Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 2b Multicenter, Randomized, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy and Safety of JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis

FRONTIER 1

Short Title

A Dose-Ranging Study of the Efficacy and Safety of JNJ-77242113 in Participants with Moderate-to-Severe Plaque Psoriasis

Protocol 77242113PSO2001; Phase 2b

JNJ-77242113 Amendment 2

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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).

Regulatory Agency Identifier Number(s):

IND: 156446
EudraCT NUMBER: 2021-003700-41

Status: Approved
Date: 12 January 2022
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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DOCUMENT HISTORY	
Document	**Date**
Amendment 2	12 January 2022
Amendment 1	17 November 2021
Original Protocol	23 September 2021

Amendment 2 (12 January 2022)

Overall Rationale for the Amendment: The protocol is primarily being amended to update the study intervention dosing instructions to include a fasting requirement and to update the analysis strategy regarding discontinuations due to COVID-19 (intercurrent event number 3) to a Treatment Policy strategy.

Section Number and Name	Description of Change	Brief Rationale
SOA	Update Footnote e text to remove examples of the samples that need to be recorded per study manual.	The study manual will outline which samples the date and time should be recorded for and where that information should be recorded.
Section 2.2, Background	Add interim results from an ongoing bioavailability study (77242113PSO1003).	This information was added to justify the change from dosing with or without food to dosing on an empty stomach as defined in Section 4.1 and Section 6.1.
Section 4.1, Overall Design; Section 6.1, Study Interventions Administered	Update study intervention administration instructions to include taking study intervention on an empty stomach.	Interim results from an ongoing, multipart, randomized, open-label, single-dose, crossover study in healthy participants (77242113PSO1003) indicate that the oral bioavailability and PK profile of JNJ-77242113 administered under fasted conditions as an immediate-release (IR) tablet formulation is similar to the oral solution used in the FIH study PN-235-01. The PK results also indicate that concomitant food (high calorie, high-fat breakfast) increased the median time to reach tmax and significantly reduced the rate (Cmax) and extent (AUC) of JNJ 77242113 absorption. Based on the interim food effect data from protocol 77242113PSO1003, study intervention should be administered under fasted conditions.
Section 5.2, Exclusion Criteria	Modified Exclusion Criterion #5 to clarify it refers to agents that deplete B cells.	Clarify the exclusion criterion.
Section 8.2.1, Physical Examinations	Update timing of full physical exams to align with the SoA.	Error in text. Timing of the full physical exam was updated to match the SoA.
Section 9.4.2.1.1.1, Primary Estimand	Changed the analysis strategy for addressing Intercurrent Event 3 (Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) to Treatment	Since COVID-19 can no longer be viewed as a temporary problem, all COVID-19 related reasons will be treated similarly to

Section Number and Name	Description of Change	Brief Rationale
	Policy strategy and combined it with Intercurrent Event 4	"Discontinuations of study intervention due to other reasons (excluding reasons indicative of lack of efficacy)" for which treatment policy strategy was used in the past.
Section 8.2.4 Clinical Safety Laboratory Assessments; Section 10.2, Appendix 2: Clinical Laboratory Tests	The text was modified since some of the listed laboratory tests will be performed locally, instead of centrally. The location is defined in the study manual.	Error in text.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

1. PROTOCOL SUMMARY:

1.1. Synopsis

A Phase 2b Multicenter, Randomized, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy and Safety of JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis

DESCRIPTION OF COMPOUND

JNJ-77242113 is a 13-amino acid peptide that binds directly to the interleukin 23 receptor (IL-23R) subunit and prevents IL-23p19 from engaging its receptor, thereby inhibiting proximal IL-23R signaling and downstream effector functions (eg, cytokine secretion). JNJ-77242113 has high potency with an IC_{50} of ~20 to 30 pM in peripheral human cell based functional assays, so despite its very low oral bioavailability (<1%), it has the potential to provide systemic/skin efficacy.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the dose response of JNJ-77242113 at Week 16 in participants with moderate-to-severe plaque psoriasis	Proportion of participants achieving PASI 75 (≥75% improvement from baseline in PASI) at Week 16
Secondary	
To characterize additional efficacy of JNJ-77242113 versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in PASI total score at Week 16 • Proportion of participants achieving PASI 90 (≥90% improvement from baseline in PASI) at Week 16 • Proportion of participants achieving PASI 100 (100% improvement from baseline in PASI) at Week 16 • Proportion of participants achieving an IGA score of cleared (0) or minimal (1) at Week 16 • Proportion of participants achieving an IGA score of cleared (0) at Week 16 • Change from baseline in BSA at Week 16
To evaluate the effect of JNJ-77242113 treatment on patient-reported psoriasis severity versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptoms score at Week 16 • Change from baseline in PSSD signs score at Week 16 • Proportion of participants achieving PSSD symptoms score=0 at Week 16 among participants with a baseline symptoms score ≥1. • Proportion of participants achieving PSSD signs score=0 at Week 16 among participants with a baseline signs score ≥1.
To evaluate the effect of JNJ-77242113 treatment on dermatology-specific health-related quality of life versus placebo in participants with moderate-to-severe plaque psoriasis	• Proportion of participants achieving a DLQI of 0 or 1 at Week 16 among participants with baseline DLQI score >1

Objectives	Endpoints
To evaluate the effect of JNJ-77242113 treatment on general health-related quality of life versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in domain scores of the Patient-Reported Outcomes Measurement Information System (PROMIS-29) at Week 16 • Proportion of participants who achieve at least a 5-point improvement from baseline in each PROMIS-29 domain at Week 16
To assess the safety and tolerability of JNJ-77242113 in participants with moderate-to-severe plaque psoriasis	• Frequency and type of AEs and SAEs
Exploratory	
To evaluate the PK and immunogenicity of JNJ-77242113, and explore the PK/PD relationship of JNJ-77242113 for biomarkers, efficacy, and safety in participants with moderate-to-severe plaque psoriasis	• JNJ-77242113 PK parameters (ie, plasma concentration just prior to the beginning or at the end of the dosing interval [Ctrough], C_{max}, tmax, and AUC) • The relationship between PK parameters and PD (ie, skin, blood cellular and molecular biomarker activity as well as clinical endpoints and safety parameters) • The incidence of anti-drug antibodies to JNJ-77242113
To characterize additional efficacy of JNJ-77242113 versus placebo for the treatment of regional psoriasis	• Proportion of participants achieving an ss-IGA score of absence of disease (0) or very mild disease (1) and at least a 2-grade improvement from baseline at Week 16 among those participants randomized with scalp psoriasis and an ss-IGA score ≥2 at baseline • Percent change from baseline in NAPSI at Week 16 among participants randomized with a NAPSI score >0 at baseline • Proportion of participants achieving an f-PGA score of clear (0) or minimal (1) at Week 16 among those participants randomized with nail psoriasis and an f-PGA ≥2 score at baseline • Proportion of participants who achieve an hf-PGA score of clear (0) or almost clear (1) and a reduction of at least 2 grades on the hf-PGA scale from baseline at Week 16 among those participants with hand and/or foot psoriasis and an hf-PGA score ≥2 at baseline • Proportion of participants achieving a sPGA of genitalia score of clear (0) or minimal (1) at Week 16 among participants randomized with genital psoriasis and an sPGA of genitalia score ≥3 at baseline

Objectives	Endpoints
	• Proportion of participants achieving a GenPs-SFQ item 2 score of never (0) or rarely (1) at Week 16 among those participants with a GenPs-SFQ item 2 score ≥2 at baseline
To further assess the safety and tolerability of JNJ-77242113 in participants with moderate-to-severe plaque psoriasis	• Frequency and type of related AEs, and AEs leading to discontinuation of study intervention • Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) over time • Systolic and diastolic blood pressures over time
To explore biomarkers in participants with moderate-to-severe plaque psoriasis	• Change from baseline in levels of skin and blood biomarkers
To explore treatment satisfaction after using JNJ-77242113 in participants with moderate-to-severe plaque psoriasis	• Assessment of treatment satisfaction domains at Week 16 using the Treatment Satisfaction Questionnaire for Medications-9 items (TSQM-9)

Hypothesis

The hypothesis of this study is that there is a dose response relationship for JNJ-77242113 in the proportion of participants achieving a Psoriasis Area Severity Index (PASI) 75 response at Week 16.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, dose-ranging, parallel group, multicenter, interventional study in participants with moderate-to-severe plaque psoriasis.

At Week 16, eligible participants will have the option to enroll in a 36-week treatment long term extension (LTE) study; all participants will be treated with active study intervention in the LTE. The study design of the LTE will be detailed in a separate protocol (77242113PSO2002).

Efficacy, safety, pharmacokinetics (PK), immunogenicity, and biomarkers will be assessed according to the Schedule of Activities (SoA; Section 1.3). In addition, there will be four optional substudy collections for participants who consent (where local regulations permit): a pharmacogenomic blood sample, ex vivo cytokine release blood sample, skin biopsy, and photograph collection (lesional or lesional and full body).

One planned database lock (DBL) will occur at Week 16.

Two interim analyses will occur in this study at Week 4 and Week 16.

An external Independent Data Monitoring Committee (iDMC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

A target of 240 participants will be enrolled in this study with 40 participants planned per intervention group.

INTERVENTION GROUPS AND DURATION

The total duration of this study is up to 24 weeks: a screening period of ≤4 weeks, a 16-week treatment period, and a 4-week safety follow-up period after the last study intervention administration for participants who are ineligible or have decided to not enroll in the LTE study at Week 16. At the Week 16 visit, eligible participants who enroll in the LTE will continue treatment after the Week 16 visit under the LTE protocol.

Group 1: JNJ-77242113 (25 mg QD): Participants will receive JNJ-77242113 25 mg QD from Week 0 through Week 16

Group 2: JNJ-77242113 (50 mg QD): Participants will receive JNJ-77242113 50 mg QD from Week 0 through Week 16

Group 3: JNJ-77242113 (100 mg QD): Participants will receive JNJ-77242113 100 mg QD from Week 0 through Week 16

Group 4: JNJ-77242113 (25 mg BID): Participants will receive JNJ-77242113 25 mg BID from Week 0 through Week 16

Group 5: JNJ-77242113 (100 mg BID): Participants will receive JNJ-77242113 100 mg BID from Week 0 through Week 16

Group 6: Placebo: Participants will receive placebo BID from Week 0 through Week 16

EFFICACY EVALUATIONS

Investigator assessments and patient-reported outcomes (PROs) of efficacy include the following:

- PASI
- IGA
- BSA
- NAPSI
- f-PGA
- s-PGA of genitalia
- hf-PGA
- ss-IGA
- Photographs
- PRO measures to assess: PSSD, DLQI, PROMIS-29, GenPs-SFQ, PGI-S, PGI-C, TSQM-9

PHARMACOKINETIC EVALUATIONS

Plasma samples will be used to evaluate the PK of JNJ-77242113.

IMMUNOGENICITY EVALUATIONS

Antibodies to JNJ-77242113 will be evaluated in serum samples collected from all participants according to the Schedule of Assessments (SoA). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Pharmacodynamic markers will be evaluated using blood and skin (optional) samples collected at visits as indicated in the SoA. Biomarker assessments will be made to examine the biological response to treatment

and to identify biomarkers that are relevant to JNJ-77242113 treatment response and/or psoriasis, where local regulations permit. Assessments will include the evaluation of relevant biomarkers in serum, plasma, whole blood, peripheral blood mononuclear cells, and skin biopsy samples (optional) collected as specified in the SoA where local regulations permit**.**

PHARMACOGENOMIC (DNA) EVALUATIONS

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

SAFETY EVALUATIONS

Key safety assessments include adverse events (AE)s, serious adverse events (SAE)s, adverse events of special interest (AESI), laboratory parameters (hematology and chemistry, including lipid panel, and urinalysis), vital signs, systolic and diastolic blood pressures over time, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

STATISTICAL METHODS

Simple descriptive summary statistics, such as n, mean, standard deviation (SD), median, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

To assess the primary objective of the dose response profile of JNJ-77242113 dose groups and facilitate the selection of JNJ-77242113 doses and dosing regimen for future studies, Multiple Comparison Procedures with modeling (MCP-Mod) techniques will be used to analyze the primary endpoint, the proportion of participants achieving PASI 75 at Week 16.

In addition, for binary response efficacy endpoints, comparisons between each of the JNJ-77242113 groups versus placebo will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by the baseline weight (≤90 kg, >90 kg). For continuous efficacy endpoints, treatment comparisons will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model. The MMRM model will have treatment group, baseline weight (≤90 kg, >90 kg), and baseline value for the corresponding efficacy endpoint as explanatory factors. The MMRM model will also include visit, treatment group by visit interaction, baseline weight (≤90 kg, >90 kg) by visit interaction, and baseline value by visit interaction as additional explanatory factors. The Least Square mean (LSmean) estimates and their corresponding 95% confidence interval (CI) will be provided at each time point. In addition, the estimates of LSmean difference and 95% CIs between the JNJ-77242113 groups and placebo will be provided.

In general, all statistical testing will be performed at a significance level of 0.05 (2-sided) unless otherwise specified. Nominal p-values will be displayed for all treatment comparisons.

Efficacy Analyses

Primary Endpoint(s)

The primary efficacy endpoint is the proportion of participants achieving PASI 75 response at Week 16, defined as at least a 75% reduction from baseline in PASI total score.

Estimand

Primary Estimand

The primary estimand (ie, a precise definition of the primary targeted treatment effect) is defined by the following 5 attributes:

Study intervention:

- JNJ-77242113 25 mg QD, 50 mg QD, 25 mg BID, 100 mg QD, and 100 mg BID
- Placebo

Population: adult participants with moderate to severe plaque psoriasis

Variable/endpoint: Response binary variable, where a responder is defined as a participant achieving a PASI 75 response at Week 16 who does not have intercurrent events in categories 1-2 (defined below).

Intercurrent Events (ICEs) and their corresponding strategies.

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Discontinuation of study intervention due to lack of efficacy or due to an AE of worsening of psoriasis 2. Initiation of a protocol-prohibited medication or therapy during the study that could improve psoriasis	**Composite Strategy:** Participants with these intercurrent events are considered as PASI 75 non-responders after these events, and prior to Week 16. The occurrence of these intercurrent events is captured in the variable definition.
3. Discontinuation of study intervention for reasons other than ICE 1	**Treatment Policy:** observed data will be used regardless of whether or not this intercurrent event had occurred.

Note: For participants experiencing multiple ICEs, ICE 2 will override ICE 3.

Population level summary: Difference in the proportions of participants achieving a PASI 75 response at Week 16 between the JNJ-77242113 and placebo intervention groups.

Primary Endpoint Analysis

In the primary efficacy analysis, data from all randomized participants who received at least 1 administration of study intervention will be analyzed according to their assigned treatment group.

A unified strategy that combines MCP-Mod techniques, will be used to analyze the dose-response relationship for the JNJ-77242113 doses in PASI 75 at Week 16. This approach consists of 2 major steps. The first step consists of testing the dose-response signal via multiple contrast tests while controlling the overall Type 1 error. If a dose-response signal is detected, the second step is to select a model that best describes the observed data, which may be used to support dose selection in future studies. In addition, a simple semi-parametric Bayesian normal dynamic linear model (NDLM) will also be explored to complement the frequentist MCP-Mod analysis. The details of the dose-response analysis will be provided in the statistical analysis plan (SAP).

The study will be considered positive if a dose-response signal for the primary endpoint is detected. In addition to the dose-response analysis, pairwise comparisons of the JNJ-77242113 groups versus the placebo group will be performed for PASI 75 at Week 16; these comparisons will not be adjusted for multiplicity. For these comparisons, a CMH stratified by baseline weight category (≤ 90kg, >90kg) will be

used. The proportion difference between each JNJ-77242113 group and placebo group and its 2-sided 95% CI will be provided based on normal approximation with Mantel-Haenszel weights adjusting for baseline weight category.

To examine the robustness of the primary endpoint analysis, additional analyses will be conducted using different missing data approaches; these analyses will be described in the SAP. In addition, sensitivity analyses will be performed for the primary endpoint using the per-protocol population, which includes participants who are generally compliant with the protocol. To evaluate the consistency of the efficacy, subgroup analyses of the primary endpoint will be performed.

Secondary Endpoint(s)

In addition to the primary endpoint analysis, the analyses for secondary efficacy endpoints will be performed. No adjustments for multiple comparisons will be made for the secondary endpoints and nominal p-values will be provided. Additional efficacy analyses may be performed and will be documented in the SAP.

- The proportion of participants who achieve a PASI 100 response at Week 16, will be compared between each of the JNJ-77242113 groups and the placebo group.
- The proportion of participants who achieve a PASI 90 response at Week 16, will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in PASI total score at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo.
- The proportion of participants who achieve an IGA score of cleared (0) at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The proportion of participants who achieve an IGA score of cleared (0) or minimal (1) at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in PSSD symptoms score at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in PSSD signs score at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The proportion of participants who achieve PSSD symptoms score=0 at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with a baseline PSSD symptoms score ≥1.
- The proportion of participants who achieve PSSD signs score=0 at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with a baseline PSSD signs score ≥1.
- The proportion of participants with DLQI=0 or 1 at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group respectively among participants with a baseline DLQI score >1.
- The proportion of participants who achieve 5-point improvement or higher in each PROMIS-29 domain from baseline to Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in BSA at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.

- The change from baseline in PROMIS-29 domain scores at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.

Safety Analyses

Safety data, including but not limited to, AEs, SAEs, AESIs (active TB, malignancy, potential Hy's Law cases), discontinuation of study intervention due to AEs, changes in laboratory assessments, changes in vital signs, and changes in weight will be summarized. Intervention-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Details will be specified in the SAP.

Adverse Events

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify AEs will be coded using the MedDRA. Intervention-emergent AEs are AEs with onset during the intervention period or that are a consequence of a preexisting condition that has worsened since baseline. All intervention-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 intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

The following analyses will also be used to assess the safety of participants in the study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of severe AEs.
- The incidence and type of related AEs as assessed by the investigator.
- The incidence and type of AEs leading to discontinuation of study.

Listings of participants with SAEs, severe AEs, AEs for psoriasis, AEs leading to discontinuation of study and anaphylactic reaction/serum sickness reactions will also be provided. All safety analyses will be based on the population of participants who received at least 1 administration of study intervention; participants will be summarized by the intervention they received.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test (eg, hematology, clinical chemistry, urinalysis). Selected laboratory parameters will be summarized by treatment groups. Common Terminology Criteria for Adverse Events (CTCAE) and Upper Limit of Normal (ULN) will be used to identify abnormal laboratory test results, and the incidence and severity of abnormal laboratory parameters (hematology and chemistry) will be summarized by treatment group.

In addition, a listing of participants with Grade 2 or higher laboratory test results (based on the CTCAE criteria) will also be provided.

C-SSRS

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized descriptively by treatment group.

Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point.

Weight

Descriptive statistics of changes from baseline will be summarized at selected scheduled time points.

Other Analyses

Pharmacokinetic Analyses

The PK evaluable population is defined as all the participants who received at least 1 complete dose of JNJ-77242113 and had at least 1 valid blood sample drawn for PK analysis after their first dose of JNJ-77242113.

Plasma JNJ-77242113 concentrations will be summarized by visit and treatment group. Descriptive statistics will be calculated at each sampling timepoint. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. PK data may also be displayed graphically.

If feasible, population PK analysis of plasma concentration-time data of JNJ-77242113 may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (eg, demographics, laboratory variables, genotypes, race) will be tested as potential covariates affecting PK parameters. 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.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between plasma JNJ-77242113 concentration and efficacy may be examined when appropriate. If a relationship is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship and will be presented in a separate technical report.

Immunogenicity Analyses

The incidence and titers of antibodies to JNJ-77242113 will be summarized for all participants who receive at least 1 dose of JNJ-77242113 and have appropriate samples for detection of antibodies to JNJ-77242113 (ie, participants with at least 1 sample obtained after their first dose of JNJ-77242113).

A listing of participants who are positive for antibodies to JNJ-77242113 will be provided. The maximum titers of antibodies to JNJ-77242113 will be summarized for participants who are positive for antibodies to JNJ-77242113.

The incidence of neutralizing antibodies (NAbs) to JNJ-77242113 will be summarized for participants who are positive for antibodies to JNJ-77242113 and have samples evaluable for NAbs to JNJ-77242113.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Biomarkers Analyses

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

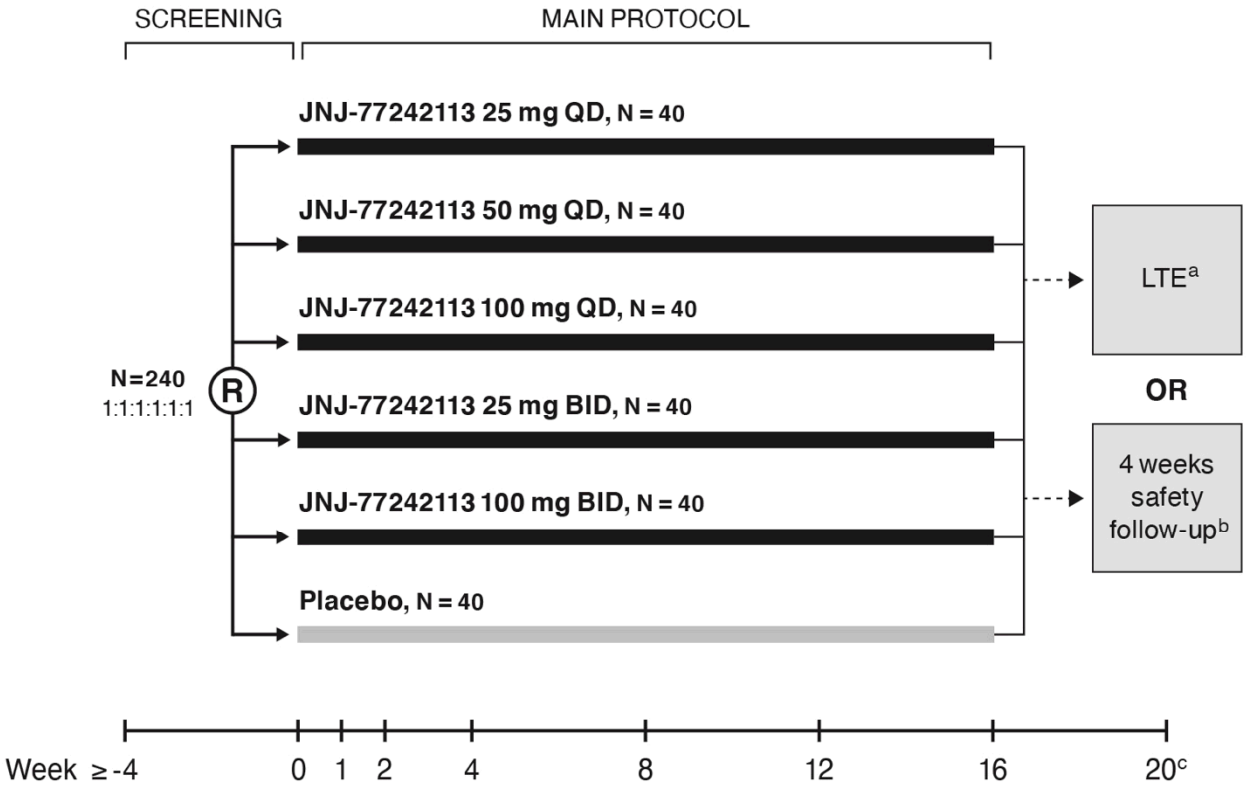
Changes in biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. The analyses will aim to identify biomarker relevant to treatment. Results of biomarker analyses will be reported in separate technical reports.

Pharmacogenomic Analyses

DNA samples will be used for research related to JNJ-77242113 or psoriasis. They may also be used to develop tests/assays related to JNJ-77242113 and/or psoriasis. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to JNJ-77242113 or psoriasis clinical endpoints. Results will be presented in a separate report.

1.2. Schema

Figure 1: Schematic Overview of 77242113PSO2001



BID = twice daily LTE = Long-term extension QD = once daily Ⓡ = Randomization

[a] The LTE will be detailed in a separate protocol (77242113PSO2002). All eligible participants who enroll in the LTE will transition to the LTE protocol for further visit instructions.

[b] All ineligible participants for the LTE and eligible participants for the LTE who choose not to enroll in the LTE will complete 4 weeks of safety follow-up to complete the study.

[c] Final safety follow-up for participants who do not enter the LTE.

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1.3. Schedule of Activities (SoA)

Table 1: 77242113PSO2001 SOA Screening through Week 16

Period	Screening	Placebo-Controlled Active Treatment							Final Safety Follow-up Visit[a]	Early Termination[b]	
Timeframe (Weeks)	-4 to 0	0	1[c]	2	4	8	12	16	20		
Visit Window (Days)			(+/- 2 days)		(+/- 4 days)						
Study Procedure[d]											Notes:
Screening/Administrative											
Informed consent (ICF)	X										Must be signed before first study-related activity.
ICF for optional biomarker substudy	X										
ICF for optional DNA/genomics substudy	X										
ICF for optional photograph substudy	X										
Demographics	X										
Review of Medical history	X										
Inclusion/exclusion criteria	X	X									Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 5.1 and Section 5.2. Check clinical status again before first dose of study intervention.
Chest radiograph	X										Chest radiograph may be taken within 3 months prior to first administration of study intervention.
Interferon gamma release assay (IGRA)	X										IGRA testing includes either QuantiFERON-TB® or T-SPOT® TB. A tuberculin skin test in addition to IGRA testing maybe also used to screen for latent TB if preferred by local health authorities, or at the request of the investigator based on their judgment that both tests are

Table 1: 77242113PSO2001 SOA Screening through Week 16

Period	Screening	Placebo-Controlled Active Treatment							Final Safety Follow-up Visit[a]	Early Termination[b]	
Timeframe (Weeks)	-4 to 0	0	1[c]	2	4	8	12	16	20		
Visit Window (Days)			(+/- 2 days)		(+/- 4 days)						
Study Procedure[d]											Notes:
											clinically indicated to evaluate a participant at high risk for latent TB.
Hepatitis B and C serology	X										
HIV antibody test	X										
Study Intervention Administration											
Randomization		X									
Dispense study intervention[d]		X	X	X	X	X	X				Study intervention may also be dispensed between visits.
Administer study intervention		Daily Self-Administration									At the Week 0 visit, the participant should take the first dose of study intervention in the presence of the investigator or trained study site personal and be observed for signs and symptoms of a hypersensitivity reaction during the first administration (Section 6.1).
Study intervention accountability			X	X	X	X	X	X		X	
Efficacy Assessments											
Patient-reported Outcomes (PRO)											To be completed before any tests, procedures, or other consultations for all visits to prevent influencing participants' perceptions, unless otherwise noted.
PSSD (7-Day recall)		X	X	X	X	X	X	X	X	X	
DLQI		X				X		X		X	
PROMIS-29 (v2.1)		X				X		X		X	
GenPs-SFQ		X				X		X		X	
PGI-S		X				X		X		X	
PGI-C						X		X		X	
TSQM-9		X				X		X		X	
Clinician-reported Outcomes (ClinRO)											

Table 1: 77242113PSO2001 SOA Screening through Week 16

Period	Screening	Placebo-Controlled Active Treatment							Final Safety Follow-up Visit[a]	Early Termination[b]	
Timeframe (Weeks)	-4 to 0	0	1[c]	2	4	8	12	16	20		
Visit Window (Days)			(+/- 2 days)		(+/- 4 days)						
Study Procedure[d]											Notes:
PASI	X	X	X	X	X	X	X	X	X	X	
IGA	X	X	X	X	X	X	X	X	X	X	
BSA	X	X			X	X	X	X		X	
NAPSI		X				X		X		X	
f-PGA		X				X		X		X	
sPGA of Genitalia		X				X		X		X	
hf-PGA		X				X		X		X	
ss-IGA		X				X		X		X	
Photographs		X				X		X		X	For participants who are participating in the applicable substudy.
Safety Assessments											
Full physical examination	X							X	X	X	
Targeted physical examination		X	X	X	X	X	X				
Height		X									
Weight		X						X		X	
Vital signs	X	X	X	X	X	X	X	X	X	X	Vital signs include temperature, heart rate, respiratory rate, and blood pressure.
Tuberculosis Evaluation	X	X	X	X	X	X	X	X	X	X	
12-lead triplicate ECG	X	X	X					X		X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	The Baseline/Screening version of the C-SSRS will be performed at the screening visit. At Week 0 and all other subsequent visits the Since Last Visit C-SSRS version will be performed.
Pregnancy test	X	X	X	X	X	X	X	X	X	X	Women of childbearing potential must have a negative serum pregnancy test

Table 1: 77242113PSO2001 SOA Screening through Week 16

Period	Screening	Placebo-Controlled Active Treatment							Final Safety Follow-up Visit[a]	Early Termination[b]	
Timeframe (Weeks)	-4 to 0	0	1[c]	2	4	8	12	16	20		
Visit Window (Days)			(+/- 2 days)		(+/- 4 days)						
Study Procedure[d]											Notes:
											result during screening and a negative urine pregnancy test at all other required visits prior to dispensing study intervention. The urine assessment can be performed any time during the study visit including prior to the PRO collection.
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	
Clinical Laboratory Tests[e]											
Hematology	X	X	X		X	X	X	X	X	X	
Chemistry	X	X	X		X	X	X	X	X	X	
Lipid Panel	X	X						X		X	Nonfasting lipid panel (at the screening and early termination visits) Fasting lipid panel (at Week 0 and Week 16) Fasting is recommended for at least 6 hours unless medically contraindicated.
hs-CRP		X						X		X	
Urinalysis	X	X	X		X	X	X	X	X	X	This assessment can be performed any time during the study visit including prior to the PRO collection.
Clinical Pharmacology Assessments[e]											
JNJ-77242113 plasma concentrations		X	X	X	X	X	X	X	X	X	At least two trough samples and two peak samples will be collected during the study. Instructions for scheduling

Table 1: 77242113PSO2001 SOA Screening through Week 16

Period	Screening	Placebo-Controlled Active Treatment							Final Safety Follow-up Visit[a]	Early Termination[b]	
Timeframe (Weeks)	-4 to 0	0	1[c]	2	4	8	12	16	20		
Visit Window (Days)			(+/- 2 days)		(+/- 4 days)						
Study Procedure[d]											Notes:
											those collections will be provided during site training.
Serum Antibodies to JNJ-77242113		X		X	X	X		X	X	X	
Biomarkers[e]											
Serum Biomarkers		X		X	X	X	X	X		X	
Whole Blood Peripheral blood mononuclear cells (PBMC) collection		X			X			X			
Skin biopsy		X			X			X			For participants who are participating in the applicable substudy, two biopsies (lesional and non-lesional) will be collected at baseline. At Week 4 and Week 16, one lesional biopsy will be collected.
Tape stripping		X			X			X			
Ex vivo cytokine release blood sample		X		X	X			X			For participants who are participating in the applicable substudy.
Pharmacogenomics (DNA)[e]											
Whole blood sample collection		X									For participants who are participating in the applicable substudy.

Abbreviations: ADA=anti-drug antibody; ClinRO=clinician-reported outcome; BSA=Body Surface Area; C-SSRS=Columbia-Suicide Severity Rating Scale; DLQI=Dermatological Life Quality Index; DNA=deoxyribonucleic acid; ECG=electrocardiogram; f-PGA=Fingernail Physician's Global Assessment; GenPs-SFQ=Genital Psoriasis Sexual Frequency Questionnaire; hs-CRP=High sensitivity C-reactive protein; HIV=human immunodeficiency virus; ICF=informed consent form; IGA=Investigator Global Assessment; IGRA=Interferon gamma release assay; LTE=long-term extension; NAPSI=Nail Psoriasis Area and Severity Index; PASI=Psoriasis Area and Severity Index; PBMC= peripheral blood mononuclear cells; PGI-C=Patient Global Assessment-Change; PGI-S=Patient Global Assessment – Severity; PK=pharmacokinetic(s); PRO=patient-reported outcome; PROMIS-29=Patient Reported Outcomes Measurement Information System-29; PSSD=Psoriasis Symptom and Sign Diary; SoA=Schedule of Activities; s-PGA=Static Physician's Global Assessment; ss-IGA=Scalp Specific Investigator Global Assessment; TB=tuberculosis; TSQM-9=Treatment Satisfaction Questionnaire for Medications

Footnotes:

a. For participants who DO NOT enter the LTE protocol, a Final Safety Follow-up Visit (ie, Week 20) will be conducted approximately 4 weeks after the last administration of study intervention. Participants who enter the LTE will enter at or after the Week 16 visit.
b. Participants who terminate study intervention early should have an Early Termination Visit approximately 4 weeks after their last administration of study intervention.
c. Length of time between Week 1 and Week 2 visits must not exceed 10 days.
d. At all visits where study intervention will be dispensed, all study procedures and evaluations are to be completed before study intervention is dispensed.
e. At Week 0, all blood samples should be collected prior to study intervention administration and the date and time of collection should be recorded in the source document. At all other study visits where applicable, the date and time of the two previously administered doses and the date and time of the samples should be recorded as instructed in the study manual.

2. INTRODUCTION

Interleukin (IL)-23 is a disulfide-linked heterodimer of the IL-23p19 and IL-12/23p40 subunits. The receptor for IL-23 comprises the IL-23R and IL-12R subunits (Bloch 2018). Interleukin-23p19 binding to the N-terminal immunoglobulin (Ig)-like domain of IL-23R is followed by IL-12/23p40 binding to IL-12Rβ1. Ligand binding results in the phosphorylation of Janus kinase (JAK2) and tyrosine kinase 2 (TYK2), leading to phosphorylation and nuclear translocation of signal transducer and activator of transcription (STAT) proteins.

JNJ-77242113 is a 13-amino acid peptide that binds directly to the IL-23R subunit and prevents IL-23p19 from engaging its receptor, thereby inhibiting proximal IL-23R signaling and downstream effector functions (eg, cytokine secretion). JNJ-77242113 has high potency with a half maximal inhibitory concentration IC_{50} of ~20-30 pM in peripheral human cell based functional assays, so despite its very low oral bioavailability (<1%), it has the potential to provide systemic/skin efficacy. This makes JNJ-77242113 a promising candidate for development in systemic, IL-23-driven diseases, such as psoriasis and psoriatic arthritis (PsA). Once present in the systemic circulation, JNJ-77242113 is expected to have good distribution to target organs such as the skin.

To date, JNJ-77242113 has been studied in one Phase 1a clinical study (PN-235-01) of healthy participants to assess the safety and tolerability of JNJ-77242113 over the dose range tested.

For the most comprehensive nonclinical and clinical information regarding JNJ-77242113, refer to the latest version of the Investigator's Brochure (IB) for JNJ-77242113.

The term “study intervention” throughout the protocol, refers to study drug as defined in Section 6.1.

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

In the United States (US), European Union (EU), and Japan, there are approximately 3.5 million patients living with moderate to severe psoriasis (body surface area [BSA] >10%). These patients are traditionally managed with topical and conventional therapies prior to advancing to subcutaneously administered biologics targeting tumor necrosis factor (TNF), IL-23, IL-12/23, or IL-17. Oral therapies, such as apremilast (phosphodiesterase 4 [PDE4] inhibitor), are also available as advanced therapeutic options, but only provide modest efficacy relative to subcutaneously administered biologics (Armstrong 2019) and have demonstrated gastrointestinal intolerability in some patients (Otezla USPI 2017). For those patients who prefer oral medication, healthcare providers agree that oral therapies with high efficacy and long-term clinical remission, remain a substantial unmet need (Nasa 2019).

Targeting IL-23 is a highly validated approach for treating moderate to severe psoriasis. Interleukin-23 is composed of a unique p19 subunit coupled with the common p40 subunit shared

with IL-12, and signals through the heterodimeric IL-23 receptor (IL-23R)/IL-12 receptor beta 1 (IL-12Rβ1) complex (Teng 2015). The IL-23R is expressed by cells of both the innate and adaptive immune systems, including innate lymphoid cells, natural killer (NK) cells, NK T cells, gamma delta T cells, and subsets of memory CD4+ and CD8+ alpha beta T cells (Teng 2015). Binding of IL-23 to the IL-23R complex leads to phosphorylation of STAT3 and IL-23 induced expression of proinflammatory cytokines, such as IL-17A/F and IL-22.

Existing highly successful biologic therapies targeting the p19 subunit of IL-23, such as guselkumab (Blauvelt 2017; Reich 2017) and risankizumab (Gordon 2018), act by preventing engagement of this ligand with the IL-23R and ultimately cause reduced signaling through IL-23R. Moreover, since polymorphisms in IL-23R are associated with susceptibility to psoriasis and the precise anatomical expression of IL-23R dictates where disease develops (Sherlock 2012), targeting this receptor directly is expected to treat psoriasis at a fundamental level and in a way comparable to inhibiting the ligand.

JNJ-77242113 is a 13-amino acid peptide that binds directly to the IL-23R subunit and prevents IL-23 p19 from engaging its receptor, inhibiting proximal IL-23R signaling and downstream effector functions (eg, cytokine secretion). Because of this validated mechanism of action in the treatment of moderate to severe psoriasis patients, JNJ-77242113 has the potential to have similar efficacy and safety profiles to subcutaneously administered anti-IL23 biologics, but with the convenience of oral administration. Validation of this treatment pathway in an orally administered form would significantly increase the therapeutic options for those patients in need of advanced therapies who prefer oral to subcutaneously administered medications.

This study, 77242113PSO2001, is a randomized, double-blinded, dose-ranging, placebo-controlled study of JNJ-77242113 and is designed to evaluate the efficacy and safety of JNJ-77242113 in adults with moderate-to-severe plaque psoriasis.

2.2. Background

Nonclinical Pharmacology and Toxicology

The toxicology profile of JNJ-77242113 has been evaluated in a comprehensive program of Good Laboratory Practice (GLP)-compliant studies that have also included toxicokinetic profiles. The Sprague-Dawley rat and cynomolgus monkey were selected for toxicology testing based on the ability of JNJ-77242113 to bind to IL-23R from rat and cynomolgus monkey and inhibit its activity.

JNJ-77242113 was not genotoxic in the bacterial reverse mutation (Ames) assay, in the in vitro chromosome aberration assay, and in the in vivo rat comet and micronucleus assay. JNJ-77242113, given orally via gavage, did not elicit any treatment-related adverse effects in any in vivo GLP safety pharmacology studies assessing effects on cardiovascular function in telemeterized cynomolgus monkeys, (up to 300 mg/kg), and respiratory function and neurobehavioral endpoints in rats (up to 600 mg/kg).

In repeat-dose studies in rats, JNJ-77242113 was well tolerated with no adverse toxicological findings at oral doses up to 1000 mg/kg/day for 7 days (non-GLP), 600 mg/kg/day for 14 days (GLP), 70 mg/kg/day for 6 weeks (GLP), or 20 mg/kg for 4 months (GLP). The no-observed-adverse-effect-level (NOAEL) was the highest dose tested in each study. In the 2-week study, area under the plasma concentration versus time curve (AUC) exposures on Day 14 were higher (5 to 47 times) than Day 1 exposures and the accumulation ratio further increased up to 300 times following 6 weeks of dosing, and up to 206 times following 4 months of dosing. [redacted]

In cynomolgus monkeys, JNJ-77242113 was well tolerated with no adverse toxicological findings following a single oral dose up to 1000 mg/kg/day (non-GLP) and repeat-doses up to 300 mg/kg for 14 days (GLP) or up to 600 mg/kg/day for 17 weeks (GLP). The NOAEL was the highest dose tested in each study. In the 2-week study, plasma AUC exposures on Day 14 were within 2-fold of the Day 1 exposures, indicating no meaningful accumulation. [redacted]

JNJ-77242113 was evaluated for effects on embryo fetal development in rats dosed up to 1000 mg/kg (for 12 days) and rabbits dosed up to 500 mg/kg (for 13 days). In rats, no maternal or fetal developmental toxicity was reported at any dose and the NOAEL was the highest dose tested (1000 mg/kg). [redacted]. In rabbits, JNJ-77242113 dosing was associated with maternal toxicity leading to abortions in 2 dams on GD26. There was a slight increase, above historical control values, in the incidence of fused ribs in fetuses from dams dosed at 500 mg/kg. [redacted] The NOAEL was the [redacted] dose of [redacted], and AUC exposure was [redacted] over the expected exposure level in humans following a dose of [redacted] [redacted] Although the relevance to humans of these adverse findings at the high dose (150 times exposure margins) is unknown, based on the high margins at the NOAEL, the risk to pregnant women is considered low (International Council for Harmonisation [ICH] S5[R3] Guidance 2020).

CCI [redacted] of JNJ-77242113 in humans. It is not uncommon with biologics to have only one species to assess toxicity (generally on-target). CCI [redacted]

In summary, the available in vitro and in vivo pharmacology and nonclinical safety evaluation studies support the proposed Phase 2b clinical study in participants with moderate-to-severe plaque psoriasis.

Pharmacokinetic Profile

The pharmacokinetics (PK), distribution, and metabolism of JNJ-77242113 have been evaluated in multiple in vitro and in vivo studies in nonclinical species. JNJ-77242113 has low passive permeability and poor absorption. Oral bioavailability ranged from 0.1% to 0.3% in rat and monkey studies. JNJ-77242113 is not a P-glycoprotein substrate or inhibitor.

Plasma exposure levels were evaluated in multiple nonclinical safety studies. The longest GLP nonclinical safety studies to date were conducted in rat (4 months of daily dosing) and cynomolgus monkey (17 weeks of daily dosing). In the 6-week rat study, male and female Sprague-Dawley rats were orally administered JNJ-77242113 at dose levels of 0, 5, 20, or 70 mg/kg/day. Increases in JNJ-77242113 Cmax and AUC0-24 values were generally dose proportional or less than dose proportional. CCI [redacted] The NOAEL was the highest dose tested in the study (70 mg/kg/day); Cmax and AUC0-24 values on Day 42 at this dose were 614 ng/mL and 11,300 ng*hr/mL in males; the corresponding values were 720 ng/mL and 12,100 ng*hr/mL in females. In the most recent GLP rat study, male and female Sprague-Dawley rats were orally administered JNJ-77242113 at 0, 1, 5, and 20 mg/kg/day for 4 months. Following repeated daily oral administration of JNJ-77242113, exposure generally increased with dose and notable accumulation of JNJ-77242113 was observed on Days 23, 58, and 114 when compared to Day 1, with Day 114/Day 1 AUC accumulation ratios ranging from 22.2 to 206. The NOAEL was the highest dose tested in the study (20 mg/kg/day); Cmax and AUC0-24 values on Day 114 at this dose were 324 ng/mL and 4,170 ng*hr/mL in males; the corresponding values were 116 ng/mL and 760 ng*hr/mL in females. In general, there was no significant difference in exposure between sexes across the study arms; the difference in this group was mostly due to one animal with higher exposure. In the 17-week monkey study, cynomolgus monkeys were orally administered JNJ-77242113 at dose levels of 0, 30, 200, or 600 mg/kg/day. JNJ-77242113 mean Cmax and AUC0-24 values were similar or slightly higher on Day 28 and 116 compared to Day 1, indicating

minor accumulation of JNJ-77242113 after multiple doses. CCI [redacted] The NOAEL was the highest dose tested in the study (600 mg/kg/day); Cmax and AUC0-24 values on Day 116 at this dose were 989 ng/mL and 9,440 ng*hr/mL in males; the corresponding values were 438 ng/mL and 4,610 ng*hr/mL in females.

Clinical Studies

The PN-235-01 study was a first-in-human (FIH), randomized, placebo-controlled study of single and multiple ascending (SAD and MAD) doses of JNJ-77242113. The objectives were to assess the safety and tolerability of JNJ-77242113 after single (10, 25, 100, 300, or 1000 mg, Part 1, double-blinded) and multiple (10, 25, 100, 300, or 1000 mg, once daily [QD] dosing for 10 days, Part 2, double-blinded) ascending oral dose administration in healthy participants, to evaluate the PK and PD of JNJ-77242113, to assess the bioavailability of a tablet formulation of JNJ-77242113 relative to a solution, and to evaluate the effect of a high-fat meal on the tablet formulation PK (25 mg, Part 3).

Safety results from PN-235-01 show that JNJ-77242113 was well tolerated with no significant safety signals or concerns identified. There were no deaths or SAEs reported. The final cohort of the MAD (1000 mg QD) was interrupted after a preliminary echocardiogram for a single participant was misread and on final report was deemed to be normal. At the time the study was interrupted, in the 1000 mg QD cohort, 8 participants had completed 8 out of the planned 10 days of treatment, and 2 participants had completed 7 days of treatment.

Refer to the JNJ-77242113 IB for the most up to date safety information from this clinical study.

Pharmacokinetic Summary

Preliminary PK data from FIH study PN-235-01 indicate that systemic exposure (C_{max} and AUC) to JNJ-77242113 is approximately dose proportional across the dose range evaluated to date. After multiple QD dosing, steady state was achieved by Day 7 (earliest timepoint evaluated), with minimal drug accumulation consistent with the observed mean terminal phase half-life of approximately 9 to 12 hours.

Interim results from an ongoing, multipart, randomized, open-label, single-dose, crossover study in healthy participants (77242113PSO1003) indicate that the oral bioavailability and PK profile of JNJ-77242113 administered under fasted conditions as an immediate-release (IR) tablet formulation is similar to the oral solution used in the FIH study PN-235-01. The PK results also indicate that concomitant food (high calorie, high-fat breakfast) increased the median time to reach t_{max} and significantly reduced the rate (C_{max}) and extent (AUC) of JNJ-77242113 absorption. Based on the interim food effect data from protocol 77242113PSO1003, study intervention should be administered under fasted conditions.

Refer to the JNJ-77242113 IB for more information on human PK.

2.3. Benefit-Risk Assessment

Study 77242113PSO2001 is the first JNJ-77242113 study conducted in participants with psoriasis. Therefore, the benefit-risk profile of JNJ-77242113 in patients with psoriasis has not been established. No risks have been observed for JNJ-77242113. The risks described in Table 2 are based on the drug platform (ie, a peptide therapeutic), risks that could occur from blocking the IL-23 pathway based on information from monoclonal antibodies (mAbs), or study procedures.

2.3.1. Risks for Study Participation

More detailed information about the known and expected benefits and risks of JNJ-77242113 may be found in the IB.

Table 2: Potential Risks of JNJ-77242113 for the Treatment of Psoriasis

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Risks Due to Study Intervention		
Hypersensitivity Reactions	Exogenous peptides administered orally or systemically have the potential to cause hypersensitivity reactions.	• This potential risk will be explained in the ICF and participants will be trained to recognize early signs of impending anaphylaxis (Sampson 2006) and seek medical attention. • Participants with known allergy, hypersensitivity, or intolerance to JNJ-77242113 or its excipients will be excluded from the study. • Sites are instructed that before the first administration of study intervention (Week 0), appropriately trained personnel and medications (eg, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. In addition, all participants must be observed carefully for signs and symptoms of a hypersensitivity reaction during the first administration (eg, urticaria, pruritus, angioedema, wheezing, dyspnea, or hypotension; Section 6.1). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1).
ADA production	Exogenous peptides administered orally or systemically can have the potential to induce ADA	• This potential risk will be explained in the ICF and evaluated

Table 2: Potential Risks of JNJ-77242113 for the Treatment of Psoriasis

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	production, which may mediate untoward reactions such as reduced efficacy or hypersensitivity.	by measuring ADAs and PK for analysis. • Participants are encouraged to consistently take their study intervention 12 hours apart, as directed. • Drug accountability will be performed at each study visit to assess study intervention compliance.
Infection	Clinical experience with marketed IL-23 pathway blockers include precautions for infections and TB.	• This risk is included in the ICF. • Participants with a history of, or ongoing, chronic or recurrent infectious disease, including human immunodeficiency virus (HIV), Hepatitis B or C virus (HBV, HCV), will be excluded from the study. Similarly, participants with evidence of active or untreated latent tuberculosis (TB) will be excluded from the study (Section 5.2). • Participants who have received a live viral or bacterial vaccination within 12 weeks of baseline or who have received the BCG vaccine within 12 months of baseline, will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccination during the study and for 4 weeks after receiving the last dose of study intervention (Section 5.2). • Participants will be educated and instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators will be instructed to monitor for signs or symptoms of infections, including TB (Section 8.2.8). • Discontinuation of a participant's study intervention must be strongly considered if the participant develops a serious infection, including but not limited to sepsis or pneumonia. In

Table 2: Potential Risks of JNJ-77242113 for the Treatment of Psoriasis

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		addition, any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete (Section 7.1).
Risks Due to Study Procedures		
Skin biopsy (optional substudy)	Mild bleeding, pain, discomfort, scarring, discoloration, and infection may occur as part of biopsy procedure.	This risk will be included in the sub-study ICF. Trained and experienced physicians will be performing the procedure during this study.

2.3.2. Benefits for Study Participation

Inhibiting IL-23 has been shown to be efficacious in patients with psoriasis as shown in studies with monoclonal antibodies such as ustekinumab (IL-12/23), guselkumab, tildrakizumab, and risankizumab (IL-23). The clinical benefit of JNJ-77242113 in patients with psoriasis remains to be established.

2.3.3. Benefit-Risk Assessment for Study Participation

Study 77242113PSO2001 is the first study conducted in patients with psoriasis, and therefore, the benefit-risk profile of JNJ-77242113 in patients with psoriasis has not been established. However, JNJ-77242113 blocks the IL-23 receptor and thereby targets the IL-23 pathway, similar to approved mAbs, ustekinumab (targeting IL-12/IL-23), guselkumab, tildrakizumab, and risankizumab (targeting IL-23). JNJ-77242113 has the potential for efficacy in psoriasis given the observed systemic exposures and high potency against the IL-23 receptor. The potential benefits should justify the risks, which will be mitigated by measures taken during the conduct of the study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the dose response of JNJ-77242113 at Week 16 in participants with moderate-to-severe plaque psoriasis	Proportion of participants achieving PASI 75 (≥75% improvement from baseline in PASI) at Week 16
Secondary	
To characterize additional efficacy of JNJ-77242113 versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in PASI total score at Week 16 • Proportion of participants achieving PASI 90 (≥90% improvement from baseline in PASI) at Week 16

Objectives	Endpoints
	• Proportion of participants achieving PASI 100 (100% improvement from baseline in PASI) at Week 16 • Proportion of participants achieving an IGA score of cleared (0) or minimal (1) at Week 16 • Proportion of participants achieving an IGA score of cleared (0) at Week 16 • Change from baseline in BSA at Week 16
To evaluate the effect of JNJ-77242113 treatment on patient-reported psoriasis severity versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptoms scores at Week 16 • Change from baseline in PSSD signs score at Week 16 • Proportion of participants achieving PSSD symptoms score=0 at Week 16 among participants with a baseline symptoms score ≥1 • Proportion of participants achieving PSSD signs score=0 at Week 16 among participants with a baseline signs score ≥1
To evaluate the effect of JNJ-77242113 treatment on dermatology-specific health-related quality of life versus placebo in participants with moderate-to-severe plaque psoriasis	• Proportion of participants achieving a DLQI of 0 or 1 at Week 16 among participants with baseline DLQI score >1
To evaluate the effect of JNJ-77242113 treatment on general health-related quality of life versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in domain scores of the Patient-Reported Outcomes Measurement Information System (PROMIS-29) at Week 16 • Proportion of participants who achieve at least a 5-point improvement from baseline in each PROMIS-29 domain at Week 16
To assess the safety and tolerability of JNJ-77242113 in participants with moderate-to-severe plaque psoriasis	• Frequency and type of AEs and SAEs
Exploratory	
To evaluate the PK and immunogenicity of JNJ-77242113, and explore the PK/PD relationship of JNJ-77242113 for biomarkers, efficacy, and safety in participants with moderate-to-severe plaque psoriasis	• JNJ-77242113 PK parameters (ie, plasma concentration just prior to the beginning or at the end of the dosing interval [Ctrough], C_{max}, tmax, and AUC) • The relationship between PK parameters and PD (ie, skin, blood cellular and molecular biomarker activity as well as clinical endpoints and safety parameters) • The incidence of anti-drug antibodies to JNJ-77242113
To characterize additional efficacy of JNJ-77242113 versus placebo for the treatment of regional psoriasis	• Proportion of participants achieving an ss-IGA score of absence of disease (0) or very mild disease (1) and at least a 2-grade improvement from baseline at Week 16

Objectives	Endpoints
	among those participants randomized with scalp psoriasis and an ss-IGA score ≥2 at baseline • Percent change from baseline in NAPSI at Week 16 among participants randomized with a NAPSI score >0 at baseline • Proportion of participants achieving an f-PGA score of clear (0) or minimal (1) at Week 16 among those participants randomized with nail psoriasis and an f-PGA score ≥2 at baseline • Proportion of participants who achieve an hf-PGA score of clear (0) or almost clear (1) and a reduction of at least 2 grades on the hf-PGA scale from baseline at Week 16 among those participants with hand and/or foot psoriasis and an hf-PGA score ≥2 at baseline • Proportion of participants achieving a sPGA of genitalia score of clear (0) or minimal (1) at Week 16 among participants randomized with genital psoriasis and an sPGA of genitalia score ≥3 at baseline • Proportion of participants achieving a GenPs-SFQ item 2 score of never (0) or rarely (1) at Week 16 among those participants with a GenPs-SFQ item 2 score ≥2 at baseline
To further assess the safety and tolerability of JNJ-77242113 in participants with moderate-to-severe plaque psoriasis	• Frequency and type of related AEs, and AEs leading to discontinuation of study intervention • Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) over time • Systolic and diastolic blood pressures over time
To explore biomarkers in participants with moderate-to-severe plaque psoriasis	• Change from baseline in levels of skin and blood biomarkers
To explore treatment satisfaction after using JNJ-77242113 in participants with moderate-to-severe plaque psoriasis	• Assessment of treatment satisfaction domains at Week 16 using the Treatment Satisfaction Questionnaire for Medications-9 items (TSQM-9)

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

HYPOTHESIS:

The hypothesis of this study is that there is a dose response relationship for JNJ-77242113 in the proportion of participants achieving a PASI 75 response at Week 16.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, dose-ranging, parallel group, multicenter, interventional study in participants with moderate-to-severe plaque psoriasis.

A target of 240 participants will be enrolled in this study with 40 participants planned per intervention group.

Participants will be instructed to take the study intervention in the morning (AM) and in the evening (PM) on an empty stomach with approximately 240 mL of noncarbonated water at approximately the same time every day. An empty stomach is defined as abstaining from food intake for at least 2 hours before taking the study intervention and abstaining from food and liquid intake for at least 30 min after taking the study intervention. Dietary intake should be recorded per study manual.

The study intervention may be delivered directly to the participants from a courier as permitted by local requirements and/or regulations if approved by the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB); Section 6.2. Details regarding delivery are provided in the study manual. The participant has the ability to opt-in or opt-out of using this service throughout the duration of the study.

Group 1: JNJ-77242113 (25 mg QD): Participants will receive JNJ-77242113 25 mg QD from Week 0 through Week 16

Group 2: JNJ-77242113 (50 mg QD): Participants will receive JNJ-77242113 50 mg QD from Week 0 through Week 16

Group 3: JNJ-77242113 (100 mg QD): Participants will receive JNJ-77242113 100 mg QD from Week 0 through Week 16

Group 4: JNJ-77242113 (25 mg BID): Participants will receive JNJ-77242113 25 mg BID from Week 0 through Week 16

Group 5: JNJ-77242113 (100 mg BID): Participants will receive JNJ-77242113 100 mg BID from Week 0 through Week 16

Group 6: Placebo: Participants will receive placebo BID from Week 0 through Week 16

At Week 16, eligible participants will have the option to enroll in a 36-week treatment long term extension (LTE) study; all participants will be treated with active study intervention in the LTE. The study design of the LTE will be detailed in a separate protocol (77242113PSO2002).

The total duration of this study is up to 24 weeks: a screening period of ≤4 weeks, a 16-week treatment period, and a 4-week safety follow-up period after the last study intervention administration for participants who are ineligible or have decided to not enroll in the LTE study at

Week 16. All eligible participants who enroll in the LTE will continue treatment after the Week 16 visit under the LTE protocol.

Efficacy, safety, PK, immunogenicity, and biomarkers will be assessed according to the Schedule of Activities (SoA; Section 1.3, Table 1). In addition, there will be 4 optional substudy collections for participants who consent (where local regulations permit): a pharmacogenomic blood sample, ex vivo cytokine release blood sample, skin biopsy, and photograph collection (lesional or lesional and full body).

One planned database lock (DBL) will occur at Week 16.

Two interim analyses will occur in this study at Week 4 and Week 16, as specified in Section 9.5.

An external Independent Data Monitoring Committee (iDMC) will be commissioned for this study (Section 10.3.6).

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

4.2. Scientific Rationale for Study Design

Blinding, Control, 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 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 (eg, 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.

DNA and Biomarker Collection

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 DNA to allow the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of JNJ-77242113 and to identify genetic factors associated with psoriasis.

Biomarker samples will be collected to evaluate the mechanism of action of JNJ-77242113 or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the PD of JNJ-77242113 and aid in evaluating the intervention-clinical response relationship.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. 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.

The study design includes a placebo treatment arm through Week 16. All eligible participants will have the option to enroll into a 36-week treatment LTE study where all participants will receive active treatment (LTE design detailed in a separate protocol).

Participants will be discontinued from study intervention if the investigator considers it is in the best interest of the participant.

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 the American Red Cross standard limit for whole blood donation (approximately 450 mL every 8 weeks) and is, therefore, considered an acceptable amount of blood to be collected over this time. (Section 8).

4.3. Justification for Dose

A FIH study, (PN-235-01) was conducted to evaluate single ascending and multiple (QD for 10 days) ascending doses of JNJ-77242113 (10, 25, 100, 300, and 1000 mg) in healthy participants. The study demonstrated that single and multiple oral doses up to 1000 mg/day are safe and generally well tolerated with no safety signal of concern. Systemic exposure (C_{max} and AUC) to JNJ-77242113 was approximately dose-proportional across the dose range evaluated. After multiple QD dosing, steady state was achieved by Day 7 (earliest timepoint evaluated), consistent with the observed mean terminal phase half-life of approximately 9 to 12 hours. Refer to the IB for additional details regarding the FIH study results.

The dose selection for the Phase 2b study is based on observed PK and ex vivo PD data (ie, inhibition of IL-23-stimulated interferon gamma production in whole blood) from the FIH study and a comparative analysis of in vitro IL-23/IL-23R pathway inhibition for JNJ-77242113 relative to CCI [redacted] The observed human CCI [redacted] were used to develop preliminary population CCI [redacted] along with the in vitro pathway inhibition data. The observed data from the FIH study are consistent with these predictions and indicate that CCI [redacted]

are associated with systemic activity as evidenced by CCI (whole blood IL-23-stimulated interferon gamma production and peripheral blood mononuclear cells [PBMC] pSTAT3 assays).

The daily doses selected for the Phase 2b study range from 25 mg to 200 mg per day and include both once-daily (25 mg QD, 50 mg QD, and 100 mg QD) and BID dosing regimens (25 mg BID and 100 mg BID). CCI

In summary, the doses and dosing regimens of JNJ-77242113 selected for this Phase 2b study are based on preclinical and clinical exposure-response modeling to maximize the likelihood of a positive study outcome and supported by human safety/tolerability data from the FIH study and the toxicology margins.

4.4. End of Study Definition

End of Study Definition

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

Study Completion Definition

Participants who enroll in the LTE will be considered to have completed the study if they complete all scheduled study interventions through Week 16. Participants who do not enroll in the LTE will be considered to have completed the study if they complete all assessments at the safety follow-up visit (ie, Week 20).

5. STUDY POPULATION

Screening for eligible participants will be performed up to 28 days before randomization. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

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.

For a discussion of the statistical considerations of participant selection, refer to Section 9.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. Be ≥18 (or the legal age of consent if it is higher in the jurisdiction in which the study is taking place) years of age, inclusive.

Type of Participant and Disease Characteristic

2. Criterion modified per Amendment 1

   2.1 Has a diagnosis of plaque psoriasis, with or without PsA, for at least 6 months prior to the first administration of study intervention.

3. Has a total BSA ≥10% at screening and baseline.

4. Has a total PASI ≥12 at screening and baseline.

5. Has a total IGA ≥3 at screening and baseline.

6. Be a candidate for phototherapy or systemic treatment for plaque psoriasis.

7. Must agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet (UV) light sources during the study.

8. Otherwise healthy on the basis of physical examination, medical history, and vital signs, and 12-lead triplicate electrocardiogram (ECG) performed at screening. Any abnormalities, must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.

Sex and Contraceptive/Barrier Requirements

9. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine pregnancy test at Week 0 prior to administration of study intervention.

10. Before randomization, a woman must be either:

    a. Not of childbearing potential (Section 10.8).

b. Of childbearing potential and

- Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) prior to receiving study intervention, during the study, and for at least 12 weeks after receiving the last administration of study intervention, consistent with local regulations regarding the use of birth control methods for participants participating in clinical studies. Examples of highly effective methods of contraception are located in Section 10.8.
- The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.

Note: If a female participant's childbearing potential changes after start of the study (eg, a woman who is not heterosexually active becomes active, a premenarchal woman experiences menarche), she must begin practicing a highly effective method of birth control, as described above.

11. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for at least 12 weeks after receiving the last administration of study intervention.

12. A male participant who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale), during the study and for at least 12 weeks after receiving the last administration of study intervention. Male participants should also be advised of the benefit for female partner to use a highly effective method of contraceptive as condoms may break or leak.

13. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for at least 12 weeks after receiving the last administration of study intervention.

Screening Laboratory Test Parameters

14. Have screening laboratory test results within the following parameters. If one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:

a. Hemoglobin ≥10 g/dL (SI: ≥100 g/L)

b. White blood cells ≥3.5 x 10^3/µL (SI: ≥3.5 GI/L)

c. Neutrophils ≥1.5 x 10^3/µL (SI: ≥1.5 GI/L)

d. Platelets ≥100 x 10^3/µL (SI: ≥100 GI/L)

e. Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2

f. Aspartate aminotransferase ≤2 × upper limit of normal (ULN)

g. Alanine aminotransferase ≤2 × ULN

h. Alkaline phosphatase ≤2 × ULN

Vaccination

15. Agree not to receive a live virus or live bacterial vaccination during the study, or within 4 weeks after the last administration of study intervention.

General

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

17. Must sign a separate ICF(s) if he or she agrees to provide optional deoxyribonucleic acid (DNA) and/or biomarkers samples and/or photographs for research (where local regulations permit). Refusal to give consent for the optional DNA and/or biomarker samples and/or photographs does not exclude a participant from participation in the study.

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

5.2. Exclusion Criteria

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

Disease Characteristics

1. Has a nonplaque form of psoriasis (eg, erythrodermic, guttate, or pustular).

2. Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).

Prior/Concomitant Therapy

3. Has previously received any other therapeutic agent directly targeted to IL-23 (including but not limited to guselkumab, tildrakizumab, or risankizumab).

4. Has received any therapeutic agent directly targeted to IL-17 or IL-12/23 (including but not limited to secukinumab, ixekizumab, brodalumab, or ustekinumab) or has received anti-TNFα biologic therapy (including, but not limited to adalimumab) within 12 weeks or 5 half-lives, whichever is longer, of the first administration of study intervention.

5. Criterion modified per Amendment 2

   Has received agents that deplete B cells (including, but not limited to, rituximab, or alemtuzumab) within 26 weeks of the first administration of study intervention.

6. Has received natalizumab, belimumab, or agents that modulate T cells (including, but not limited to abatacept or visilizumab) 12 weeks or 5 half-lives, whichever is longer, of the first administration of study intervention.

7. Has received JAK inhibitor therapy within 4 weeks of the first administration of study intervention.

8. Has received phosphodiesterase 4 (PDE4) inhibitor therapy (including but not limited to apremilast) within 4 weeks of the first administration of study intervention.

9. Has received any systemic immunosuppressants (including, but not limited to, methotrexate [MTX], azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, and tacrolimus) within 4 weeks of the first administration of study intervention.

10. Has received, or is expected to receive, any live virus or bacterial vaccination within 12 weeks before the first administration of study intervention. For exclusions related to the bacille Calmette Guerin (BCG) vaccine, see Exclusion 11.

11. Has received the BCG vaccine within 12 months of the first administration of study intervention.

12. Has received phototherapy or any systemic medications that could affect psoriasis or the PASI or IGA evaluations (including, but not limited to, oral or injectable corticosteroids, acitretin, retinoids, 1,25-dihydroxy vitamin D3 and analogues, herbal treatments or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks of the first administration of study intervention.

13. Has received topical therapies that could affect psoriasis or the PASI or IGA evaluation (including, but not limited to corticosteroids, tar, anthralin, calcipotriene, tazarotene, methoxsalen, pimecrolimus, tacrolimus, and traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks of the first administration of study intervention.

Prior/Concurrent Clinical Study Experience

14. Has received an experimental antibody or biologic therapy within 12 weeks or 5 half-lives of the first administration of study intervention or received any other experimental therapy or new investigational agent within 4 weeks or 5 half-lives (whichever is longer) of the first study intervention administration or is currently enrolled in another study using an investigational agent, device, or procedure.

Medical Conditions

15. Has a current diagnosis or signs or symptoms of severe, progressive, or uncontrolled renal, liver, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances.

16. Known allergies, hypersensitivity, or intolerance to JNJ-77242113 or its excipients (refer to the JNJ-77242113 IB).

17. Has had major surgery within 8 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.

18. Has a transplanted organ (with exception of a corneal transplant >3 months before the first administration of study intervention).

19. Has suicidal ideation or suicidal behavior in the last 6 months that may be defined as a Columbia-Suicide Severity Rating Scale (C-SSRS) rating at screening of: Suicidal Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt), and is considered to be at risk by the investigator based on an evaluation by a mental health professional. In addition, participants with C-SSRS ratings of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act ("Ideation level 3") or non-suicidal self-injurious behavior who are determined to be at risk by the investigator may not be randomized.

Infections or Predisposition to Infections

20. Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.

21. Has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

22. Has had a serious infection (eg, sepsis, pneumonia, or pyelonephritis), or has been hospitalized or received IV antibiotics for an infection during the 2 months before screening.

23. Has or has had herpes zoster within the 2 months before screening.

24. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Exclusion Criterion 32 for information regarding eligibility with a history of latent TB.

25. Has a chest radiograph within 3 months before the first administration of study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB.

26. Has ever had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystis, or aspergillosis).

27. Tests positive for hepatitis B virus (HBV) infection (Section 10.10) or who are seropositive for antibodies to hepatitis C virus (HCV) at screening.

28. Has a history of human immunodeficiency virus (HIV) antibody positive or tests positive for HIV at screening.

29. Criteria modified per Amendment 2.

    29.1 COVID-19 Infection:

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

    - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test:
      (i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, [eg, fever, cough, or dyspnea])

      AND

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

    NOTE on COVID-related exclusion:

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

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

Malignancy or Increased Potential for Malignancy

30. Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a non-melanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study intervention administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study intervention administration).

31. Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as splenomegaly or significant lymphadenopathy.

Tuberculosis

32. Meet **ANY** of the following tuberculosis (TB) screening criteria.

    Note: Interferon gamma release assay (IGRA) testing includes either QuantiFERON-TB® or T-SPOT®TB.

    a. Have a history of active TB or show signs or symptoms suggestive of active TB upon medical history and/or physical examination at screening.

    b. Have a history of untreated latent TB prior to screening. An exception is made for participants who are currently receiving treatment or will initiate treatment for latent TB prior to first administration of study intervention.
    Note: For participants with a history of treated latent TB there must be documentation of appropriate treatment prior to the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation. IGRA testing is not required at screening for participants with a history of treated latent TB or ongoing treatment for latent TB.

    c. Have had recent close contact with a person with active TB. An exception is made if such participants are referred to a physician specializing in TB to determine if treatment is warranted or not. This evaluation must be adequately documented and, if treatment is recommended, the participant must be receiving appropriate treatment prior to the first administration of study intervention.

    d. Have a positive IGRA test result within 2 months prior to the first administration of study intervention. An exception is made for participants who:

- have a history of adequately treated latent TB described above.
- have a newly identified positive IGRA test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study intervention.
- have a false-positive IGRA test as determined by the following:
    - A suspected false-positive initial IGRA test must be repeated. If repeat testing is **NOT** positive, the participant must be referred to a physician specializing in TB to determine if the initial test can be considered a false-positive. This evaluation must be adequately documented prior to the first administration of study intervention. If repeat testing is positive, however, it will be considered a true-positive and the participant is only eligible if active TB has been ruled out and appropriate treatment for latent TB has been initiated as described above.

Note: Indeterminate/borderline results should be handled as outlined in Section 8.2.8.

e. Have a chest radiograph or chest computed tomography within 3 months prior to the first administration of study intervention that shows abnormalities suggestive of active or inactive TB.

Other Exclusions

33. Is an 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.

34. Is pregnant, nursing, or planning a pregnancy (both men and women) while enrolled in the study or within 12 weeks following the last dose of study intervention.

35. Has a history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria within 12 months before screening.

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

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. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3.10.

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 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

   It is recommended to be up to date on all age-appropriate vaccinations prior to screening as per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (or emergency use-authorized) COVID-19 vaccination regimen at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labelling, guidelines, and standards-of-care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (Section 6.8).

2. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (Inclusion Criterion 10) during the study and for at least 12 weeks after receiving the last administration of study intervention.

3. A woman must agree not to donate eggs (ova, oocytes; Inclusion Criterion 11) during the study and for a period of at least 12 weeks following the last administration of study intervention.

4. A man who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control (Inclusion Criterion 12) during the study and for at least 12 weeks after receiving the last administration of study intervention.

5. A man must agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of study intervention (Inclusion Criterion 13).

6. Agree to use sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen), limit prolonged exposure to natural sunlight, and avoid artificial sunlight (tanning beds or phototherapy) during the study.

7. Agree to remove nail polish and/or artificial nails prior to or at all visits where nail psoriasis is assessed.

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

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 age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Retesting

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening phase, as long as this is done within the specified screening window of up to 4 weeks. In such cases, the first abnormal test result will not constitute a screen failure. If a laboratory abnormality occurs, the site is encouraged to wait for all laboratory tests to be completed to ensure other laboratory tests do not need to be repeated, as only 1 retest of laboratory tests is allowed. A screening laboratory test(s) analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the screening period.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then start a new screening phase. Waivers to eligibility criteria are not permitted. Previous TB evaluation results (including IGRA testing and chest radiograph) from the first screening event may be used if they meet the specified protocol criteria as described in Sections 5.1 and 5.2. Medical Monitor approval is required prior to the study site obtaining a new informed consent for rescreening. The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the study.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Study site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

JNJ-77242113 will be manufactured and provided under the responsibility of the sponsor. Refer to the JNJ-77242113 IB for a list of excipients.

For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

6.1. Study Interventions Administered

Group/Arm Name	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Intervention Name	JNJ-77242113	JNJ-77242113	JNJ-77242113	JNJ-77242113	JNJ-77242113	Placebo
Dose Formulation	Yellow colored, film-coated tablets	Yellow colored, film-coated tablets	Yellow colored, film-coated tablets	Yellow colored, film-coated tablets	Yellow colored, film-coated tablets	Yellow colored, film-coated tablets
Unit Dose Strength(s)	25 mg	25mg	100mg	25mg	100mg	N/A
Dosage Level(s) and Frequency	25 mg QD (AM) and placebo (PM)	50mg QD (AM) and placebo (PM)	100mg QD (AM) and placebo (PM)	25mg BID (AM and PM)	100mg BID (AM and PM)	Placebo (AM) and (PM)
Route of Administration	☒ Oral	☒ Oral	☒ Oral	☒ Oral	☒ Oral	☒ Oral
Dosing instructions	Participants should take study intervention in the morning (AM) and in the evening (PM) on an empty stomach with approximately 240 mL of noncarbonated water. An empty stomach is defined as abstaining from food intake for at least 2 hours before taking the study intervention and abstaining from food and liquid intake for at least 30 minutes after taking the study intervention. Placebo will be administered to maintain the blind.	Participants should take study intervention in the morning (AM) and in the evening (PM) on an empty stomach with approximately 240 mL of noncarbonated water. An empty stomach is defined as abstaining from food intake for at least 2 hours before taking the study intervention and abstaining from food and liquid intake for at least 30 minutes after taking the study intervention. Placebo will be administered to maintain the blind.	Participants should take study intervention in the morning (AM) and in the evening (PM) on an empty stomach with approximately 240 mL of noncarbonated water. An empty stomach is defined as abstaining from food intake for at least 2 hours before taking the study intervention and abstaining from food and liquid intake for at least 30 minutes after taking the study intervention. Placebo will be administered to maintain the blind.	Participants should take study intervention in the morning (AM) and in the evening (PM) on an empty stomach with approximately 240 mL of noncarbonated water. An empty stomach is defined as abstaining from food intake for at least 2 hours before taking the study intervention and abstaining from food and liquid intake for at least 30 minutes after taking the study intervention. Placebo will be administered to maintain the blind.	Participants should take study intervention in the morning (AM) and in the evening (PM) on an empty stomach with approximately 240 mL of noncarbonated water. An empty stomach is defined as abstaining from food intake for at least 2 hours before taking the study intervention and abstaining from food and liquid intake for at least 30 minutes after taking the study intervention. Placebo will be administered to maintain the blind.	Participants should take study intervention in the morning (AM) and in the evening (PM) on an empty stomach with approximately 240 mL of noncarbonated water. An empty stomach is defined as abstaining from food intake for at least 2 hours before taking the study intervention and abstaining from food and liquid intake for at least 30 minutes after taking the study intervention.

Group/Arm Name	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Use	☒ Experimental	☒ Experimental	☒ Experimental	☒ Experimental	☒ Experimental	☒ Placebo
Investigational Medicinal Product (IMP)	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No
Non-Investigational Medicinal Product (NIMP)	☐ Yes ☒ No	☐ Yes ☒ No	☐ Yes ☒ No	☐ Yes ☒ No	☐ Yes ☒ No	☐ Yes ☒ No

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

The study intervention may be delivered directly to the participants from the site by a courier. Each courier will adhere to privacy requirements approved by the IEC/IRB. The capability to utilize these direct-to-patient shipments will be assessed by the sponsor to ensure that it is allowable per local regulations.

All study intervention must be stored at controlled temperatures ranging from 2°C to 8°C. Study site personnel will instruct participants on how to store and administer study intervention for at-home use as indicated in this protocol.

Refer to the Site Investigational Product 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 containers, whether empty or containing study intervention.

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

Potentially hazardous materials should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

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. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Dynamic central randomization will be implemented in conducting this study. Participants will be assigned to 1 of 6 intervention groups based on an algorithm implemented in the interactive web response system (IWRS) before the study. Dynamic central randomization minimizes the imbalance in the distribution of the number of participants across intervention groups within the levels of each individual stratification factor: study site and baseline weight (≤90 kg, >90 kg). In addition, the Japanese sites will be pooled in the randomization process to better ensure treatment balance across Japanese participants. Based on the algorithm, the IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the interactive web response system (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 (ie, study intervention plasma concentrations, anti-JNJ-77242113 antibodies, study intervention preparation/accountability data, intervention allocation, and biomarker data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may, in an emergency, determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the 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 by the IWRS 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 intervention assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed, and the clinical database is closed. However, for the interim analyses (Section 9.5), the randomization codes and, if required, the translation of randomization codes into intervention and control groups

will be disclosed to those authorized (ie, internal independent IAC) and only for those participants included in the interim analysis.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit during the treatment period by counting returned tablets.

A participant will be considered noncompliant if he or she misses more than 20% of the prescribed doses of study intervention during the study, unless study intervention is withheld for safety reasons. Similarly, a participant will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken 20% or more than prescribed amount of study intervention during the study.

If a participant's study intervention intake is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol. If necessary, the participant maybe discontinued from study intervention by the investigator or medical monitor (Section 7).

Study intervention compliance will be further detailed in the statistical analysis plan (SAP).

6.5. Dose Modification

Dose modifications will not be applicable to this study.

6.6. Continued Access to Study Intervention After the End of the Study

Participants will be instructed that study intervention will not be made available to them after they have discontinued study intervention for any reason outlined in Section 7.1 and that they should return to their primary physician to determine standard of care.

At the end of study treatment (Week 16), participants who meet all eligibility requirements outlined in the LTE protocol, (77242113PSO2002), will be offered the opportunity to enter the 36-week treatment LTE study. Further details about the LTE study design will be outlined in a separate protocol (772424113PSO2002).

6.7. Treatment of Overdose

For this study, any dose of JNJ-77242113 greater than the highest dose at a single day will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

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

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

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.

- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted.
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).

6.8. Concomitant Therapy

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study. Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study intervention to 4 weeks after the last dose of study intervention.

All therapies (prescription or over-the-counter medications) different from the study intervention must be recorded in the eCRF. Every effort should be made to keep participants on stable concomitant medications. If a medication is temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a procedure, the change and reason for it should be clearly documented in the participant's medical records.

Any questions regarding treatment with concomitant medication during the study should be directed to the medical monitor.

Prohibited Therapy

All experimental therapies or new investigational interventions (except for JNJ-77242113), including therapies for psoriasis or other conditions, must be discontinued prior to the first administration of study intervention per Exclusion Criteria (Section 5.2) and remain prohibited during the study. For guidance regarding the COVID-19 vaccine see Section 6.8.1.

If a prohibited therapy is administered during the active treatment phase (ie, Week 0 to Week 16), the medical monitor should be notified, and the participant may be required to discontinue from the study treatment per medical monitor's discretion. If a prohibited therapy is initiated during the safety follow-up period, the participant should still complete his or her final study visit, and the medication should be recorded as a concomitant medication.

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

Psoriasis Concomitant Medications

Topical Therapy

Topical therapies that could affect psoriasis or the PASI/IGA evaluation (eg, corticosteroids, tar, anthralin, calcipotriene, tazarotene, methoxsalen, pimecrolimus, tacrolimus, and traditional Taiwanese, Korean, or Chinese medicines) are not permitted during the study. The only allowable concomitant treatments throughout the study are shampoos (containing salicylic acid only) and

topical moisturizers. Participants should not use these topical agents (shampoos and moisturizers) the day of a study visit. Nonmedicated shampoos may be used on the day of the study visit.

Phototherapy or Systemic Therapy

The use of phototherapy or systemic medications that could affect psoriasis or the PASI/IGA evaluation is not permitted at any time during the study. These medications include, but are not limited to, those targeted for reducing TNF (including but not limited to infliximab or etanercept), drugs targeted for reducing IL-12/23, IL-17, or IL-23 (including but not limited to ustekinumab, guselkumab, tildrakizumab [MK3222], secukinumab, risankizumab [BI-655066], ixekizumab [LY2439821], or brodalumab [AMG827]), alpha-4 integrin antagonists (including but not limited to natalizumab), JAK inhibitors (including but not limited to tyrosine kinase 2 inhibitors), phosphodiesterase 4 (PDE4) inhibitors (including but not limited to apremilast), oral and injectable (IV, intramuscular, or intralesional) corticosteroids, any other conventional systemic therapies that could affect psoriasis or the PASI/IGA evaluation (including but not limited to methotrexate, cyclosporine, acitretin, or other retinoids), 1,25-dihydroxy vitamin D3 and analogues, antimalarial agents, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines, and any other biological agent or other systemic medication that could affect psoriasis or the PASI/IGA evaluation.

The use of systemic corticosteroids for indications other than psoriasis should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for ≤2 weeks. Longer term use of corticosteroids should be discussed with the medical monitor or designee and may require discontinuation of study intervention. Inhaled, otic, ocular, nasal, or other routes of mucosal delivery of corticosteroids are allowed throughout the study.

6.8.1. Vaccinations (including COVID-19)

Live attenuated vaccines are prohibited for the duration of study participation.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.

- The participant meets the Sampson criteria for anaphylaxis (Sampson 2006) following study intervention administration (Section 10.12).
- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an administration of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- The participant becomes pregnant or plans a pregnancy during the study period. Refer to Section 10.8.
- The initiation of protocol-prohibited medications, treatments, or interventions (outlined in Section 6.8) that have an impact on psoriasis efficacy evaluations at the discretion of the medical monitor.
- The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allow participants, who develop ≤2 basal cell skin cancers and who are adequately treated with no evidence of residual disease, to continue to receive study intervention.
- The participant develops a systemic opportunistic infection during the study period.
- The participant develops a recurrent or chronic serious infection during the study period.
- The participant meets **ANY** of the following TB related conditions:
  - A diagnosis of active TB is made.
  - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.
  - A participant undergoing evaluation has chest imaging with evidence of current active TB and/or a positive IGRA test result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study intervention and continued to completion. Indeterminate/borderline results should be handled as outlined in Section 8.2.8.
  - A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy
- The participant is unable to adhere to the study visit schedule or comply with protocol requirements.
- The participant has a possible Hy's Law case, as defined by the occurrence of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3xULN, together with total bilirubin ≥2xULN or International Normalized Ratio (INR) >1.5 (if measured) without an identifiable cause (Section 10.9).
- The participant has his/her treatment assignment unblinded by the investigator.
- Sponsor decision.

Discontinuation of a participant's study intervention should be considered for participants with any type of suicidal ideation or behavior, or any self-injurious behavior, who are deemed to be at risk by the investigator. Discussion of such participants with the medical monitor or designee is required.

For participants who report Suicidal Ideation with Intention to Act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) or any self-injurious behavior on a post-baseline C-SSRS assessment, the investigator risk assessment must be based upon evaluation by a mental health professional (Section 10.7).

Participants who decide to discontinue study intervention administration for reasons other than those outlined above must be interviewed by the investigator to determine if a specific reason for discontinuing study intervention can be identified. Participants should be explicitly asked about the possible contribution of AEs to their decision to discontinue study intervention; investigators should confirm that any AE information elicited has been documented. If a participant elects to discontinue study intervention due to an AE, the event should be recorded as the reason for study intervention discontinuation, even if the investigator's assessment is that the AE would not require study intervention discontinuation. The reason for study intervention discontinuation must be documented in the eCRF and in source documents. Study intervention assigned to a participant who discontinues may not be assigned to another participant.

A participant will not be automatically withdrawn from the study if he or she must discontinue treatment before the end of the treatment regimen. Participants who discontinue study intervention but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 4 weeks following the last administration of study intervention. The procedures and evaluations listed for the Early Termination Visit should also be performed approximately 4 weeks after the last administration of study intervention.

All procedures and evaluations must be conducted prior to a participant's withdrawal of consent.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- The participant is not in compliance with requirements of the study, including prohibitions and restrictions
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF 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 (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research sample:

- The collected sample will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research sample, in which case the sample will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research sample will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3.5, 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 and in the separate ICF for optional research samples.

7.3. 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, eg, 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 he or she 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, 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). Locator agencies may also be used as local regulations permit. 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.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, pharmacogenomic, and safety measurements applicable to this study. It is strongly recommended that the same investigator perform the efficacy assessments at every visit.

Participants will be provided with an electronic device to enter patient-reported outcome (PRO) data at each study visit. Study-site personnel will train participants on how to use the electronic device (ePRO).

All visit-specific PRO assessments should be conducted/completed before any tests, procedures or other clinical assessments, with the exception of the urine pregnancy test and urinalysis, to prevent influencing participant perceptions. Refer to the site manual for instructions on the administration of PROs.

Electrocardiograms (ECGs) should precede vital signs and both procedures should be completed prior to any invasive procedures. Vital signs should be recorded from the opposite arm from which blood samples are being taken.

All samples (including safety, efficacy, PK, and biomarkers) must be obtained after the PRO and ECG assessments. Blood collections for PK and biomarker assessments should be kept as close to the specified time as possible. Actual dates of all assessments and blood collections will be recorded in the source documentation; in addition, times of all blood collections will be recorded in the source documentation (laboratory requisition form).

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. Results of all pregnancy testing should be documented in the participants' source documents.

Guidelines for handling of assessments affected by the COVID-19 pandemic are found in Section 10.11.

Blood Sample Collection

The total blood volume to be collected from each participant through Week 16 of the study will be approximately 215 mL. An additional ~6 mL blood volume will be collected at the safety follow-up visit for those participants who do not enter the LTE (total ~221 mL). In addition, repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples. Total blood volume may vary slightly per region.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Schedule of Activities (Section 1.3) for the timing and frequency of all sample collections.

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:

- Protocol
- Investigator's Brochure for JNJ-77242113
- Site Investigational Product Procedures Manual
- Laboratory manual
- Laboratory Kits
- IWRS Manual
- Sample eCRF
- eCRF Completion Guidelines
- ePRO equipment (tablet device questionnaires, completion instructions)
- Participant Study Participation Card
- Investigative Site File
- Recruitment materials, as needed
- Digital photographic equipment and instruction manual, as needed

8.1. Efficacy Assessments

Investigator assessments and PROs of efficacy are included in this section.

- The 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.
- The PRO and AE data will not be reconciled with one another.

8.1.1. Psoriasis Area and Severity Index (PASI)

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy (Section 10.4; Fredriksson, 1978). In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed and scored separately for erythema, induration, and scaling, which are each rated on a scale of 0 to 4 and extent of involvement on a scale of 0 to 6. The PASI produces a numeric score that can range from 0 to 72. A higher score indicates more severe disease.

8.1.2. Body Surface Area (BSA)

Body Surface Area is a commonly used measure of severity of skin disease. It is defined as the percentage of surface area of the body involved with the condition being assessed, (ie, plaque psoriasis). The handprint method for assessing BSA will be used in this study, where the surface area of the patient's hand including the palm and all five digits is used as a guide to estimate 1% BSA (Long 1992; Rossiter 1996; Thomas 2007).

8.1.3. Investigator's Global Assessment (IGA)

The IGA documents the investigator's assessment of the participant's psoriasis at a given time point. Overall lesions are graded for induration, erythema, and scaling. The participant's psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4).

8.1.4. Nail Psoriasis Area and Severity Index (NAPSI)

The NAPSI is an index used for assessing and grading the severity of nail psoriasis (Rich, 2003). Each of the participant's 20 nails (fingernails and toenails) is divided into quadrants and is assessed for any presence of nail psoriasis in the nail matrix (pitting, leukonychia, red spots in the lunula, and nail plate crumbling) and any presence of nail psoriasis in the nail bed (onycholysis, splinter hemorrhages, oil drop discoloration, and nail bed hyperkeratosis). Both the nail matrix (score 0-4) and nail bed (score 0-4) scores equal the number of quadrants affected by nail/nailbed psoriasis. The total individual nail score is the sum of the nail matrix and nail bed score and ranges from 0 to 8. The sum of all 20 individual nail scores is the total NAPSI score (0 to 160).

8.1.5. Fingernail Physician's Global Assessment (f-PGA)

The f-PGA is used to evaluate the current status of a participant's fingernail psoriasis on a scale of 0 to 4 similar to the IGA (clear [0], minimal [1], mild [2], moderate [3], or severe [4]).

8.1.6. Static Physician's Global Assessment of Genitalia (s-PGA-G)

The s-PGA-G is a 6-point numerical rating scale to assess the severity of genital psoriasis at a given time point (Merola 2017). The s-PGA-G evaluates erythema, plaque elevation and scale of genital psoriatic lesions. The severity of genital psoriasis is assessed as clear [0], minimal [1], mild [2], moderate [3], severe [4], and very severe [5].

8.1.7. Physician's Global Assessment of Hands and/or Feet (hf-PGA)

The severity of hand and foot psoriasis has been assessed in various clinical studies using an hf-PGA instrument (Leonardi 2011; Goldblum 2013). The plaques on the hands and feet are scored on a 5-point scale as: clear [0], almost clear [1], mild [2], moderate [3], and severe [4].

8.1.8. Scalp Specific Investigator Global Assessment (ss-IGA)

The ss-IGA instrument is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed in terms of the clinical signs of redness, thickness, and scaliness which are scored as: absence of disease (0), very mild disease (1), mild disease (2), moderate disease (3), and severe disease (4).

8.1.9. Psoriasis Symptom and Sign Diary (PSSD)

The PSSD includes PRO questionnaires designed to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefit (Feldman 2016). This study will use a 7-day recall version of the PSSD that asks the participant to answer the questions thinking about the last 7 days. The PSSD is a self-administered PRO instrument and includes 11 items covering symptoms (itch, pain, stinging, burning, and skin tightness) and patient-observable signs (skin dryness, cracking, scaling, shedding or flaking, redness, and bleeding) using 0 to 10 numerical rating scales for severity. Two subscores will be derived each ranging from 0 to 100: the psoriasis symptom score and the psoriasis sign score. A higher score indicates more severe disease.

8.1.10. Dermatological Life Quality Index (DLQI)

The DLQI is a dermatology-specific health-related quality of life (HRQoL) instrument designed to assess the impact of the disease on a participant's HRQoL (Finlay 1994). It is a 10-item questionnaire that assesses HRQoL over the past week and in addition to evaluating overall HRQoL, can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The total score ranges from 0 to 30 with a higher score indicating greater impact on HRQoL.

8.1.11. Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29)

The PROMIS-29 is a 29-item generic HRQoL survey, assessing each of the 7 PROMIS domains (depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities) with 4 questions. The questions are ranked on a 5-point Likert Scale. There is also one 11-point rating scale for pain intensity (Cella 2010).

8.1.12. Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ)

The GenPs-SFQ is a 2-item patient reported survey used to assess the impact of genital psoriasis on the frequency of sexual activity in the last 7-days; Gottlieb 2018). Item 1 assesses overall frequency of sexual activity in the last 7-days (none/zero, once, or two or more times) and item 2 assesses how frequently genital psoriasis symptoms have limited the frequency of sexual activity in the last 7-days (never [0], rarely [1], sometimes [2], often [3], or always [4]).

8.1.13. Patient Global Impression- Severity (PGI-S) and Change (PGI-C)

Interpreting meaningful change in scores on PRO instruments is an important step in evaluating results and is included in FDA guidelines (FDA Guidance 3). The methods for interpreting meaningful change have evolved over time and various approaches exist. Anchor-based methods are often preferred. Anchor-based methods link scores on the PRO to an external criterion that identifies participants who have experienced an important change in their condition. The PGI-S and PGI-C will be used as anchors, external criteria, to determine meaningful change in scores for other PROs in this population. The PGI-S contains 1 question on how the participant would currently rate severity of disease in the past 7 days, with responses ranging from 1=”None” to 5=”Very severe.” The PGI-C contains 1 question on how the participant would rate the change from their first treatment in this study. The response options are presented on a 7-point scale from 1="A lot better now” to 7="A lot worse now.”

8.1.14. Treatment Satisfaction Questionnaire for Medications (TSQM-9 domains)

The abbreviated 9-item TQSM-9 includes 3 treatment satisfaction domains: effectiveness, convenience, and global satisfaction. Positive changes in domain scores (0 to 100) indicate improvement. The questions are ranked on a 5-point or 7-point Likert Scale (Bharmal 2009).

8.1.15. Photographs

Efforts to standardize efficacy assessments in inflammatory dermatologic conditions have been challenging, but the visual nature of many manifestations of dermatologic disease provides opportunity for photographic assessment of efficacy endpoints. In this substudy, photographs of either two lesional psoriasis areas or two lesional psoriasis areas and full body (front and back) will be taken. These photographs will be used to virtually assess psoriasis disease severity by comparing investigator reported PASI scores to PASI scores assessed by a central reader. See Section 10.5 for details regarding the assessment. Details of these analyses will be provided in a separate sub-study SAP. See site manual for photography instructions.

8.2. Safety Assessments

Details regarding the Independent Data Monitoring Committee are provided in Section 10.3.6.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Section 10.6.

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 if possible.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

Physical Examination

Physical examinations will be performed by the investigator or designated physician, nurse practitioner or physician assistant as specified in the SoA (Section 1.3). A full physical examination will be completed at Screening, Week 16, and either the final safety visit or early termination visit. A targeted physical examination will be completed at all other visits as specified in the SoA. Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

Height and Weight

Height and weight will be measured as specified in the SoA (Section 1.3). Participants will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

8.2.2. Vital Signs

Vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained at visits specified in the SoA (Section 1.3).

8.2.3. Electrocardiograms

A triplicate 12-lead ECG will be performed during screening to serve as a baseline reference for comparison, should a subsequent cardiovascular related safety event occur. The 3 individual ECG tracings should be obtained as closely as possible in succession about 2 minutes apart. The full set of triplicates should be completed in about 5 minutes. Additional 12-lead triplicate ECGs will be performed at visits specified in the SoA (Section 1.3). Details regarding collection of ECGs are available in the site manual.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and urine samples for urinalysis will be collected as noted in Section 10.2. 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 eCRF. The laboratory reports must be filed with the source documents.

The tests that will be performed by the central laboratory unless otherwise specified in the study manual or approved by the medical monitor are specified in Section 10.2.

8.2.5. Concomitant Medication

Concomitant medications will be reviewed at each visit and recorded in the source documents and eCRF.

8.2.6. Pregnancy Testing

Pregnancy testing (serum and urine) is planned at times indicated in the SoA (Section 1.3).

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.

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

The C-SSRS defines 5 subtypes of suicidal ideation and 4 possible suicidal behaviors, as well as non-suicidal self-injurious behavior and completed suicide. It will be used as a screening tool to prospectively evaluate suicidal ideation and behavior in this study, as part of a comprehensive evaluation of safety. The C-SSRS is an investigator-administered questionnaire and will be conducted on the electronic clinical outcomes assessment (eCOA) device provided to the site.

Two versions of it will be used in this study: the 'Baseline/Screening' version of the C-SSRS (Section 10.7) will be conducted during the screening visit and the 'Since Last Visit' version of the C-SSRS ([Section 10.7) will be completed at Week 0 and all other visits through the end of the study.

The investigator or trained study-site personnel will interview the participant in a private place and complete the C-SSRS on the eCOA device. At the conclusion of each assessment, the trained personnel administering the C-SSRS will determine the level of suicidal ideation or behavior, if any. They will then determine the next course of action if any level of suicidal ideation or behavior is reported. The participant should not be released from the site until the C-SSRS has been reviewed by the investigator and the participant's risk has been assessed and follow-up determined, as appropriate.

At screening (within the last 6 months) and Week 0, participants with a C-SSRS rating of Suicidal Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt), must be determined to not be at risk by the investigator based on an evaluation by a mental health professional (eg, psychiatrist, psychologist, or appropriately trained social worker or nurse) in order to be randomized. Participants with C-SSRS ratings of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act ("Ideation level 3") or non-suicidal self-injurious behavior must be determined not to be at risk by the investigator in order to be randomized. Any questions regarding eligibility of such participants should be discussed with the medical monitor or designee.

For each assessment after Week 0, the following actions should be taken, if applicable:

- No suicidal ideation or behaviors (including self-injurious behavior without suicidal intent): No further action is needed.

- Suicidal ideation levels 1-3 or non-suicidal self-injurious behavior: Participant risk is assessed by the investigator.

- Suicidal ideation levels 4 or 5 or any suicidal behavior: Participant risk assessed and referral to a mental health professional.

Interruption or the discontinuation of study intervention should be considered for any participant who reports Suicidal Ideation with Intention to Act ("Ideation level 4"), Suicidal Ideation with Specific Plan and Intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline C-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. If a participant can be adequately treated with psychotherapy and/or pharmacotherapy then the participant, at the discretion of the investigator, may be continued with treatment if agreed to by the medical monitor or designee. Discussion of such participants with the medical monitor or designee is required (Section 7.1).

Any C-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (Section 10.7).

8.2.8. Tuberculosis Evaluation(s)

Initial Tuberculosis Evaluation

Participant medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest imaging results and responses to tuberculin skin or other TB testing. Investigators have the option to use the tuberculin skin test in addition to IGRA testing to screen for latent TB if preferred by local health authorities, or if they believe based on their judgment that both tests are clinically indicated to evaluate a participant at high risk for latent TB.

Participants with a negative IGRA test result are eligible to continue with prerandomization procedures. Participants with a newly identified positive IGRA test result must undergo an evaluation for active or latent TB, or suspected false-positive initial testing, and initiate appropriate treatment if needed (Section 5.2). Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Participants with indeterminate/borderline IGRA test results should have the test repeated. Participants with persistently indeterminate/borderline IGRA test results may be randomized or continued in the trial without treatment for latent TB, if active TB is ruled out, chest imaging shows no abnormality suggestive of TB (active or inactive), and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the participant's source documents and initialed by the investigator.

Ongoing Tuberculosis Evaluation

To aid in the early detection of TB infection or exposure during study participation, participants must be evaluated for TB signs, symptoms, and close contacts at scheduled visits (refer to Section 1.3) or by telephone approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

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

If the evaluation raises suspicion for TB infection or the participant has had a close contact exposure to TB, study intervention must be withheld and an immediate and thorough investigation must be undertaken, including consultation with a physician specializing in TB to determine if treatment is warranted prior to any further study intervention. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol.

Note: Investigators should be aware that TB reactivation in immunocompromised participants may also present as extrapulmonary or disseminated disease.

8.3. 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 complaint (PQC), 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.

Adverse events 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. Collection of additional medical records may be requested by the medical monitor or the sponsor to support safety monitoring and reporting.

Further details on AEs, SAEs, and PQC can be found in Section 10.6.

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Any clinically relevant changes during the study must be recorded in the AE section of the eCRF.

Serious Adverse Events

All SAEs, as well as PQC, 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 4 weeks 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 SAE Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a 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.

8.3.2. 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.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.3.3. 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.

AEs, including pregnancy, will be followed by the investigator as specified in Section 10.6.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

8.3.5. 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 (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using a SAE reporting form. Any participant who becomes pregnant during the study must promptly discontinue further study intervention. Participants who are found to be pregnant in between study visits should immediately stop taking the study intervention and contact the investigator.

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

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

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

8.3.7. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and expedited communication (within 24 hours) by the investigator to the sponsor is warranted. The AESIs for JNJ-77242113 are, active TB, malignancy, and potential Hy's Law cases.

Any newly identified malignancy, case of active TB, or potential Hy's law case occurring after the first study intervention administration(s) must be reported by the investigator according to the procedures in Section 10.6). Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Pharmacokinetics

Plasma samples will be used to evaluate the PK of JNJ-77242113. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or

after the study period. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

Venous blood samples for determination of JNJ-77242113 plasma concentrations will be collected at the time points indicated in the SoA (Section 1.3). During the study, the nominal sample collection times may be changed by the sponsor with clear communication to the investigator, but the total blood volume will not exceed 450 mL every 8 weeks. The exact dates and times of blood sample collection must be recorded in the CRF or on the laboratory requisition form.

The laboratory manual contains further information regarding the collection, handling, labeling, and shipment of plasma samples.

8.4.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of JNJ-77242113 using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor. The sponsor, or its designee, under conditions in which the participants' identity remains blinded, will assay these samples.

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

Pharmacokinetic analysis will be performed by or under the responsibility of the sponsor.

Using the actual sampling times (see the SoA [Section 1.3]), if feasible, the following pharmacokinetic parameters will be estimated for JNJ-77242113 using a population PK approach:

C_{max}	Maximum observed plasma analyte concentration.
t_{max}	Actual sampling time to reach the maximum observed plasma analyte concentration.
AUC_{24h}	Area under the plasma analyte concentration-time curve from time 0 to 24 hours postdose, calculated by linear-linear trapezoidal summation.
AUC_{last}	Area under the plasma analyte concentration vs time curve from time 0 to time of the last measurable (non-below quantification limit [BQL]) concentration calculated by linear-linear trapezoidal summation.
AUC_{∞}	Area under the analyte concentration vs. time curve from time 0 to infinite time, calculated as $AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last observed measurable (non-BQL) plasma analyte concentration; extrapolations of more than 20.00% of the total AUC are reported as approximations.
$t_{1/2}$	Apparent elimination half-life calculated as $0.693/\lambda_z$
λ_z	Apparent terminal elimination rate constant, estimated by linear regression using the terminal log-linear phase of the log transformed concentration-time curve.

8.5. Genetics and Pharmacogenomics

Participation in pharmacogenomic research is optional. A pharmacogenomic (DNA) blood sample will be collected, preferably at baseline, from participants who consent separately to this component of the study to allow for pharmacogenomic research, where local regulations permit.

Genetic (DNA) variation may be an important contributory factor to interindividual variability in drug response and associated clinical outcomes. Genetic and epigenetic factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to an intervention.

The optional pharmacogenomic samples may be analyzed for identification of genetic and epigenetic factors that may be associated with the disease and/or the response to JNJ-77242113. This research may consist of the analysis of one or more candidate genes, or the analysis of genetic and epigenetic markers throughout the genome, or analysis of the entire genome (as appropriate) in relation to the disease and the treatments. Whole blood samples of approximately 6 mL will be collected for the genetic and pharmacogenomics analyses.

These analyses will be performed at the sponsor's discretion and may be reported separately.

8.6. Biomarkers

Biomarker assessments will be used to define and identify PD markers of therapeutic response to better understand the mechanism of action of JNJ-77242113 in participants with psoriasis, and aid in evaluating the drug exposure clinical response relationship, and the pathophysiology of psoriasis. This will include evaluation of relevant disease and pathway engagement biomarkers in skin, serum, whole blood and PBMCs. These assessments could also help explain inter-individual variability including differences between responders and non-responders to support patient stratification. Biomarker samples may also be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies as well as development of tests/ assays related to JNJ-77242113 and psoriasis.

Biomarker samples will be collected per the Schedule of Activities (Section 1.3). Instructions for collection and shipment of samples will be outlined in the Laboratory and Biopsy reference manuals and will include the following assessments.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis 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 is based on justification and intended utility of the data.

8.6.1. Ex vivo whole blood cytokine release assay

An optional ex vivo whole blood IL-23 induced cytokine release assay will be used to measure systemic PD activity from inhibition of IL-23 induced signaling as it relates to exposure to confirm systemic IL-23 pathway engagement with JNJ-77242113 in participants with psoriasis.

8.6.2. Serum Psoriasis Pharmacodynamic Changes

Inflammatory mediators relevant to the pathophysiology of psoriasis including but not limited to IL-22, IL-17A, IL-17F and beta-defensin-2 will be evaluated to assess the impact of JNJ-77242113 on inflammatory proteins in the serum.

8.6.3. Skin Psoriasis-Associated Gene Expression Changes

Total RNA will be extracted from lesional and non-lesional skin biopsies to assess impact of JNJ-77242113 on psoriasis-associated gene signatures and individual genes to better define the therapeutic response. Non-invasive tape strip sampling will be performed as an additional approach to characterize JNJ-77242113 driven skin transcriptional changes in participants with psoriasis.

8.6.4. Flow cytometric analysis

Peripheral blood mononuclear cells isolated from whole blood will be used to determine the impact of JNJ-77242113 on psoriasis-relevant immune cell subset distribution changes in the periphery.

8.7. Immunogenicity Assessments

Antibodies to JNJ-77242113 will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to JNJ-77242113 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to JNJ-77242113 and/or further characterize the immunogenicity of JNJ-77242113.

Serum samples will be used to evaluate the immunogenicity of anti-JNJ-77242113 antibodies. Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to JNJ-77242113 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to JNJ-77242113 will also be evaluated for corresponding JNJ-77242113 plasma concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored up to 15 years (or according to local regulations) following

the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to JNJ-77242113.

8.8. Medical Resource Utilization and 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.

9.1. Statistical Hypotheses

The hypothesis of this study is that there is a dose response relationship for JNJ-77242113 in the proportion of participants achieving a PASI 75 response at Week 16.

9.2. Sample Size Determination

This study is designed to enroll approximately 240 participants, in order to provide sufficient data to have adequate power to detect a JNJ-77242113 dose-response signal for the proportion of participants achieving PASI 75 at Week 16 using the Multiple Comparison Procedures with modeling techniques (MCP-Mod) method.

The sample size of 240 participants was also chosen in order to have sufficient power to detect a difference between the JNJ-77242113 groups and the placebo group for the primary endpoint of the proportion of participants achieving PASI 75 at Week 16.

The assumptions for the sample size and power calculations specified below were mainly based on the clinical data from the guselkumab Phase 2 and Phase 3 clinical studies that evaluated the safety and efficacy of guselkumab in the treatment of adult participants with moderate-to-severe plaque psoriasis.

The null hypothesis of no dose-response relationship is to be tested at an overall Type 1 error rate of 0.05 (2-sided). Assuming a PASI 75 response rate of 6% and 70% in the placebo and JNJ-77242113 highest dose groups, respectively, a sample size of approximately 40 participants in the placebo group and each of the JNJ-77242113 treatment groups will provide an average power of at least 90% to detect a dose-response signal across different candidate dose-response models (to be detailed in the SAP).

Furthermore, assuming PASI 75 response rates at Week 16 are 5% to 10% for placebo, 30% to 80% for the JNJ-77242113 dose groups, respectively, with 40 participants in each of the treatment groups, approximately 240 participants are planned to be randomized in equal ratio to the placebo and each of JNJ-77242113 dose groups (n=40/arm), this study provides:

- At least 90% power to detect a 35% treatment difference between the JNJ-77242113 treatment groups (n=40) and the placebo group (n=40) in the proportion of participants who achieve a PASI 75 response at Week 16 at a significant level of 0.05 (2-sided) based on a 2-sample Z-test.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

For the efficacy analyses in this study, the full analysis set (FAS) will be used according to the participants' assigned treatment to which they were randomized, regardless of the treatment they actually received. The FAS includes all randomized participants who receive at least 1 administration of study intervention. The FAS will be used for all primary and secondary efficacy analyses.

Safety analyses will include all randomized participants who received at least 1 administration of study intervention and participants will be analyzed based on the treatment they actually received, regardless of the treatment groups to which they were assigned. Pharmacokinetics analyses for JNJ-77242113 will include all randomized participants who receive at least 1 complete dose of JNJ-77242113 and have at least 1 valid blood sample drawn for PK analysis after their first dose of JNJ-77242113. Antibodies to JNJ-77242113 will be analyzed for all randomized participants who receive at least 1 dose of JNJ-77242113 and have at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113.

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who were randomized in the study
FAS	All randomized participants who take at least 1 dose of study intervention
Safety Analysis Set	All randomized participants who take at least 1 dose of study intervention.
PK Analysis Set	All randomized participants who received at least 1 complete dose of JNJ-77242113 and had at least 1 valid blood sample drawn for PK analysis after their first dose of JNJ-77242113
Immunogenicity Analysis Set	All randomized participants who received at least 1 dose of JNJ-77242113 and who had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113

9.4. Statistical Analyses

9.4.1. Statistical Methods

Simple descriptive summary statistics, such as n, mean, standard deviation (SD), median, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

To assess the primary objective of the dose response profile of JNJ-77242113 dose groups and facilitate the selection of JNJ-77242113 doses and dosing regimen for future studies, Multiple

Comparison Procedures with modeling (MCP-Mod) techniques will be used to analyze the primary endpoint, the proportion of participants achieving PASI 75 at Week 16.

In addition, for binary response efficacy endpoints, comparisons between each of the JNJ-77242113 groups versus placebo will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by the baseline weight (≤90 kg, >90 kg). For continuous efficacy endpoints, treatment comparisons will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model. The MMRM model will have treatment group, baseline weight (≤90 kg, >90 kg), and baseline value for the corresponding efficacy endpoint as explanatory factors. The MMRM model will also include visit, treatment group by visit interaction, baseline weight (≤90 kg, >90 kg) by visit interaction, and baseline value by visit interaction as additional explanatory factors. The Least Square mean (LSmean) estimates and their corresponding 95% confidence interval (CI) will be provided at each time point. In addition, the estimates of LSmean difference and 95% CIs between the JNJ-77242113 groups and placebo will be provided.

In general, all statistical testing will be performed at a significance level of 0.05 (2-sided) unless otherwise specified. Nominal p-values will be displayed for all treatment comparisons.

9.4.2. Efficacy Analyses

9.4.2.1. Primary Endpoint(s)

The primary efficacy endpoint is the proportion of participants achieving PASI 75 response at Week 16, defined as at least a 75% reduction from baseline in PASI total score.

9.4.2.1.1. Estimand

9.4.2.1.1.1. Primary Estimand

The primary estimand (ie, a precise definition of the primary targeted treatment effect) is defined by the following 5 attributes:

Study intervention:

- JNJ-77242113 25 mg QD, 50 mg QD, 25 mg BID, 100 mg QD, and 100 mg BID
- Placebo

Population: adult participants with moderate to severe plaque psoriasis

Variable/endpoint: Response binary variable, where a responder is defined as a participant achieving a PASI 75 response at Week 16 who does not have intercurrent events in categories 1-2 (defined below).

Intercurrent Events (ICEs) and their corresponding strategies

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Discontinuation of study intervention due to lack of efficacy or due to an AE of worsening of psoriasis	**Composite Strategy:** Participants with these intercurrent events are considered as PASI 75 non-responders after these events, and prior to Week 16. The occurrence of these intercurrent events is captured in the variable definition.

2. Initiation of a protocol-prohibited medication or therapy during the study that could improve psoriasis	
3. Discontinuation of study intervention for reasons other than ICE 1	**Treatment Policy:** observed data will be used regardless of whether or not this intercurrent event had occurred.

Note: For participants experiencing multiple ICEs, ICE 2 will override ICE 3.

Population level summary: Difference in the proportions of participants achieving a PASI 75 response at Week 16 between the JNJ-77242113 and placebo intervention groups.

Primary Endpoint Analysis

In the primary efficacy analysis, data from all randomized participants who received at least 1 administration of study intervention will be analyzed according to their assigned treatment group.

A unified strategy that combines MCP-Mod techniques, will be used to analyze the dose-response relationship for the JNJ-77242113 doses in PASI 75 at Week 16. This approach consists of 2 major steps. The first step consists of testing the dose-response signal via multiple contrast tests while controlling the overall Type 1 error. If a dose-response signal is detected, the second step is to select a model that best describes the observed data, which may be used to support dose selection in future studies. In addition, a simple semi-parametric Bayesian normal dynamic linear model (NDLM) will also be explored to complement the frequentist MCP-Mod analysis. The details of the dose-response analysis will be provided in the SAP.

The study will be considered positive if a dose-response signal for the primary endpoint is detected. In addition to the dose-response analysis, pairwise comparisons of the JNJ-77242113 groups versus the placebo group will be performed for PASI 75 at Week 16; these comparisons will not be adjusted for multiplicity. For these comparisons, a CMH stratified by baseline weight category (≤ 90kg, >90kg) will be used. The proportion difference between each JNJ-77242113 group and placebo group and its 2-sided 95% CI will be provided based on normal approximation with Mantel-Haenszel weights adjusting for baseline weight category.

To examine the robustness of the primary endpoint analysis, additional analyses will be conducted using different missing data approaches; these analyses will be described in the SAP. In addition, sensitivity analyses will be performed for the primary endpoint using the per-protocol population, which includes participants who are generally compliant with the protocol. To evaluate the consistency of the efficacy, subgroup analyses of the primary endpoint will be performed.

9.4.3. Secondary Endpoint(s)

In addition to the primary endpoint analysis, the analyses for secondary efficacy endpoints will be performed. No adjustments for multiple comparisons will be made for the secondary endpoints

and nominal p-values will be provided. Additional efficacy analyses may be performed and will be documented in the SAP.

- The proportion of participants who achieve a PASI 100 response at Week 16, will be compared between each of the JNJ-77242113 groups and the placebo group.
- The proportion of participants who achieve a PASI 90 response at Week 16, will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in PASI total score at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo.
- The proportion of participants who achieve an IGA score of cleared (0) at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The proportion of participants who achieve an IGA score of cleared (0) or minimal (1) at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in PSSD symptoms score at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in PSSD signs score at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The proportion of participants who achieve PSSD symptoms score=0 at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with a baseline PSSD symptoms score ≥1.
- The proportion of participants who achieve a PSSD signs score=0 at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with a baseline PSSD signs score ≥1.
- The proportion of participants with DLQI=0 or 1 at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group respectively among participants with a baseline DLQI score >1.
- The proportion of participants who achieve 5-point improvement or higher in each PROMIS-29 domain from baseline to Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in BSA at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.
- The change from baseline in PROMIS-29 domain scores at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group.

9.4.4. Tertiary/Exploratory Endpoint(s)

The following endpoints will be explored as exploratory endpoints. The secondary efficacy endpoints specified in Section 9.4.2 and selected efficacy endpoints in this section will also be summarized over time as tertiary/exploratory analyses. Detailed analyses will be specified in the SAP.

- The proportion of participants who achieve an ss-IGA score of absence of disease (0) or very mild disease (1) and at least a 2-grade improvement from baseline at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with scalp psoriasis and an ss-IGA score ≥2 at baseline.
- The proportion of participants who achieve an f-PGA score of clear (0) or minimal (1) and have at least a 1-grade improvement from baseline at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with nail psoriasis and an f-PGA score ≥2 at baseline.
- The percent improvement from baseline in NAPSI at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with a NAPSI >0 at baseline.
- The proportion of participants who achieve an hf-PGA score of clear (0) or almost clear (1) and a reduction of at least 2 grades on the hf-PGA scale from baseline at Week 16 will be compared between each of JNJ-77242113 groups and the placebo group among participants with hand and/or foot psoriasis and an hf-PGA score ≥2 at baseline.
- The proportion of participants who achieve an sPGA of genitalia score of clear (0) or minimal (1) at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with genital psoriasis and an sPGA of genitalia score ≥3 at baseline.
- The proportion of participants who achieve a score of never (0) or rarely (1) in GenPs-SFQ item 2 at Week 16 will be compared between each of the JNJ-77242113 groups and the placebo group among participants with an item 2 score ≥2 at baseline.
- Assessment of Treatment Satisfaction Questionnaire for Medications (TSQM-9) domains at Week 16 will be summarized.

9.4.5. Safety Analyses

Safety data, including but not limited to, AEs, SAEs, AESIs (active TB, malignancy, potential Hy's Law cases), discontinuation of study intervention due to AEs, changes in laboratory assessments, changes in vital signs, and changes in weight will be summarized. Intervention-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Details will be specified in the SAP.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the MedDRA. Intervention-emergent AEs are AEs with onset during the intervention period or that are a consequence of a preexisting condition that has worsened since baseline. All intervention-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 intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

The following analyses will also be used to assess the safety of participants in the study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of severe AEs.
- The incidence and type of related AEs as assessed by the investigator.
- The incidence and type of AEs leading to discontinuation of study.

Listings of participants with SAEs, severe AEs, AEs for psoriasis, AEs leading to discontinuation of study and anaphylactic reaction/serum sickness reactions will also be provided. All safety analyses will be based on the population of participants who received at least 1 administration of study intervention; participants will be summarized by the intervention they received.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test (eg, hematology, clinical chemistry). Selected laboratory parameters will be summarized by treatment groups. Common Terminology Criteria for Adverse Events (CTCAE) and ULN will be used to identify abnormal laboratory test results, and the incidence and severity of abnormal laboratory parameters (hematology and chemistry) will be summarized by treatment group.

In addition, a listing of participants with Grade 2 or higher laboratory test results (based on the CTCAE criteria) will also be provided.

C-SSRS

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized descriptively by treatment group.

Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point.

Weight

Descriptive statistics of changes from baseline will be summarized at selected scheduled time points.

9.4.6. Other Analyses

Pharmacokinetic Analyses

The PK evaluable population is defined as all the participants who received at least 1 complete dose of JNJ-77242113 and had at least 1 valid blood sample drawn for PK analysis after their first dose of JNJ-77242113.

Plasma JNJ-77242113 concentrations will be summarized by visit and treatment group. Descriptive statistics will be calculated at each sampling timepoint. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All plasma

concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. PK data may also be displayed graphically.

If feasible, population PK analysis of plasma concentration-time data of JNJ-77242113 may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (eg, demographics, laboratory variables, genotypes, race) will be tested as potential covariates affecting PK parameters. 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.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between plasma JNJ-77242113 concentration and efficacy may be examined when appropriate. If a relationship is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship and will be presented in a separate technical report.

Immunogenicity Analyses

The incidence and titers of antibodies to JNJ-77242113 will be summarized for all participants who receive at least 1 dose of JNJ-77242113 and have appropriate samples for detection of antibodies to JNJ-77242113 (ie, participants with at least 1 sample obtained after their first dose of JNJ-77242113).

A listing of participants who are positive for antibodies to JNJ-77242113 will be provided. The maximum titers of antibodies to JNJ-77242113 will be summarized for participants who are positive for antibodies to JNJ-77242113.

The incidence of neutralizing antibodies (NAbs) to JNJ-77242113 will be summarized for participants who are positive for antibodies to JNJ-77242113 and have samples evaluable for NAbs to JNJ-77242113.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Biomarkers Analyses

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

Changes in biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. The analyses will aim to identify biomarker relevant to treatment. Results of biomarker analyses will be reported in separate technical reports.

Pharmacogenomic Analyses

DNA samples will be used for research related to JNJ-77242113 or psoriasis. They may also be used to develop tests/assays related to JNJ-77242113 and/or psoriasis. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to JNJ-77242113 or psoriasis clinical endpoints. Results will be presented in a separate report.

9.5. Interim Analysis

An internal independent interim analysis committee (IAC) will be established to review the interim data including data from the LTE available at the time of the IA to formulate recommended decisions and/or actions in accordance with the objectives of the interim analyses. The IAC will consist of at least a clinician and a statistician (neither of whom are involved in study conduct), one of whom will chair the committee, and other members as required. The details will be provided in a separate IAC charter.

The IAC will review the unblinded efficacy data and provide recommendations about the next step of study conduct and the future development of the compound based upon the results of the first (when approximately 50% (n=120) of the participants reach Week 4) and/or second (when approximately 2/3 (n=160) of the participants reach Week 16) interim efficacy analyses. The first IA will be for nonbinding futility based on the proportion of participants achieving PASI 50 response at Week 4. The second IA will be used for planning of future studies and will be based on the primary endpoint which is the proportion of participants achieving PASI 75 response at Week 16. Other selected supportive efficacy endpoints could also be reviewed. The unblinded results will be limited to specific sponsor personnel not involved in the study conduct. Interim analysis results will not be disseminated to investigators or individuals associated with the conduct of the study.

Details of the plan for the interim analyses will be specified in the Interim Analysis SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADAs	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
anti-HCV	hepatitis C antibody
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{0-24}	area under the plasma analyte concentration-time curve from time 0 to 24 hours postdose
BCG	bacille Calmette-Guerin
BID	twice daily
BSA	body surface area
ClinRO	clinician-reported outcome
C_{max}	maximum observed plasma concentration
COVID-19	Coronavirus Disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	plasma concentration just prior to the beginning or at the end of the dosing interval
DBL	database lock
DILI	drug-induced liver injury
DLQI	Dermatological Life Quality Index
ECG	Electrocardiogram
eCOA	electronic clinical outcomes assessment
eDC	electronic data capture
eCRF	electronic case report form(s)
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
f-PGA	Fingernail Physician's Global Assessment
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GenPs-SFQ	Genital Psoriasis Sexual Frequency Questionnaire
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein
hf-PGA	Physician's Global Assessment of Hands and/or Feet
HIV	human immunodeficiency virus
HRQOL	Health-Related Quality of life
HRT	hormone replacement therapy
IAC	Interim Analysis Committee
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICEs	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGA	Investigator Global Assessment
IGRA	Interferon gamma release assay
IL	Interleukin
IL-12Rβ1	interleukin 12 receptor beta 1
IL-23R	interleukin 23 receptor

IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IWRS	interactive web response system
JAK	Janus kinase
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDL	low-density lipoprotein
LSmeans	Least Square means
LTE	long-term extension
MAD	multiple ascending doses
MedDRA	Medical Dictionary for Regulatory Activities
NAbs	neutralizing antibodies
NAPSI	Nail Psoriasis Area and Severity Index
NIMP	Non-Investigational Medicinal Product
NK	natural killer
NOAEL	no-observed-adverse-effect-level
PASI	Psoriasis Area and Severity Index
PCC	protocol clarification communication
PD	pharmacodynamic(s)
PDE	Phosphodiesterase
PGI-C	Patient Global Impression-Change
PGI-S	Patient Global Impression-Severity
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PROMIS-29	Patient-Reported Outcomes Measurement Information System-29
PSSD	Psoriasis Symptom and Sign Diary
QD	once daily
RBC	red blood cell
SAD	single ascending doses
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	Schedule of Activities
s-PGA	Static Physician's Global Assessment
ss-IGA	Scalp Specific Investigator Global Assessment
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
t_{max}	time to maximum plasma concentration
TNF	tumor necrosis factor
TSQM-9	Treatment Satisfaction Questionnaire for Medications-9 items
TYK	tyrosine kinase
ULN	upper limit of normal
US	United States
WBC	white blood cell

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	<u>RBC Indices:</u> MCV MCH % Reticulocytes	<u>White Blood Cell (WBC) count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose (nonfasting) Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT) eGFR	Total and Direct bilirubin Alkaline phosphatase Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Cholesterol Triglycerides Magnesium	
	Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.9. Potential Hy's Law case (ALT or AST ≥3 x ULN and Tbili ≥2 x ULN) reporting requirements are defined in Section 8.3.1		
Lipid Panel	Total cholesterol HDL LDL [calculated] Triglycerides		
	Note: Under fasting conditions except at Screening and Early Termination Visits		

<table>
<tr><td rowspan="2">Routine Urinalysis</td><td>Dipstick
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td>Sediment
Red blood cells
White blood cells
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td colspan="2">If dipstick result is abnormal, microscopy will be used to measure sediment.

In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.

Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. Red blood cells, WBCs, epithelial cells, crystals, casts, and bacteria will be measured using microscopy. If there is discordance between the dipstick results, the sediment will be examined microscopically.</td></tr>
<tr><td>Other Tests</td><td colspan="2">• Serum Pregnancy Testing for women of childbearing potential only (at Screening only)
• Urine Pregnancy Testing for women of childbearing potential only (all other visits)
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)
• hs-CRP</td></tr>
</table>

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) 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 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, ICF, 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 (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, 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 (eg, 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 (eg, 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 ICF (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.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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 ICF 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).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

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) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant (or a legally acceptable representative) 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.

Informed consent may be obtained remotely. Refer to the Monitoring Guideline.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants or their legally acceptable representatives 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. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. 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. By signing the ICF the participant or legally acceptable representative is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

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

Participants who are rescreened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

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

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

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 (or his or her legally acceptable representative) 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, PK, immunogenicity, and photographic 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-77242113, to understand psoriasis, to understand differential intervention responders, and to develop tests/assays related to

JNJ-77242113 and psoriasis. 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 (Section 7.2.1).

10.3.6. Committees Structure

Data Monitoring Committee

An external independent data monitoring committee (iDMC) whose members are not directly involved in the conduct of the 77242113PSO2001 study, will review unblinded safety data to ensure the safety of the participants enrolled in this study. The committee will meet regularly to review unblinded safety data. After the review, the iDMC will make recommendations to the sponsor regarding the conduct of the study. The iDMC will consist of at least one clinical physician and one statistician, not involved in the conduct of the study. The iDMC responsibilities, authorities, and procedures will be documented in the iDMC charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding JNJ-77242113 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, exploratory biomarker, or photographic 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-77242113, 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 pharmacogenomic, exploratory biomarker, or photographic 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 and 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.

10.3.8. 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, and 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 eCRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor may review the eCRF 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 upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Electronic 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 eCRF. All eCRF 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 eCRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, 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 eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF 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 (eg, pain scale information 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 an eCRF are needed after the initial entry into the eCRF, 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.

10.3.10. 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 eCRF and will be considered source data:

- Race
- History of smoking, all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination
- Investigator-completed scales and assessments and 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 or
- 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 (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is 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.

10.3.11. 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 may compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the

eCRF 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.

10.3.12. 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.

10.3.13. 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.

10.3.14. 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: Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) are: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = no involvement
1 = 1% to 9% involvement
2 = 10% to 29% involvement
3 = 30% to 49% involvement
4 = 50% to 69% involvement
5 = 70% to 89% involvement
6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

a. The neck is considered part of the head
b. The axillae and groin are part of the trunk
c. The buttocks are part of the lower extremities

The PASI formula is:

$$PASI = 0.1 (E_h + I_h + S_h) A_h + 0.3 (E_t + I_t + S_t) A_t + 0.2 (E_u + I_u + S_u) A_u + 0.4 (E_l + I_l + S_l) A_l$$

Where E = erythema, I = induration, S = scaling, and A = area

10.5. Appendix 5: Photographs

Background and rationale

Objective measurement and quantification of skin lesion characteristics derived from longitudinal photographic images of the enrolled patients may provide robust metrics of disease activity. Historically, total body photography has been employed in dermatology for the process of "mole mapping," ie, documenting, monitoring and assessing the development or change of nevi on the skin over time.

While PASI score provides a non-invasive approach to measure severity of psoriasis, it is poorly correlated with Quality-of-Life measures [1] and is not widely used by clinicians in real-world practice. The PASI score is also susceptible to inter and intra-clinician variability.

In the current study, imaging is planned for visual evaluation of disease severity and to contribute to our objective of developing a computer vision approach for quantifying of disease activity. Photographic imaging in the current study will allow for assessing the efficacy of JNJ-77242113 with objectivity and sensitivity.

Approach

In the proposed study, visible photography will be employed in a subset of patients, acquired at the clinical site. Participating patients will have two options for image collection:

1. Lesional photographs: two areas of lesional skin will be photographed per patient. The same two areas will be photographed over time.
2. Full body photographs + lesional photographs: In addition to the two lesional photographs, full body photographs (front and back) will be collected.

Photographic imaging will be conducted with quasi-standardized photographic equipment (iPhone or iPad based, handheld imaging) following instructions that establish specific imaging conditions, such as approximate distance between the camera and the surface of interest, and uniformity of light distribution. Images will be collected at baseline, Week 8, and Week 16 (primary endpoint timing).

Lesion assessment of relevant PSO lesional features (such as erythema, desquamation, and induration) will be conducted by central readers in a blinded fashion. As an exploratory analysis and depending on the volume and quality of image data collected, the images may be used to create an automated image-based disease severity assessment via deep learning modeling or low-level vision, such as traditional image analysis algorithms.

[1] Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. Dermatology. 2005;210(3):194-9. doi: 10.1159/000083509. PMID: 15785046.

Images acquired in this study will also contribute to broader effort to develop a curated image database of dermatological conditions for use in development of computer vision algorithms to automate assessment of disease states of interest.

[1] Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. Dermatology. 2005;210(3):194-9. doi: 10.1159/000083509. PMID: 15785046.

10.6. Appendix 6: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.6.1. 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 for 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 Section 8.3.1, 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 (eg, 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.

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-77242113, the expectedness of an AE will be determined by whether or not it is listed in the IB. For standard-of-care background therapies with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

10.6.2. 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.

10.6.3. 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).

10.6.4. 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, eg, 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.

10.6.5. 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 eCRF). 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.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

The cause of death of a participant in a study within 4 weeks 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 eCRF, 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.

10.6.6. 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.

10.6.7. 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.

10.7. Appendix 7: Columbia Suicide Severity Rating Scale

Appendix 7a: Columbia Suicide Severity Rating Scale – Baseline-screening

(Past x months = Past 6 months)

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to the "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete the "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or a wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life / commit suicide (e.g. "*I've thought about killing myself*") without thoughts of ways to kill oneself / associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different from a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "*I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it*". ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to "*I have the thoughts but I definitely will not do anything about them*". ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e. 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation*** <u>Past X Months</u> - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts, how long do they last?***	____	____

(1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous		
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attemptin suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOUR *(Tick all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behaviour was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behaviour or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/storey). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent maybe inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behaviour without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behaviour?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (*if not for that, actual attempt would have occurred*). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed towards self, gun is taken away by someone else, or he/she is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Interrupted _____	**Yes** ☐ **No** ☐ Total # of Interrupted _____

Aborted Attempt: When person begins to take steps towards making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behaviour. Examples are similar to interrupted attempts, except that the individual stops him/herself instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:		**Yes** ☐ **No** ☐ Total # of Aborted _____	**Yes** ☐ **No** ☐ Total # of Aborted _____
Preparatory Acts or Behaviour: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalisation or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:		**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behaviour: Suicidal behaviour was present during the assessment period?		**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech, first degree burns, mild bleeding, sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive, second degree burns, bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalisation and likely intensive care required (e.g. comatose with reflexes intact, third degree burns less than 20% of body, extensive blood loss but can recover, major fractures). 4. Severe physical damage; *medical* hospitalisation with intensive care required (e.g. comatose without reflexes, third degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun failed to fire so no medical damage; lay on train tracks with oncoming train but pulled away before run over). 0 = Behaviour not likely to result in injury 1 = Behaviour likely to result in injury but not likely to cause death 2 = Behaviour likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 7b: Columbia Suicide Severity Rating Scale (Since Last Visit)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to the "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete the "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or a wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life / commit suicide (e.g. "*I've thought about killing myself*") without thoughts of ways to kill oneself / associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different from a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "*I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it*". ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan Active suicidal thoughts of killing one self and subject reports having some intent to act on such thoughts, as opposed to "*I have the thoughts but I definitely will not do anything about them*". ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e. 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***	

(1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you	(4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.	(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	

SUICIDAL BEHAVIOUR *(Tick all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behaviour was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behaviour or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/storey). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behaviour without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behaviour?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (*if not for that, actual attempt would have occurred*). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed towards self, gun is taken away by someone else, or he/she is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of Interrupted _____
Aborted Attempt: When person begins to take steps towards making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behaviour. Examples are similar to interrupted attempts, except that the individual stops him/herself instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of Aborted _____
Preparatory Acts or Behaviour:	**Yes No** ☐ ☐

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalisation or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	
Suicidal Behaviour: Suicidal behaviour was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech, first degree burns, mild bleeding, sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive, second degree burns, bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalisation and likely intensive care required (e.g. comatose with reflexes intact, third degree burns less than 20% of body, extensive blood loss but can recover, major fractures). 4. Severe physical damage; *medical* hospitalisation with intensive care required (e.g. comatose without reflexes, third degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area). 5. Death	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun failed to fire so no medical damage; lay on train tracks with oncoming train but pulled away before run over). 0 = Behaviour not likely to result in injury 1 = Behaviour likely to result in injury but not likely to cause death 2 = Behaviour likely to result in death despite available medical care	*Enter Code* ____

10.8. Appendix 8: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.3.5 and Section 10.3.

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, bilateral salpingectomy, and bilateral oophorectomy.

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

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 FOR FEMALE PARTICIPANTS 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 FOR FEMALE PARTICIPANTS (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)

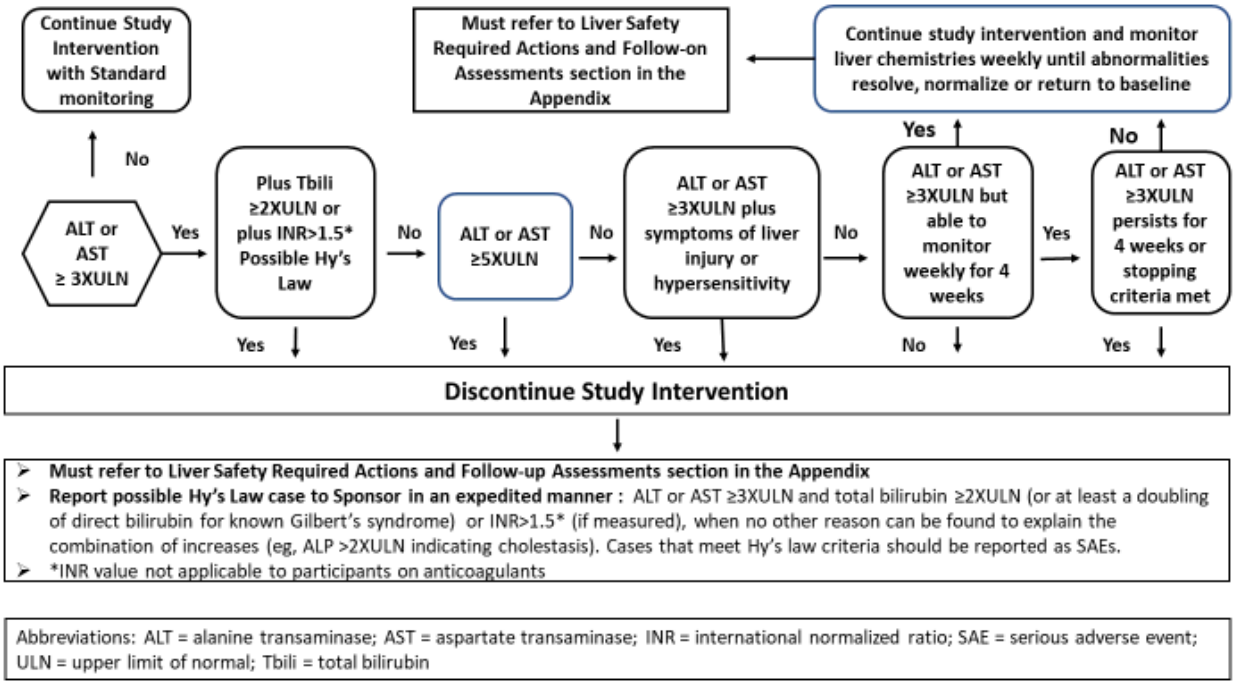
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, 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).

10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments

10.9.1. Stopping Algorithm

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

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



10.9.2. FOLLOW-UP ASSESSMENTS

10.9.2.1. Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

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

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT/AST-absolute</td><td>ALT or AST- ≥5xULN</td></tr>
<tr><td>ALT/AST-Increase</td><td>If cannot monitor:
ALT or AST- ≥3 x ULN and cannot be monitored weekly for 4 weeks

Or if able to monitor:
ALT or AST- ≥3xULN persists for ≥4 weeks</td></tr>
<tr><td>Total bilirubin[1, 2]</td><td>ALT or AST- ≥3xULN and total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert’s syndrome)</td></tr>
<tr><td>INR[2]</td><td>ALT or AST- ≥3xULN and international normalized ratio (INR) >1.5, if INR measured</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT or AST- ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Suggested Actions, Monitoring and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-up Assessments</th></tr>
<tr><td>• Immediately stop study intervention
• Report the event to the sponsor within 24 hours
• Complete the CRF according to CRF completion guidelines, and complete an SAE data collection tool if the event also met the criteria for an SAE[2]
• Perform follow-up assessments as described in the Follow Up Assessment column
• Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see MONITORING)
MONITORING:
If ALP <2 x ULN, ALT or AST- ≥3xULN AND total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert’s syndrome) or INR >1.5 (if measured):
• Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total and direct bilirubin and</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis within 48 hours after the most recent dose[5]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin
• Fractionate bilirubin
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the CRF as per CRF completion guidelines</td></tr>
</table>

INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **If ALT or AST- ≥3xULN AND total bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total and direct bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention. PERMANENTLY DISCONTINUE STUDY INTERVENTION AND CONTINUE PARTICIPANT IN THE STUDY FOR ANY PROTOCOL SPECIFIED FOLLOW-UP ASSESSMENTS	• Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) • Record alcohol use on the CRF as per CRF completion guidelines **If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 (if measured)** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete CRF as per CRF completion guidelines • Liver biopsy may be considered and discussed with local specialist if available: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation • If liver biopsy conducted complete CRF as per CRF completion guidelines

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

2. All events of ALP <2 x ULN, ALT **or AST-** ≥3 x ULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's sydnrome) or ALP <2 x ULN , ALT **or AST-** ≥3 x ULN **and** INR >1.5 (if measured) may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria are met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAgG and HBcAB; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.9.2.2. Phase 2 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criterion and Actions with Continued Study Intervention	
Criterion	**Actions**
ALT or AST- ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR<1.5 (if measured)**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the sponsor within **24 hours** of learning of the abnormality to discuss participant safety • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize or return to baseline • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 10.9 • If, after 4 weeks of monitoring, ALT or AST- <3xULN and total bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline

10.10. Appendix 10: Hepatitis B Virus (HBV) Screening with HBV DNA

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is **negative**, the participant ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this protocol.

These eligibility criteria based on HBV test results are also represented in table below. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines.

Eligibility based on hepatitis B virus test results			
HEPATITIS B TEST RESULT			**STATUS**
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	
negative	negative	negative	**Eligible**
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**Not eligible**
negative	negative	(+)	**(Require testing for presence of HBV DNA*)**

* If HBV DNA is detectable, the participant is not eligible for this protocol. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol.

For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of HBV infection is recommended.

10.11. Appendix 11: 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 guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

If, as a result of the COVID-19 pandemic, 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 after consultation between the participant and investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee 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.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and Investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures (eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration [including training where pertinent])

- procurement of study intervention by patients (or designee) or shipment of study drug from the study site directly to patients for at home administration
- laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
- other procedures may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.
    - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in eCRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

10.12. Appendix 12: Criteria for Assessing Potential Cases of Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled (Sampson 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that participant (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Key: PEF=Peak expiratory flow; BP=blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.13. Appendix 13: Protocol Amendment History

Amendment 1 (17 November 2021)

Overall Rationale for the Amendment: The protocol is being amended to clarify stratification and to clarify the contraceptive appendix.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Table 1	PGI-C evaluation at Week 0 was deleted.	This evaluation at Week 0 was added in error in the original protocol and therefore deleted.
Section 5.1 Inclusion Criteria Criterion #2	The criterion has been modified as follows: Has a diagnosis of plaque psoriasis, with or without PsA, for at least 6 months prior to the first administration of study intervention~~, confirmed by medical record~~.	Aligning this criterion with that noted in other programs conducted by the Sponsor and acknowledging the challenges in a global study to have medical record confirmation of the term "plaque psoriasis" given regional variability.
Criterion #12	The criterion has been modified as follows: A male participant who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale), during the study and for at least 12 weeks after receiving the last administration of study intervention. **Male participants should also be advised of the benefit for female partner to use a highly effective method of contraceptive as condoms may break or leak.**	To provide clarification on contraception information for male participants
Section 6.1 Study Intervention Administered Investigational Medicinal Product (IMP)	Group 6: The 'YES' box has been checked and the 'NO' box unchecked	Placebo is considered IMP.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding Intervention Allocation	Dynamic central randomization will be implemented in conducting this study. Participants will be assigned to 1 of 6 intervention groups based on an algorithm implemented in the interactive web response system (IWRS) before the study. Dynamic central randomization minimizes the imbalance in the distribution of the number of participants across intervention groups within the levels of each individual stratification factor: study site and baseline weight (≤90 kg, >90 kg). **In addition, the Japanese sites will be pooled in the**	The stratification of Japanese sites has been clarified.

Section Number and Name	Description of Change	Brief Rationale
Procedures for Randomization and Stratification	**randomization process to better ensure treatment balance across Japanese participants.** Based on the algorithm, the IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant.	
Section 10.8 Appendix 8 Contraceptive and Barrier Guidance	The headers and sub-headers in the table for Examples of Contraceptives have been modified as follows: EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY **FOR FEMALE PARTICIPANTS** INCLUDE: NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY **FOR FEMALE PARTICIPANTS** (not considered to be highly effective - failure rate of ≥1% per year)	Clarification that this table, which lists examples of contraceptives, is applicable to female participants only
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 MD

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	13-Jan-2022 14:56:44 (GMT)	Document Approval