounding bias from drug use.
10.7 Appendix 7: Study Conduct During COVID-19	COVID-19 guidance specific to this protocol was added.	Language was added to further clarify protocol specific actions needed to be taken specific to COVID-19.
9.4.1 Primary Endpoints	Primary estimand definition was updated and sensitivity analyses were added. Language was added to further clarify intercurrent events and corresponding handling strategy.	To align with FDA guidance and clarify the strategy for handling intercurrent events.
7.4 Participant Discontinuation/Withdrawal From the Study	Rephrase sentence to remove replacement. Since the additional participants not necessary receive the same intervention as the early withdrawal.	This is a clarification.
1.1 Synopsis Objectives, Overall Design; 1.3 Schedule of activities; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design	The prescreening window has been reduced to up to 3 weeks.	This represents a more realistic timeline to perform the P2RX7 Gain of function (GoF) and Loss of Function (LoF) SNP process.
2.2. Background	It was clarified that in study 55308942EDI1002 that 12 participants were dosed with JNJ-55308942 and/or the tracer [^{18}F]-JNJ-64413739.	This is a clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

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

Signature

User	Date	Reason
PPD	18-Aug-2023 15:46:43 (GMT)	Document Approval