Official Title of Study:

A Phase 4, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Deucravacitinib in Participants with Non-Pustular Palmoplantar and Genital Psoriasis (Psoriatyk Special Sites)

NCT Number: NCT06042920

Document Date (Date in which document was last revised): 08-May-2023

CLINICAL PROTOCOL IM0111112

A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DEUCRAVACITINIB IN PARTICIPANTS WITH NON-PUSTULAR PALMOPLANTAR AND GENITAL PSORIASIS (PSORIATYK SPECIAL SITES)

Compound: Deucravacitinib

Brief Title:

Randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of deucravacitinib in palmoplantar and genital psoriasis

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REGULATORY AGENCY IDENTIFIER NUMBER(S)

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Original Protocol	08-May-2023	Not applicable.

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1 PROTOCOL SUMMARY

Protocol Title:

A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DEUCRAVACITINIB IN PARTICIPANTS WITH NON-PUSTULAR PALMOPLANTAR AND GENITAL PSORIASIS (PSORIATYK SPECIAL SITES)

Brief Title:

Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of deucravacitinib in palmoplantar and genital psoriasis

Rationale:

SOTYKTU™ (deucravacitinib), a first-in-class, oral, selective, allosteric tyrosine kinase 2 (TYK2) inhibitor is approved in multiple countries for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

This approval was based on the results of completed 52-week, randomized, Phase 3, placebo-controlled studies (POETYK PSO-1 and PSO-2) of deucravacitinib 6 mg daily versus placebo and apremilast 30 mg twice daily.

In these 2 trials, in addition to the co-primary endpoints of Psoriasis Area and Severity Index (PASI)-75 and static Physician's Global Assessment (s-PGA)0/1 at Week 16, palmoplantar (PP) psoriasis was assessed using the palmoplantar physician global assessment (pp-PGA) 0/1 and palmoplantar Psoriasis Area and Severity Index (pp-PASI)-75 change from baseline in participants with a pp-PGA score ≥ 3 (moderate-to-severe PP psoriasis) at baseline. Although 16% of the subjects had a history of PP psoriasis, only 7% of subjects in the Phase 3 studies met the baseline pp-PGA ≥ 3 criterion. The individual Phase 3 studies were not sized to specifically assess PP psoriasis. Due to the small number of subjects with pre-existing PP psoriasis in each study, the pooled data from PSO-1 and PSO-2 allowed for a more meaningful evaluation. In this analysis of the pooled PSO-1 and PSO-2 population, significantly more participants receiving deucravacitinib (n = 57) versus placebo (n = 25) achieved pp-PGA 0/1 at Week 16 (49.1% versus 16%, p = 0.0052). In the pooled PSO-1 and PSO-2 population, the mean change from baseline in pp-PASI, adjusted for study, body weight, prior biologic use, and the baseline value as a covariate was -13.3 (95% confidence interval [CI]: -16.3, -10.2) and -4.2 (95% CI: -8.4, -0.0) for deucravacitinib and placebo, respectively. In PSO-1, pp-PGA 0/1 responses at Week 16 were maintained through Week 52 with continuous deucravacitinib treatment (55.6% [95% CI: 32.6, 78.5]).[1] Genital psoriasis (GenPs) has not yet been assessed in the deucravacitinib psoriasis clinical program.

Remaining key data gaps include the efficacy of deucravacitinib in improving moderate-to-severe GenPs, PP psoriasis, and health-related Quality of Life measures specifically associated with these difficult-to-treat sites.

Objectives and Endpoints:

Non-pustular Palmoplantar Psoriasis Sub-protocol Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by pp-PASI-75, of deucravacitinib versus placebo at Week 16 in participants with PP plaque psoriasis	• pp-PASI-75, defined as a 75% improvement in pp-PASI score from baseline at Week 16
Secondary	
• To compare the efficacy, as measured by pp-PGA 0/1, of deucravacitinib versus placebo at Week 16 in participants with PP plaque psoriasis	• Proportion of participants who achieve a pp-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16
Other Secondary	
• To assess the safety of deucravacitinib versus placebo in participants with PP plaque psoriasis between Week 0 and Week 16	• AEs, SAEs, laboratory parameters, and VS between Week 0 and Week 16

Abbreviations: AE, adverse event; PP, palmoplantar; pp-PASI, palmoplantar Psoriasis Area and Severity Index; pp-PGA, palmoplantar physician global assessment; SAE, serious adverse event; VS, vital signs.

Genital Psoriasis Sub-protocol Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by s-PGA-G 0/1, of deucravacitinib versus placebo at Week 16 in participants with GenPs	• s-PGA-G 0/1, defined as proportion of participants achieving s-PGA-G score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16
Key Secondary	
• To compare the efficacy, as measured by change from baseline in GenPs Itch NRS, of deucravacitinib versus placebo at Week 16 in participants with GenPs	• Change from baseline in GenPs itch NRS score at Week 16.
• To compare the efficacy, as measured by s-PGA 0/1, of deucravacitinib versus placebo at Week 16 in participants with GenPs	• s-PGA 0/1, defined as proportion of participants achieving s-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16
Other Secondary	
• To assess the safety of deucravacitinib versus placebo in participants with GenPs between Week 0 and Week 16	• AEs, SAEs, laboratory parameters, and VS between Week 0 and Week 16

Abbreviations: AE, adverse event; GenPs, genital psoriasis; NRS, Numeric Rating Scale; PP, palmoplantar; SAE, serious adverse event; s-PGA, static Physician's Global Assessment; s-PGA-G, static Physician's Global Assessment of Genitalia; VS, vital signs.

Overall Design:

This master protocol (IM0111112) with 2 sub-protocols is a Phase 4, double-blind, placebo-controlled multicenter study to assess the efficacy and safety of deucravacitinib in participants with moderate-to-severe non-pustular PP or GenPs versus placebo. Enrollment in each sub-protocol will be concurrent. Participants with involvement of both sites during screening (genital and PP) can only be randomized to 1 of the sub-protocols as per investigator's discretion. In both sub-protocols, a placebo control is included to allow the assessment of effects of the intervention. The placebo control will also provide a basis for comparison of safety assessments. For each sub-protocol participants will undergo screening evaluations within 28 days prior to the administration of study intervention to determine eligibility.

For the PP psoriasis sub-protocol following the screening process, participants will be randomized in a 2:1 ratio to either deucravacitinib 6 mg once daily (QD) or placebo, respectively. [redacted] For the purpose of this study, even the participants with the presence of very few isolated pustules and only limited to the PP plaques (See Section 6.1) are still considered to have non-pustular PP psoriasis. This will allow enrollment of these participants into this study. However, to limit the number of participants who may potentially have few isolated pustules, participants with the presence of pustules (See Section 6.1) would be limited to a maximum of 10% of all randomized participants. Participants with a significant number of pustules (> 5) and/or predominant pustular component would be categorized as PP pustular psoriasis and would not be eligible for the study.

For the GenPs sub-protocol, following the screening process, participants will be randomized in a 2:1 ratio to either deucravacitinib 6 mg QD or placebo, respectively. [redacted] Given the paucity of data on GenPs in women in the literature, the genital sub-protocol will aim to enroll at least 40% of female participants into the study as an attempt to address this data gap.

For both sub-protocols the duration of study participation is approximately 60 weeks and will be divided into the following periods: screening (up to 4 weeks), treatment (52 weeks), and follow-up (4 weeks).

At Week 16, all participants regardless of their blinded intervention, will be switched to open-label deucravacitinib 6 mg QD bottles through Week 52. Participants randomized to deucravacitinib 6 mg QD will continue their current dose through Week 52.

Participants will be followed up for safety for 4 additional weeks, from Weeks 52 through 56. Participants who discontinue study intervention early/withdraw prematurely must complete the end-of-treatment (EOT) visit. The participant will be asked to return to the clinic to complete the 28-day safety follow-up visit and encouraged to report any serious adverse events (SAEs) or adverse events (AEs) experienced during this time.

Study Population:

Male and female participants ≥ 18 years of age must meet the following criteria for entry into the study.

Non-pustular Palmoplantar Psoriasis Sub-protocol

Key Inclusion Criteria:

Type of Participant and Target Disease Characteristics

a) Men and women diagnosed with stable plaque psoriasis with involvement of the palm(s) and/or sole(s) for at least 6 months or more. Stable psoriasis is defined as no morphology changes or significant flares of disease activity in the opinion of the investigator.

b) Moderate-to-severe plaque psoriasis defined as s-PGA score of ≥ 3 on a 5-point scale at both screening visit and Day 1.

c) Moderate-to-severe non-pustular PP psoriasis, defined as pp-PGA score of ≥ 3 on a 5-point scale and pp-PASI ≥ 8 at both screening visit and Day 1.

   i) A total maximum of 5 sterile pustules across both palms and soles limited only to psoriatic plaques will be allowed.

d) Evidence of typical plaque psoriasis outside palms and soles at both screening visit and Day 1.

e) Deemed by the investigator to be a candidate for phototherapy or systemic therapy.

f) Failed to respond to, or intolerant of ≥ 1 topical therapy.

Genital Psoriasis Sub-protocol

Key Inclusion Criteria:

Type of Participant and Target Disease Characteristics

a) Men and women diagnosed with stable plaque psoriasis with involvement of the genital area for at least 6 months or more. Stable psoriasis is defined as no morphology changes or significant flares of disease activity in the opinion of the investigator.
b) Moderate-to-severe plaque psoriasis defined as s-PGA score of ≥ 3 on a 5-point scale at both screening visit and Day 1.
c) Moderate-to-severe GenPs, defined as static Physician's Global Assessment of Genitalia (s-PGA-G) score of ≥ 3 on a 6-point scale at both screening visit and Day 1.
d) Evidence of typical plaque psoriasis in a non-genital area at both screening visit and Day 1.
e) Deemed by the investigator to be a candidate for phototherapy or systemic therapy.
f) Failed to respond to, or intolerant of ≥ 1 topical therapy.

Intervention Groups and Duration:

Participants in both sub-protocols will take oral doses of one of the Investigational [Medicinal] Product (IP) either deucravacitinib or placebo QD, for 16 weeks. At Week 16, all participants regardless of their blinded intervention, will be switched to open label deucravacitinib 6 mg QD bottles through Week 52. Participants randomized to deucravacitinib 6 mg QD will continue their current dose through Week 52.

Study Intervention:

Study Intervention for IM0111112

Medication	Potency	IP/Non-IP
Deucravacitinib (BMS-986165)	6 mg	IP
Placebo	N/A	IP

Abbreviation: IP, investigational product.

Statistical Methods:

For the non-pustular PP psoriasis sub-protocol, the primary hypothesis is that the odds of achieving pp-PASI-75 at Week 16 in participants receiving deucravacitinib 6 mg QD are improved compared to participants receiving placebo.

The null hypothesis to be tested for the primary endpoint is the following:

- The odds of achieving pp-PASI-75 at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

The null hypothesis corresponding to the key secondary endpoint is:

- The odds of achieving pp-PGA 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

For the GenPs sub-protocol, the primary hypothesis is that the odds of achieving s-PGA-G 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are improved compared to participants receiving placebo.

The null hypothesis to be tested for the primary endpoint is the following:

- The odds of achieving s-PGA-G 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

The null hypothesis corresponding to the key secondary endpoint is:

- The mean change from baseline in GenPs Itch NRS score at Week 16 in participants receiving deucravacitinib 6 mg QD is not different from participants receiving placebo.

The null hypothesis corresponding to the second key secondary endpoint is:

- The odds of achieving s-PGA 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

The statistical comparisons will be carried out in a hierarchical order for each sub-protocol. The hierarchical testing will preserve the overall Type I error at 0.05 for each sub-protocol.

If statistical significance is not met for the primary endpoint, then subsequent p-values will be considered descriptive for that sub-protocol.

Data Monitoring Committee: No

A Data Monitoring Committee will not be used in the study.

Other Committee: Yes

This study will use an external Study Steering Committee.

Brief Summary:

The purpose of this study is to compare the efficacy of deucravacitinib to placebo for the treatment of participants with non-pustular palmoplantar or genital psoriasis.

The primary hypothesis for the non-pustular palmoplantar psoriasis sub-protocol is that the odds of achieving pp-PASI-75 at Week 16 in participants receiving deucravacitinib 6 mg QD are

improved compared to participants receiving placebo. The primary hypothesis for the genital psoriasis sub-protocol is that the odds of achieving s-PGA-G 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are improved compared to participants receiving placebo.

The duration of study participation for both sub-protocols is approximately 60 weeks and will be divided into the following periods: screening (up to 4 weeks/28 days), treatment (52 weeks), and follow-up (4 weeks). Following the initial screening study visit, subsequent visits will occur at Day 1, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 40, Week 52, and Week 56.

Participants who have completed the screening procedures and have met the inclusion/exclusion criteria for 1 of the sub-protocols will be randomized on Day 1 in a 2:1 ratio to either deucravacitinib 6 mg once a day or placebo, respectively, for the first 16 weeks. Participants with involvement of both sites during screening (genital and palmoplantar) can only be randomized to 1 of the sub-protocols as per investigator's discretion. At Week 16, all participants, regardless of their blinded intervention, will be switched to open-label deucravacitinib 6 mg QD bottles through Week 52. Participants and investigators will remain blinded to the double-blind study intervention from Day 1 to Week 16 until the end of the study.

Statement of expanded access: Not applicable

2 SCHEDULE OF ACTIVITIES

Non-pustular Palmoplantar Sub-protocol

The schedules of activities and procedures for the palmoplantar (PP) psoriasis sub-protocol are documented in Table 2-1 for screening, Table 2-2 for Week 0 (baseline) through Week 20, and Table 2-3 for Week 24 through Week 56.

Table 2-1: Non-pustular Palmoplantar Psoriasis Sub-protocol Screening Procedural Outline (IM0111112)

Procedure	Screening Visit (Day -28 to Day -1)	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed. Must be obtained prior to performing any screening procedures.
Enroll participant	X	Obtain number from IRT.
Inclusion/Exclusion Criteria	X	Includes duration of plaque psoriasis, PP psoriasis involvement, and documentation of evidence of typical plaque psoriasis outside palms and soles by the investigator.
Demographics and Participant Characteristics	X	Some data may be collected via electronic device. Note: SOGIIS data will be collected for US participants only.
[redacted]		
History of Tobacco Use	X	Include description of current tobacco use.
Psoriasis-related History	X	All psoriasis history including disease duration, scalp psoriasis, PP psoriasis, nail psoriasis, genital psoriasis, and PsA duration, or history of other forms of psoriasis.
Psoriasis-related Systemic Treatment	X	Includes nonbiologic conventional systemic (eg, methotrexate), biologic agents, and/or phototherapy. For each therapy, include a length of time on treatment and reason(s) for discontinuation (eg, lack of efficacy, intolerance, side effects, loss of access to treatment), if applicable.

Table 2-1: Non-pustular Palmoplantar Psoriasis Sub-protocol Screening Procedural Outline (IM0111112)

Procedure	Screening Visit (Day -28 to Day -1)	Notes
Psoriasis-related Topical Treatment	X	Includes topical treatments and shampoos for psoriasis.
Other Prior and Concomitant Treatments	X	All medications for other/non-psoriasis conditions.
Safety Assessments		
Physical Examination	X	Complete PE.
Physical Measurements	X	Includes height, weight, and BMI.
Vital Signs	X	Includes (ear or oral) body temperature, respiratory rate, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
12-lead ECG	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes. A single ECG should be collected. See Section 9.4.3.

[redacted]

Table 2-1: Non-pustular Palmoplantar Psoriasis Sub-protocol Screening Procedural Outline (IM0111112)

Procedure	Screening Visit (Day -28 to Day -1)	Notes
[redacted]		
Adverse Event Reporting		
Monitor for AE and SAE Assessment	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Clinical Efficacy [redacted]		
pp-PGA	X	Non-pustular PP plaque psoriasis. Participants with PP pustulosis or PP pustular psoriasis are not eligible for enrollment. Refer to Section 6 for detailed eligibility criteria.
pp-PASI	X	Refer to Section 6 for detailed eligibility criteria.
Number of Pustules Present	X	Participants with a total maximum of 5 sterile pustules across both palms and soles and limited only to psoriatic plaques will be eligible for enrollment. The total number and location of pustules must be documented if present.
s-PGA	X	Refer to Section 6 for detailed eligibility criteria.
Evidence of Typical Plaque Psoriasis Outside Palms and Soles	X	Refer to Section 6 for detailed eligibility criteria.
Dispense E-diary [redacted]	X	All consented participants will be given a diary device at the screening visit and will begin recording PP psoriasis symptoms on a daily basis in the diary device. Participants who are not randomized will stop recording and return

Table 2-1: Non-pustular Palmoplantar Psoriasis Sub-protocol Screening Procedural Outline (IM0111112)

Procedure	Screening Visit (Day -28 to Day -1)	Notes
		their diary device to the site. Participants who are randomized will continue recording their psoriasis symptoms on a daily basis in the diary device through Week 16 and for 7 days prior to each subsequent visit through Week 52.
[redacted]		

Abbreviations: AE, adverse event; BMI, body mass index; [redacted]; ECG, electrocardiogram; [redacted]; IRT, interactive response technology; [redacted]; PE, physical examination; [redacted]; PI, principal investigator; PP, palmoplantar; pp-PGA, palmoplantar physician global assessment; PsA, psoriatic arthritis; pp-PASI, palmoplantar Psoriasis Area and Severity Index; SAE, serious adverse event; [redacted]; SOGIIS, sexual orientation, gender identity and intersex status; s-PGA, static physician global assessment; [redacted]; US, United States; [redacted].

[redacted]

Table 2-2: On-treatment Procedural Outline Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 0 (Baseline) through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
Eligibility Assessments									
Inclusion/Exclusion Criteria	X								
Medical History	X								
Safety Assessments									
Targeted PE	X	X	X	X	X	X	X	X	Key aspects should evaluate important body systems as clinically indicated.
Body Weight	X						X		
Vital Signs	X	X	X	X	X	X	X	X	
Concomitant Medication Use	X	X	X	X	X	X	X	X	

Table 2-2: On-treatment Procedural Outline Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 0 (Baseline) through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
Adverse Event Reporting									
Monitor for AE and SAE Assessment	X	X	X	X	X	X	X	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

[redacted]

Table 2-2: On-treatment Procedural Outline Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 0 (Baseline) through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
[redacted]									
Clinical Efficacy Assessments									
PASI	X	X	X	X	X	X	X	X	
[redacted]									
s-PGA	X	X	X	X	X	X	X	X	

Table 2-2: On-treatment Procedural Outline Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 0 (Baseline) through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
Evidence of Typical Plaque Psoriasis Outside Palms and Soles	X								
pp-PGA	X	X	X	X	X	X	X	X	
Presence of pustules[a]	X						X		Participants with a total maximum of 5 sterile pustules across both palms and soles and limited only to psoriatic plaques will be eligible for enrollment. The presence of pustules (yes/no), total number, and location of pustules must be documented if present.

Table 2-2: On-treatment Procedural Outline Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 0 (Baseline) through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
pp-PASI	X	X	X	X	X	X	X	X	

[redacted]

Table 2-2: On-treatment Procedural Outline Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 0 (Baseline) through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
[redacted]									

Table 2-2: On-treatment Procedural Outline Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 0 (Baseline) through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
[redacted]									
Study Intervention									
Randomization via IRT	X								
Dispense Study Intervention	X		X	X	X	X	X	X	
Study Intervention Compliance		X	X	X	X	X	X	X	

Abbreviations: AE, adverse event; [redacted] D/d, Day; [redacted]; IRT, interactive response technology; [redacted]; PASI, Psoriasis Area and Severity Index; PE, physical examination; PP, palmoplantar; pp-PASI, palmoplantar Psoriasis Area and Severity Index; pp-PGA, palmoplantar physician global assessment; [redacted]; SAE, serious adverse event; s-PGA, static Physician Global Assessment; [redacted].

[a] Only in participants with the presence of pustules at screening and/or baseline visits the investigator will record the presence (yes/no) of pustules, total number, and location of pustules on the electronic clinical outcome assessment (eCOA) tablet.

When multiple assessments are conducted at a single visit, the following is the order in which they should be done as applicable:

1) Patient-reported outcome assessments
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests [redacted]

Table 2-3: On-treatment Procedural Outline, Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
Safety Assessments							
Complete PE					X		
Targeted PE	X	X	X	X		X	
Body Weight					X		
Vital Signs	X	X	X	X	X	X	
Concomitant Medication Use	X	X	X	X	X	X	
Adverse Event Reporting							
Monitor for AE and SAE Assessment	X	X	X	X	X	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

Table 2-3: On-treatment Procedural Outline, Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
[redacted]							
Clinical Efficacy Assessments							
PASI	X	X	X	X	X		
[redacted]							
s-PGA	X	X	X	X	X		
pp-PGA	X	X	X	X	X		
Presence of pustules[b]					X		Participants with a total maximum of 5 sterile pustules across both palms and soles and limited only to psoriatic plaques will be eligible for enrollment. The presence of pustules (yes/no),

Table 2-3: On-treatment Procedural Outline, Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
							total number, and location of pustules must be documented if present.
pp-PASI	X	X	X	X	X		

[redacted]

Table 2-3: On-treatment Procedural Outline, Non-pustular Palmoplantar Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
[redacted]							
Study Intervention							
Dispense Study Intervention	X	X	X	X			
Study Intervention Compliance	X	X	X	X	X		
Collect eDiary					X		

Abbreviations: AE, adverse event; [redacted] D/d, Day; [redacted]; EOT, end of treatment; ET, early termination; [redacted]; PASI, Psoriasis Area and Severity Index; PE, physical examination; PP, palmoplantar; pp-PGA, palmoplantar physician global assessment; pp-PASI, palmoplantar Psoriasis Area and Severity Index; [redacted]; PSO, psoriasis; SAE, serious adverse event; s-PGA, static Physician Global Assessment; [redacted].

[a] EOT/ET visit for participants who discontinue treatment any time prior to completing Week 52 of active treatment period. Safety follow-up visit occurs 28±3 days after the last dose of study treatment.

[b] Only in participants with the presence of pustules at screening and/or baseline visits the investigator will record the presence (yes/no) of pustules, total number, and location of pustules on the electronic clinical outcome assessment (eCOA) tablet.

When multiple assessments are conducted at a single visit, the following is the order in which they should be done as applicable:

1) Patient-reported outcome assessments
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests [redacted]

Genital Psoriasis Sub-protocol

The schedules of activities and procedures for the genital psoriasis (GenPs) sub-protocol are documented in Table 2-4 for screening, Table 2-5 for Week 0 (baseline) through Week 20, and Table 2-6 for Week 24 through Week 56.

Table 2-4: Genital Psoriasis Sub-protocol Screening Procedural Outline (IM0111112)

Procedure	Screening Visit Day -28 to Day -1	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed. Must be obtained prior to performing any screening procedures.
Enroll Participant	X	Obtain number from IRT.
Inclusion/Exclusion Criteria	X	Includes duration of plaque psoriasis, genital involvement, and documentation of evidence of typical plaque psoriasis outside genital involvement by the investigator.
Demographics and Participant Characteristics	X	Some data may be collected via electronic device. Note: SOGIIS data will be collected for US participants only.
[redacted]		
History of Tobacco Use	X	Include description of current tobacco use.
Psoriasis-related History	X	All psoriasis history including disease duration, scalp psoriasis, palmoplantar psoriasis, nail psoriasis, genital psoriasis, and PsA duration, or history of other forms of psoriasis.

Table 2-4: Genital Psoriasis Sub-protocol Screening Procedural Outline (IM0111112)

Procedure	Screening Visit Day -28 to Day -1	Notes
Psoriasis-related Systemic Treatment	X	Includes nonbiologic conventional systemic (eg, methotrexate), biologic agents, and/or phototherapy. For each therapy, include a length of time on treatment and reason(s) for discontinuation (eg, lack of efficacy, intolerance, side effects, loss of access to treatment), if applicable.
Psoriasis-related Topical Treatment	X	Includes topical treatments and shampoos for psoriasis.
Other Prior and Concomitant Treatments	X	All medications for other/non-psoriasis conditions.
Safety Assessments		
Physical Examination	X	Complete PE.
Physical Measurements	X	Includes height, weight, and BMI.
Vital Signs	X	Includes (ear or oral) body temperature, respiratory rate, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
12-lead ECG	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes. A single ECG should be collected. See Section 9.4.3.

[redacted]

Table 2-4: Genital Psoriasis Sub-protocol Screening Procedural Outline (IM0111112)

Procedure	Screening Visit Day -28 to Day -1	Notes
[redacted]		
Adverse Event Reporting		
Monitor for AE and SAE Assessment	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Efficacy Assessments		
s-PGA-G[a]	X	Refer to Section 6 for detailed eligibility criteria.
s-PGA	X	Refer to Section 6 for detailed eligibility criteria.
Evidence of Typical Plaque Psoriasis in Non-genital Area	X	Evidence of typical plaque psoriasis in a non-genital area is 1 of the required key inclusion criteria.
[redacted]		

Table 2-4: Genital Psoriasis Sub-protocol Screening Procedural Outline (IM0111112)

Procedure	Screening Visit Day -28 to Day -1	Notes
Dispense eDiary [redacted]	X	All consented participants will be given a diary device at the screening visit and will begin recording [redacted] on a daily basis in the diary device. [redacted].

Abbreviations: AE, adverse event; BMI, body mass index; [redacted]; ECG, electrocardiogram; [redacted]; IRT, interactive response technology; PE, physical examination; PI, principal investigator; PsA, psoriatic arthritis; SAE, serious adverse event; [redacted]; SOGIIS, sexual orientation, gender identity, and intersex status; s-PGA-G, static Physician's Global Assessment of Genitalia; [redacted]; US, United States; [redacted]

[a] In addition to s-PGA-G, the investigator will record on the electronic clinical outcome assessment (eCOA) tablet (yes/no) which exact genital regions are affected by psoriasis (labia minora, labia majora, and/or perineum in women and penis (glans and/or shaft), scrotum, and/or perineum in men; and for men the status of circumcision would be documented).

[redacted]

Table 2-5: On-treatment Procedural Outline Genital Psoriasis Sub-Protocol (IM0111112), Week 0 through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
Eligibility Assessments									
Inclusion/Exclusion Criteria	X								
Medical History	X								
Safety Assessments									
Targeted PE	X	X	X	X	X	X	X	X	Key aspects should evaluate important body systems as clinically indicated.
Body Weight	X						X		
Vital Signs	X	X	X	X	X	X	X	X	
Concomitant Medication Use	X	X	X	X	X	X	X	X	
Adverse Event Reporting									
Monitor for AE and SAE Assessment	X	X	X	X	X	X	X	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days

Table 2-5: On-treatment Procedural Outline Genital Psoriasis Sub-Protocol (IM0111112), Week 0 through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
									post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
[redacted]									
Clinical Efficacy Assessments									

Table 2-5: On-treatment Procedural Outline Genital Psoriasis Sub-Protocol (IM0111112), Week 0 through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
PASI	X	X	X	X	X	X	X	X	
[redacted]									
s-PGA	X	X	X	X	X	X	X	X	
Evidence of Typical Plaque Psoriasis in Non-genital Area	X								
s-PGA-G[a]	X	X	X	X	X	X	X	X	
[redacted]									
CAPP Objective (Genital Subindex)	X						X		
[redacted]									

Table 2-5: On-treatment Procedural Outline Genital Psoriasis Sub-Protocol (IM0111112), Week 0 through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
[redacted]									

Table 2-5: On-treatment Procedural Outline Genital Psoriasis Sub-Protocol (IM0111112), Week 0 through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
[redacted]									

Table 2-5: On-treatment Procedural Outline Genital Psoriasis Sub-Protocol (IM0111112), Week 0 through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
[redacted]									

Table 2-5: On-treatment Procedural Outline Genital Psoriasis Sub-Protocol (IM0111112), Week 0 through Week 20

Procedure	Week 0 Baseline D1 Visit 1	Week 1 D8 (±3 d) Visit 2	Week 2 D15 (±3 d) Visit 3	Week 4 D29 (±3 d) Visit 4	Week 8 D57 (±3 d) Visit 5	Week 12 D85 (±3 d) Visit 6	Week 16 D113 (±3 d) Visit 7	Week 20 D141 (±3 d) Visit 8	Notes
[redacted]									
Study Intervention									
Randomization via IRT	X								
Dispense Study Intervention	X		X	X	X	X	X	X	
Study Intervention Compliance		X	X	X	X	X	X	X	

Abbreviations: AE, adverse event; [redacted]; CAPP, Comprehensive Assessment of the Psoriasis Patient; D/d, Day; [redacted]; eCOA, electronic clinical outcomes assessments; [redacted] IRT, interactive response technology; [redacted]; PASI, Psoriasis Area and Severity Index; PE, physical examination; [redacted]; SAE, serious adverse event; s-PGA, static Physician Global Assessment; s-PGA-G, static Physician's Global Assessment of Genitalia; [redacted].

[a] In addition to s-PGA-G, the investigator will record on the electronic clinical outcome assessment (eCOA) tablet (yes/no) which exact genital regions are affected by psoriasis (labia minora, labia majora, and/or perineum in women and penis (glans and/or shaft), scrotum, and/or perineum in men; and for men the status of circumcision would be documented).

[redacted]

1) Patient-reported outcome assessments
2) Safety assessments (eg, vitals, AEs)

3) Clinical efficacy assessments
4) Laboratory tests [redacted]

Table 2-6: On-treatment Procedural Outline, Genital Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
Safety Assessments							
Complete PE					X		
Targeted PE	X	X	X	X		X	
Body Weight					X		
Vital Signs	X	X	X	X	X	X	
Concomitant Medication Use	X	X	X	X	X	X	
Adverse Event Reporting							
Monitor for AE and SAE Assessment	X	X	X	X	X	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the

Table 2-6: On-treatment Procedural Outline, Genital Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
							last scheduled visit occurs at a later time
[redacted]							
Clinical Efficacy Assessments							
PASI	X	X	X	X	X		
[redacted]							

Table 2-6: On-treatment Procedural Outline, Genital Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
s-PGA	X	X	X	X	X		
s-PGA-G[b]	X	X	X	X	X		
[redacted]							
CAPP objective (Genital Subindex)	X				X		
[redacted]							

Table 2-6: On-treatment Procedural Outline, Genital Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
[redacted]							

Table 2-6: On-treatment Procedural Outline, Genital Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
[redacted]							

Table 2-6: On-treatment Procedural Outline, Genital Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
[redacted]							
Study Intervention							
Dispense Study Intervention	X	X	X	X			

Table 2-6: On-treatment Procedural Outline, Genital Psoriasis Sub-Protocol (IM0111112), Week 24 through Week 56

Procedures	Week 24 D169 (±3 d) Visit 9	Week 28 D197 (±3 d) Visit 10	Week 32 D225 (±3 d) Visit 11	Week 40 D281 (±3 d) Visit 12	Week 52 (EOT or ET[a]) D365 (±3 d) Visit 13	Safety Follow-up (Week 56 or Post-treatment Follow-up[a]) D393 (±3 d) Visit 14	Notes
Study Intervention Compliance	X	X	X	X	X		
Collect eDiary					X		

Abbreviations: AE, adverse event; [redacted] CAPP, Comprehensive Assessment of the Psoriasis Patient; D/d, Day; [redacted] eCOA, electronic clinical outcomes assessments; EOT, end of treatment; ET, early termination; [redacted]; PASI, Psoriasis Area and Severity Index; PE, physical examination; [redacted]; SAE, serious adverse event; s-PGA, static Physician Global Assessment; s-PGA-G, static Physician's Global Assessment of Genitalia.

[a] EOT/ET visit for participants who discontinue treatment any time prior to completing Week 52 of active treatment period. Safety follow-up visit occurs 28±3 days after the last dose of study treatment.

[b] In addition to s-PGA-G, the investigator will record on the eCOA tablet (yes/no) which exact genital regions are affected by psoriasis (labia minora, labia majora, and/or perineum in women and penis (glans and/or shaft), scrotum, and/or perineum in men; and for men the status of circumcision would be documented).

[redacted]

When multiple assessments are conducted at a single visit, the following is the order in which they should be done as applicable:

1) Patient-reported outcome assessments
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests [redacted]

3 INTRODUCTION

Non-pustular Palmoplantar and Genital Plaque Psoriasis

Psoriasis is a chronic inflammatory skin disorder, characterized primarily by erythematous scaly plaques, that affects up to 3% of the general population. Men and women are equally affected and it can present at any age.[2,3] Several studies have observed a bimodal distribution of psoriasis onset with the first peak ranging from 15 to 22 years of age, and the second peak ranging from 55 to 60 years of age.[4,5,6] The most common form of psoriasis (58% to 97%) is plaque psoriasis (psoriasis vulgaris), with less common forms being guttate, pustular, inverse (flexural), and erythrodermic psoriasis. The disease can have a fluctuating relapsing course, with flares that may be induced by factors such as infections, trauma, smoking, and stress.[4] Psoriasis can involve skin in any part of the body; particularly disabling is the involvement of specific anatomic regions, such as hands and feet (PP), face, scalp, nails, and the genital region. PP psoriasis occurs in 12% to 16% of patients with psoriasis. Despite affecting less than 5% of total body surface area (BSA), PP psoriasis may be associated with greater physical limitations, such as opening a jar and reduced work productivity, as compared to patients with psoriasis in other areas.[7]

GenPs is found in about 30% to 40% of patients with psoriasis and is more common in men. Additionally, 63% of patients with psoriasis report ever having experienced GenPs.[7] Greater than two-thirds of patients with GenPs have never applied treatment to their genital lesions. Moreover, 45% of patients who discussed genital lesions with their physician reported not receiving treatment.[7] It is often overlooked and undiagnosed due to inadequate assessment for genital involvement and unwillingness of patients and medical professionals to discuss GenPs.[8]

Despite often a low total BSA involvement, the National Psoriasis Foundation (NPF) considers PP psoriasis to represent a severe form of psoriasis, because of its significant impact on Quality of Life (QoL).[9] Similarly, according to the Joint American Academy of Dermatology (AAD)-NPF Guidelines, psoriasis can be severe irrespective of BSA, when it has serious emotional consequences or when it occurs in genital area.[10] Despite a limited total BSA, patients with PP psoriasis report greater disability, burning, soreness, and QoL impairment than patients with other forms of psoriasis, with 34%, 48%, and only 18% of patients being severely, moderately, and mildly affected, respectively.[7] The QoL of participants with psoriasis affecting these difficult-to-treat areas may be disproportionately impacted relative to the affected area.[7] For example, the presence of lesions in highly visible areas can affect a participant's self-esteem, whereas involvement of the palms can make activities of daily living challenging. GenPs has a significant negative effect on QoL and sexual health.[7]

Treatments for psoriasis include topical preparations, eg, corticosteroids, vitamin D analogues, calcineurin inhibitors, salicylic acid, urea, and coal tar; phototherapy modalities, including broad-band and narrow band ultraviolet B (UVB); and systemic therapies. In moderate-to-severe disease, systemic treatments are usually needed and may include oral agents (retinoids, methotrexate, cyclosporine, and apremilast) or injectables (eg, biologics such as tumor necrosis

factor [TNF] inhibitors etanercept, infliximab, and adalimumab) anti-interleukins (IL)-12/23p40 antibody (ustekinumab), IL-17 antagonists (secukinumab, ixekizumab, and brodalumab), and anti-IL-23p19 antibody (guselkumab, tildrakizumab, and risankizumab). Many of these treatments are associated with an increased risk of adverse events (AEs) such as hepatotoxicity and neutropenia (methotrexate); [11] nephrotoxicity (cyclosporine); [12] depression and gastrointestinal (GI) effects (diarrhea; apremilast); [13] serious infections (cytokine inhibitors)[14,15,16,17] candidiasis; and Crohn's disease (IL-17 antagonists).[17,18,19] PP psoriasis is considered to be recalcitrant to therapy and is one of the difficult-to-treat sites. While biologic agents typically have better efficacy than other treatment alternatives, their efficacy in this anatomic region is lower as compared to responses of psoriasis in other parts of the body.[9] In cases of GenPs, topical agents or ultraviolet therapy are poorly tolerated or contraindicated in this region, which limits therapeutic options. Patients with genital involvement may be considered candidates for systemic therapy regardless of the total BSA involvement, but there is limited available data from clinical trials specifically designed for GenPs.[8]

Although effective therapeutic options are available, under-treatment or nontreatment of psoriasis has been reported in up to half of surveyed participants (based on absence of treatment and/or dissatisfaction with treatment).[20] Many participants with moderate-to-severe disease are still being managed with only topicals,[5,21] and many participants consider their psoriasis treatment to be inadequate. There remains a significant unmet need for more effective oral options to address difficult-to-treat sites such as PP and GenPs and their impact on symptoms and QoL.

3.1 Study Rationale

SOTYKTU™ (deucravacitinib), a first-in-class, oral, selective, allosteric tyrosine kinase 2 (TYK2) inhibitor is approved in multiple countries for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This approval was based on the results of completed 52-week, randomized, Phase 3, placebo-controlled studies of deucravacitinib 6 mg daily versus placebo and apremilast 30 mg twice daily (POETYK PSO-1 and PSO-2).

In these 2 trials, in addition to the co-primary endpoints of Psoriasis Area and Severity Index (PASI)-75 and static Physician Global Assessment (s-PGA) 0/1 at Week 16, PP psoriasis was assessed using the palmoplantar physician global assessment (pp-PGA) 0/1 and palmoplantar Psoriasis Area and Severity Index (pp-PASI)-75 change from baseline in participants with a pp-PGA score ≥ 3 (moderate-to-severe PP psoriasis) at baseline. Although 16% of the subjects had a history of PP psoriasis, only 7% of subjects in the Phase 3 studies met the baseline pp-PGA ≥ 3 criterion. The individual Phase 3 studies were not sized to specifically assess PP psoriasis. Due to the small numbers of subjects with pre-existing PP psoriasis in each study, the pooled data from PSO-1 and PSO-2 allowed for a more meaningful evaluation. In this analysis of the pooled PSO-1 and PSO-2 population, significantly more participants receiving deucravacitinib (n = 57) versus placebo (n = 25) achieved pp-PGA 0/1 at Week 16 (49.1% versus 16%, p = 0.0052). In the pooled PSO-1 and PSO-2 population, the mean change from baseline in pp-PASI, adjusted for study, body weight, prior biologic use, and the baseline value as a covariate was -13.3 (95% confidence interval

[CI]: -16.3, -10.2) and -4.2 (95% CI: -8.4, -0.0) for deucravacitinib and placebo, respectively. In PSO-1, pp-PGA 0/1 responses at Week 16 were maintained through Week 52 with continuous deucravacitinib treatment (55.6% [95% CI: 32.6, 78.5]).[1] GenPs has not yet been assessed in the deucravacitinib psoriasis clinical program.

Remaining key data gaps include the efficacy of deucravacitinib in improving moderate-to-severe GenPs, PP psoriasis, and health-related Quality of Life measures specifically associated with these difficult-to-treat sites.

The QoL of patients with psoriasis involving difficult-to-treat sites may be disproportionally impacted relative to the affected area. Involvement of these sites is often associated with a disproportionate level of physical impairment and emotional distress. Additionally, PP disease may be associated with increased financial burden due to its interference with the ability to work.[7] Given the relative paucity of data for systemic interventions specifically designed for difficult-to-treat sites, this study aims to evaluate the efficacy of deucravacitinib in improving moderate-to-severe GenPs, PP psoriasis, and health-related Quality of Life measures specifically associated with these difficult-to-treat sites.

This clinical study will use a 2-sub-protocol study design under a master protocol to evaluate the efficacy of deucravacitinib in these 2 difficult-to-treat sites (moderate-to-severe non-pustular PP and GenPs). The choice of a master protocol design to evaluate the safety and efficacy of deucravacitinib in these 2 anatomic regions is based primarily on the overlap and presence of multiple difficult-to-treat sites in psoriasis patients. Participants with involvement of both sites during screening (genital and PP) can only be randomized to 1 of the sub-protocols as per investigator's discretion. In addition, because the experience and available study populations in dermatology clinics commonly cover both of these sites, the master protocol design is likely to facilitate clinical site readiness, recruitment efficiency, and accuracy in investigator assessments. It is further expected that these logistical benefits will require fewer overall sites to complete the study.

3.2 Background

TYK2 is a nonreceptor tyrosine kinase associated with receptors for the p40-containing cytokines IL-12 and IL-23, as well as the Type I interferon (IFN) receptor, and is required for the activation of their downstream signaling pathways. TYK2 catalyzes the phosphorylation of the intracellular receptor domains and signal transducer and activator of transcription (STAT) proteins resulting in the activation of STAT-dependent transcription and functional responses specific for these cytokines.[22,23,24] Because TYK2-dependent cytokines (eg, Type I IFNs, IL-12, IL-23) are distinct from those dependent on closely related Janus kinase (JAK) family members JAK1/JAK3 (eg, IL-2, IL-15, IL-7) or JAK2 (eg, erythropoietin, thrombopoietin, GM-CSF), a TYK2 inhibitor would be expected to have a highly differentiated profile from inhibitors of other JAK family kinases. TYK2-dependent pathways and the cytokine networks they modulate (eg, IL-23/IL-17, IFNα) have been implicated in the pathophysiology of multiple immune-mediated diseases, including psoriasis, lupus, spondylarthritis, and Crohn's disease.

SOTYKTU™ (deucravacitinib), a first-in-class, oral, selective, allosteric TYK2 inhibitor is approved in multiple countries for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This approval was based on the results of completed 52-week, randomized, Phase 3, placebo-controlled studies of deucravacitinib 6 mg daily versus placebo and apremilast 30 mg BID (POETYK PSO-1 and PSO-2).

[redacted]

3.2.1 Clinical Development

The clinical development program for deucravacitinib includes multiple studies in healthy volunteers, participants with renal or hepatic insufficiency, and participants with psoriasis, alopecia areata, psoriatic arthritis, systemic lupus erythematosus, lupus nephritis, Crohn's disease, and ulcerative colitis.

In adult participants with moderate-to-severe psoriasis, one Phase 2 study (IM011011) and two Phase 3 studies (IM011046 and IM011047) have been completed. Study IM011011 was a 12-week, randomized, placebo-controlled study conducted with 5 deucravacitinib intervention arms ranging from 3 mg every other day to 12 mg once daily (QD). Studies IM011046 (PSO-1) and IM011047 (PSO-2) were pivotal, double-blind, placebo- and active-controlled, 52-week, Phase 3 studies. Based on these studies, the United States (US) Food and Drug Administration (FDA) approved SOTYKTU™ (deucravacitinib), a first-in-class, oral, selective, allosteric TYK2 inhibitor, on 09-Sep-2022 for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

There are 2 other completed Phase 3 studies for adult participants with moderate-to-severe plaque psoriasis (IM011065 and IM011066) and an ongoing long-term extension study (IM011075). IM011065 is a double-blind, placebo-controlled, 52-week study conducted in China, Singapore, South Korea, and Taiwan; IM011066 is a single-arm, open-label study conducted in Japan; IM011075 is an open-label study to evaluate the long-term safety, tolerability, and efficacy of deucravacitinib in participants with psoriasis who were previously enrolled in an applicable parent study (IM011046, IM011047, IM011065, or IM011066).

The clinical pharmacology profile of deucravacitinib has been characterized based on the results of multiple clinical pharmacology studies as well as population pharmacokinetics (PK) and exposure-response analyses that incorporated data from Phase 1, Phase 2, and Phase 3 studies in adult participants with moderate-to-severe psoriasis.

[redacted]

3.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of deucravacitinib may be found in the Package Insert or Summary of Product Characteristics.

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment for Deucravacitinib

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infection	Deucravacitinib may increase the risk of infections based on its mechanism of action of selective TYK2 inhibition. In clinical studies, deucravacitinib has been associated with an increased incidence of infections, most commonly upper respiratory infections. Although serious infections have been reported in patients treated with deucravacitinib, available cumulative information does not suggest an increased risk. Upper respiratory infections, herpes simplex infections, and herpes zoster are considered to be adverse reactions for deucravacitinib. See the deucravacitinib IB (Summary of Data and Guidance for Investigator) for further information on the risk of infection.	Specific exclusion criteria are included in this protocol to mitigate the risk of infection. Investigators, clinical personnel, and participants should be aware that this product may decrease resistance to infection. Participants will be followed closely for any signs of infection and will be instructed to immediately report signs or symptoms of infection.
Malignancy	As with any modulator of the immune system, there is a theoretical risk of increased malignancy with deucravacitinib. Mechanistic studies to evaluate the role of TYK2 in malignancies are inconclusive. Malignancies including lymphomas have been observed in clinical trials with deucravacitinib; however, based on the available clinical data and the relevant epidemiology for malignancy, and specifically lymphoma, there does not appear to be a clear association with deucravacitinib exposure. See the deucravacitinib IB (Summary of Data and Guidance for Investigator) for details. The potential role of deucravacitinib in the development of malignancies is currently unknown and will continue to be monitored.	Eligibility criteria are aimed to minimize the risk that a participant with an active or recent history of malignancy will be enrolled. Furthermore, participants will be monitored closely for any symptoms or signs of malignancy throughout the study.

Table 3.3.1-1: Risk Assessment for Deucravacitinib

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Risk from blood sampling	Blood sampling-associated risk of discomfort, syncope, dizziness, and/or infection at the site after or during venipuncture	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation, or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the participant's health.

Abbreviations: IB, Investigator's Brochure; ICF, informed consent form; TYK2, tyrosine kinase 2.

3.3.2 SARS-CoV-2 Pandemic-related Risk Assessment

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial participants in general, and it may particularly affect individuals with underlying chronic diseases who are on immunosuppressive therapies. At this time, Bristol-Myers Squibb (BMS) is tracking and accumulating data on COVID-19 and its potential effects on participants taking deucravacitinib. The data are analyzed on a regular basis. The risk of COVID-19 on participants taking deucravacitinib is still unknown due to insufficient clinical data. As described in the Investigator Brochure and the informed consent form (ICF), deucravacitinib is an immunomodulator with potential immunosuppressive effects and participants taking deucravacitinib may have a higher chance of infections. Accordingly, the studies have exclusion criteria aimed at minimizing the risk for serious infection and with study visits that allow for monitoring of participants' safety. Investigators should ensure that they are able to perform adequate safety assessments. The individual benefit/risk considerations remain the responsibility of the investigator using clinical judgment.

In addition, the Sponsor has also developed guidance for investigators on how to manage a participant with a clinical suspicion of, or a diagnosis of, COVID-19. This includes criteria for temporarily interrupting or permanently discontinuing investigational product (IP; Section 8.1 and Section 8.2), and criteria for reinitiating IP on resolution of a COVID-19 infection (Section 8.2.1). In order to facilitate reporting of COVID-19 events that occur during the study, all AEs and serious adverse events (SAEs) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 must be reported, regardless of relatedness or causality (Section 9.2.2). Such AEs or SAEs reported after randomization will also trigger additional data collection through specialized electronic case report form (eCRF) pages, which will allow the Sponsor to further evaluate these events. Testing to exclude COVID-19 infection

prior to enrollment and to inform decisions about participant care during the study should follow local standard practice and requirements.

3.3.3 Benefit Assessment

The dose selection of deucravacitinib for this study is based on the dose (6 mg QD) used in the adult Phase 3 studies in moderate-to-severe plaque psoriasis. The dose of 6 mg QD is also approved by the FDA and Health Authorities in multiple other countries.

The selection of a 6-mg QD dose in the adult Phase 3 studies was based on the results observed from the Phase 2 dose-ranging study in psoriasis (IM011011). There was a significant relationship between exposure and the PASI-75 responder rates at Week 12, with doses of deucravacitinib 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieving significantly higher PASI-75 responses compared with placebo. Overall, deucravacitinib was safe and well tolerated in all intervention groups in IM011011.

Efficacy and safety were evaluated in 2 pivotal, double-blind, placebo- and active-controlled 52-week, Phase 3 studies (PSO-1 and PSO-2) in adult participants with moderate-to-severe psoriasis. In both studies, statistical significance was achieved for the deucravacitinib group compared with placebo for the co-primary endpoints at Week 16 (s-PGA 0/1 response, PASI-75 response) and for all but the last key secondary endpoint in the statistical hierarchies versus placebo and apremilast. In the subset analysis in the pooled PSO-1 and PSO-2 population, significantly more participants receiving deucravacitinib versus placebo achieved pp-PGA 0/1 at Week 16 (49.1% versus 16%, $p = 0.0052$). Additionally, in these pivotal Phase 3 studies, deucravacitinib demonstrated an acceptable safety and tolerability profile compared with placebo and apremilast. With additional exposure up to 52 weeks, there was no evidence of increased incidence or pattern of AEs, SAEs, or AEs leading to intervention discontinuation.

Based on the totality of in vitro data and clinical data, deucravacitinib doses at clinically-evaluated doses are not anticipated to cause clinically meaningful exposure changes of co-administered agents that are substrates of carboxylesterase 2 (CES2), UDP-glucuronosyltransferase (UGT) enzymes, cytochrome P450s (CYPs), or drug transporters. Details are described in the IB.

Study IM011039 was an open-label, 2-cycle, multiple-dose, single-sequence, crossover study to assess the effect of deucravacitinib 12 mg BID on the PK of norethindrone (NET) and ethinyl estradiol (EE). There were no differences in NET or EE geometric mean maximum concentration (C_{max}) following the coadministration of NET/EE and deucravacitinib compared to NET/EE administration alone. Minimal increases in NET and EE geometric mean AUC(TAU) of approximately 10% and 4%, respectively, were observed following the coadministration of NET/EE and deucravacitinib compared to NET/EE administration alone. Deucravacitinib can be co-administered with oral contraceptives since it has a minor impact on the PK of NET and EE.

3.3.4 Overall Benefit/Risk Conclusion

Taken together, the nonclinical data and clinical data in healthy participants and in those with psoriasis indicate an overall risk/benefit assessment that is appropriate for the investigation of

deucravacitinib as an oral intervention for adult participants with moderate-to-severe non-pustular PP and GenPs.

4 OBJECTIVES AND ENDPOINTS

Objectives and endpoints for non-pustular PP psoriasis sub-protocol are presented in Table 4-1; those for GenPs sub-protocol are presented in Table 4-2.

Table 4-1: Objectives and Endpoints for Non-pustular Palmoplantar Psoriasis Sub-protocol

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by pp-PASI-75, of deucravacitinib versus placebo at Week 16 in participants with PP plaque psoriasis	• pp-PASI-75, defined as a 75% improvement in pp-PASI score from baseline at Week 16
Key Secondary	
• To compare the efficacy, as measured by pp-PGA 0/1, of deucravacitinib versus placebo at Week 16 in participants with PP plaque psoriasis	• Proportion of participants who achieve a pp-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16
Other Secondary	
• To assess the safety of deucravacitinib versus placebo in participants with PP plaque psoriasis between Week 0 and Week 16	• AEs, SAEs, laboratory parameters, and VS between Week 0 and Week 16
[redacted]	

Abbreviations: AE, adverse event; [redacted]; PP, palmoplantar; pp-PASI, palmoplantar Psoriasis Area and Severity Index; pp-PGA, palmoplantar physician global assessment; [redacted] SAE, serious adverse event; VS, vital signs.

Table 4-2: Objectives and Endpoints for Genital Psoriasis Sub-protocol

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by s-PGA-G 0/1, of deucravacitinib versus placebo at Week 16 in participants with GenPs	• s-PGA-G 0/1, defined as proportion of participants achieving s-PGA-G score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16
Key Secondary	
• To compare the efficacy, as measured by change from baseline in GenPs Itch NRS, of deucravacitinib versus placebo at Week 16 in participants with GenPs	• Change from baseline in GenPs itch NRS score at Week 16
• To compare the efficacy, as measured by s-PGA 0/1, of deucravacitinib versus placebo at Week 16 in participants with GenPs	• s-PGA 0/1, defined as proportion of participants achieving s-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16
Other Secondary	
• To assess the safety of deucravacitinib versus placebo in participants with GenPs between Week 0 and Week 16	• AEs, SAEs, laboratory parameters, and VS between Week 0 and Week 16

[redacted]

Abbreviations: AE, adverse event; [redacted]; GenPs, genital psoriasis; [redacted] NRS, numerical rating scale; [redacted]; [redacted] SAE, serious adverse event; s-PGA, static Physician Global Assessment; s-PGA-G, static Physician's Global Assessment of Genitalia; VS, vital signs.

5 STUDY DESIGN

5.1 Overall Design

This master protocol (IM0111112) with 2 sub-protocols is a Phase 4 double-blind, placebo-controlled, multicenter study to compare the efficacy and safety of deucravacitinib in participants with moderate-to-severe non-pustular PP and GenPs versus placebo. Enrollment in each sub-protocol will be concurrent. In both sub-protocols, a placebo control is included to allow the assessment of effects of the intervention. The placebo control will also provide a basis for comparison of safety assessments.

Physical exams, 12-lead electrocardiograms (ECGs; screening only), and clinical laboratory evaluations will be done at selected visits during the study. Participants in this study will be monitored for AEs.

[redacted]

5.1.1 Screening period

For each sub-protocol participants will undergo screening evaluations within 28 days prior to the administration of study intervention to determine eligibility. A detailed medical history will be done at this time, as well as a complete physical examination (PE). Psoriasis-related history, which will include length of diagnosis, GenPs symptoms, PP psoriasis symptoms, scalp symptoms, nail involvement, psoriatic arthritis (PsA)/joint pain, history of other forms of psoriasis, and history of systemic intervention will be assessed here. [redacted].

5.1.2 Intervention period

Participants who have completed the screening procedures and have met the inclusion/exclusion for PP psoriasis sub-protocol will be randomized in a 2:1 ratio to either deucravacitinib 6 mg QD or placebo, respectively. [redacted]. Participants with the presence of pustules (see Section 6.1) would be limited to maximum of 10% of all randomized participants.

Participants who have completed the screening procedures and have met the inclusion/exclusion for the GenPs sub-protocol will be randomized in a 2:1 ratio to either deucravacitinib 6 mg QD or placebo, respectively. [redacted] In addition, the genital sub-protocol will aim to enroll at least 40% of female participants into the study.

Dummy tablets (placebo to deucravacitinib 6 mg tablets) will be administered to participants to maintain blinding. Additional details on maintaining the blind are provided in Section 7.3.1.

5.1.3 Week 16

All efficacy endpoints and safety will be assessed at Week 16 for each sub-protocol independently. At Week 16, all participants regardless of their blinded intervention, will be switched to open label deucravacitinib 6 mg QD bottles through Week 52. Participants randomized to deucravacitinib 6 mg QD will continue their current dose through Week 52.

5.1.4 Week 20

For the PP psoriasis sub-protocol, at Week 20 and at any of the subsequent study visits, a participant with [redacted] may be treated with restricted topical rescue medications/shampoos, such as high potency corticosteroids (World Health Organization [WHO] Classes I-V), > 3% salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene at the discretion of the investigator. Initiated rescue medication may be continued through end of study.

For the GenPs sub-protocol, at Week 20 and at any of the subsequent study visits, a participant with static Physician's Global Assessment of Genitalia [redacted] may be treated with restricted topical rescue medications, such as corticosteroids and/or calcineurin inhibitors at the discretion of the investigator. Participants with [redacted] at week 20, may be treated with restricted topical rescue medications/shampoos, such as high potency corticosteroids (WHO Classes I-V), > 3% salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene for areas outside the genital region at the discretion of the investigator. Initiated rescue medication may be continued through end of study.

5.1.5 Week 52 and Safety Follow-up Period

Participants who discontinue study intervention early/withdraw prematurely must complete the end-of-treatment visit. The participant will be asked to return to the clinic to complete the 28-day safety follow-up visit and encouraged to report any SAEs or AEs experienced during this time.

Participants will be followed up for safety for 4 additional weeks, from Weeks 52 through 56.

[redacted]

5.1.6 Data Monitoring Committee and Other Committees

A Data Monitoring Committee will not be used in the study.

Other Committee Charters will describe the procedures related to the committee operations in greater detail.

5.1.6.1 Study Steering Committee

The Study Steering Committee (SSC) is a committee composed of external experts who assist with the study strategy, protocol development, site identification and patient recruitment strategies. The SSC responsibilities, authorities, and procedures will be documented and followed according to the SSC Charter.

[redacted]

5.3 End of Study Definition

For this master protocol, because each sub-protocol will enroll participants independently of each other, each sub-protocol will have its separate, independent start, primary completion date, and the study end. The start of the study is defined as the first participant's first visit in any of the 2 sub-protocols.

The primary completion date for each sub-protocol is defined as the date on which the last data point is collected for that sub-protocol's primary endpoint. If the sub-protocol has multiple primary endpoints, the primary completion date is the date on which the last data point is collected for the last primary endpoint.

End of study is defined as the last participant's last visit in a remaining sub-protocol.

A participant is considered to have completed each sub-protocol if he/she has completed the last visit or the last procedure shown in the Schedule of Activities (Section 2).

5.4 Scientific Rationale for Study Design

Both Phase 4 studies as part of the master protocol will be conducted in a population of participants with stable moderate-to-severe non-pustular PP and genital plaque psoriasis who are candidates for systemic psoriasis therapy. The PP psoriasis sub-protocol is designed to compare the efficacy and safety of deucravacitinib to placebo in achieving pp-PASI-75 at Week 16. pp-PASI-75 is a standard measure in clinical trials of demonstrating efficacy of systemic psoriasis treatments on

palms and soles. The GenPs sub-protocol is designed to compare the efficacy and safety of deucravacitinib to placebo in achieving s-PGA-G 0/1 at Week 16. s-PGA-G 0/1 is a standard measure in clinical trials of demonstrating efficacy of systemic psoriasis treatments in GenPs. A placebo arm in both sub-protocols is included for a short duration of 16 weeks to provide a control for the natural fluctuation of psoriasis activity that may occur and to provide a safety standard for comparison. Participants in the placebo arm in both sub-protocols will be switched to open-label deucravacitinib at Week 16 to provide them psoriasis treatment after the endpoints are collected. Week 16 was chosen for the primary endpoint evaluations, as it will allow enough time for deucravacitinib to treat psoriasis and was the primary endpoint used in the PSO-1/PSO-2 Phase 3 trials. The purpose of doing a 52-week study is to demonstrate the maintenance of improvement in clinical response and patient-reported outcomes (PROs).

[redacted]

5.5 Justification for Dose

The dose of 6 mg QD is the approved dose by health authorities in multiple countries for the treatment of adults with moderate-to-severe plaque psoriasis. The recommended dose for deucravacitinib in each of the sub-protocols aims to achieve similar exposure level to that of 6 mg QD used in the Phase 3 studies in adult psoriasis participants, which is based on the efficacy and safety results from the Phase 2, placebo-controlled, dose-ranging study of this compound in adult participants with moderate-to-severe plaque psoriasis (IM011011). The results from the two Phase 3 studies demonstrated that deucravacitinib at 6 mg QD achieved significantly higher PASI-75 and s-PGA 0/1 responses compared with placebo at Week 16.

[redacted]

5.7 Rationale for Optional Future Research

Future research may be performed using residual samples originally collected for another test required in this study from consented participants only. Future research is intended to allow for research aimed at emergent or future questions that are not addressed elsewhere in the protocol and may include research that is unrelated to the study intervention(s) and/or disease under study.

[redacted]

6 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure: 1) selection of appropriate participants with PP and GenPs, 2) safety of the study participants. It is imperative that participants fully meet all eligibility criteria.

All screening and randomization evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

2) Type of Participant and Target Disease Characteristics

Non-pustular Palmoplantar Psoriasis Sub-protocol

a) Men and women diagnosed with stable plaque psoriasis with involvement of the palm(s) and/or sole(s) for at least 6 months or more. Stable psoriasis is defined as no morphology changes or significant flares of disease activity in the opinion of the investigator.
b) Moderate-to-severe plaque psoriasis defined as s-PGA score of ≥ 3 on a 5-point scale at both screening visit and Day 1.
c) Moderate-to-severe non-pustular PP psoriasis, defined as pp-PGA score of ≥3 on a 5-point scale and pp-PASI ≥ 8 at both screening visit and Day 1.
    i) A total maximum of 5 sterile pustules across both palms and soles limited only to psoriatic plaques will be allowed.
d) Evidence of typical plaque psoriasis outside palms and soles at both screening visit and Day 1.
e) Deemed by the investigator to be a candidate for phototherapy or systemic therapy.
f) Failed to respond to, or intolerant of ≥ 1 topical therapy.

Genital Psoriasis Sub-Protocol

a) Men and women diagnosed with stable plaque psoriasis with involvement of the genital area for at least 6 months or more. Stable psoriasis is defined as no morphology changes or significant flares of disease activity in the opinion of the investigator.
b) Moderate-to-severe plaque psoriasis defined as s-PGA score of ≥ 3 at both screening visit and Day 1.

c) Moderate-to-severe GenPs, defined as s-PGA-G score of ≥ 3 on a 6-point scale at both screening visit and Day 1.

d) Evidence of typical plaque psoriasis in a non-genital area at both screening visit and Day 1

e) Deemed by the investigator to be a candidate for phototherapy or systemic therapy.

f) Failed to respond to, or intolerant of ≥ 1 topical therapy.

3) Age of Participant

a) Participant must be ≥ 18 years of age inclusive at the time of signing the ICF.

4) Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP; as defined in Appendix 4) participants and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

- The investigator shall evaluate the effectiveness of the contraceptive method in relation to the first dose of study intervention.

- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants:

i) To be considered not of childbearing potential, female participants must have documented proof that they are not of childbearing potential.

(1) Women who are not of childbearing potential (as defined in Appendix 4) are exempt from contraceptive requirements.

ii) WOCBP must have a negative highly sensitive serum pregnancy test at the screening visit, and a negative highly sensitive urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in the Schedule of Activities (Section 2).
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to potentially decrease the risk for inclusion of a woman with an undetected pregnancy.

iii) WOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.

- WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

iv) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 4, during the study period until the end of the study.

b) Male Participants

i) Male participants should maintain their usual practice regarding contraception (if any); no specific or additional contraceptive measures are required.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Target Disease Exceptions

a) Has non-plaque psoriasis (ie, PP pustulosis, PP pustular psoriasis, isolated pustules on palms or soles with or without erythema outside psoriatic plaques, guttate, pustular, erythrodermic, and drug-induced psoriasis) at screening or Day 1.

2) Reproductive Status

a) Pregnancy, lactation, breastfeeding, or planning pregnancy during the study period.

3) Infectious/Immune-related Exclusions

a) History or evidence of outpatient active infection and/or febrile illness within 7 days prior to Day 1.

b) History of serious bacterial, fungal, or viral infection requiring hospitalization and/or intravenous (IV) antimicrobial treatment within 60 days prior to Day 1.

c) Any untreated bacterial infection within 60 days prior to Day 1.

d) Any ongoing evidence of chronic, bacterial infection (eg, chronic pyelonephritis, chronic osteomyelitis, chronic bronchiectasis).

e) Any history of proven infection of a joint prosthesis in which the prosthesis was not removed or replaced, or received antibiotics for suspected infection of a joint prosthesis in which the prosthesis was not removed or replaced.

f) Received live vaccines within 60 days prior to Day 1, or plans to receive a live vaccine during the study, or within 60 days after completing study treatment.

g) Received any non-live vaccine within 30 days prior to Day 1 including any COVID-19 vaccine (first, second, or booster dose).

h) Presence of herpes zoster lesions at screening or Day 1.

i) History of serious herpes zoster or serious herpes simplex infection which includes, but is not limited to, any episode of disseminated herpes simplex, multidermatomal herpes zoster, herpes encephalitis, ophthalmic herpes, or recurrent herpes zoster (recurrent is defined as 2 episodes within 2 years).

j) Evidence of, or test positive for, hepatitis B virus (HBV) at screening. Positive hepatitis B lab testing is defined as (please see Appendix 6 for details):

i) Positive hepatitis B surface antigen (HBsAg+)

OR

ii) Positive anti-hepatitis B core antibody without concurrent positive hepatitis B surface antibody (HBcAb+ and HBsAb-).

k) Evidence of, or test positive for, hepatitis C virus (HCV) at screening. A positive test for HCV is defined as:

i) Positive for anti-hepatitis C antibody (anti-HCVAb)

AND

ii) Positive via a confirmatory test for HCV (eg, HCV polymerase chain reaction).

l) Positive for human immunodeficiency virus by antibody testing (HIV1 and 2 Ab) at screening.

m) Any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the participant's immune status (eg, history of opportunistic infections [eg, Pneumocystis jirovecii pneumonia, histoplasmosis, or coccidioidomycosis], history of splenectomy, primary immunodeficiency).

n) Severe SARS-CoV-2 infection within 4 weeks prior to screening. Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the clinical study physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

4) Any of the following TB criteria:

a) Participant has a history of active TB prior to screening visit, regardless of completion of adequate treatment.

b) Participant has signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator.

[redacted]

[redacted]

5) Medical History and Concurrent Diseases

a) Any major surgery within 8 weeks prior to Day 1, or any major planned surgery for the first 52 weeks of the study.

b) Drug or alcohol abuse, as determined by the investigator, within 6 months prior to Day 1.

c) Medical marijuana or prescription marijuana taken for medicinal reasons.

d) Any major medical or neuropsychiatric illness/condition or evidence of an unstable clinical condition (eg, systemic inflammatory or immune-mediated disease, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, psychiatric, or neurologic) that, in the investigator's judgment or after consultation with the BMS Medical Monitor, will substantially increase the risk to the participant if he or she participates in the study.

e) Unstable cardiovascular disease, defined as a recent clinical cardiovascular event (eg, unstable angina, myocardial infarction, stroke, rapid atrial fibrillation) in the last 3 months prior to screening, or a cardiac hospitalization (eg, revascularization procedure, pacemaker implantation) within 3 months prior to screening.

f) Has uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg.

Note: Determined by 2 consecutive elevated readings. If an initial BP reading exceeds this limit, the BP may be repeated once after the participant has rested sitting for ≥ 10 minutes. If the repeat value is less than the criterion limits, the second value may be accepted.

g) Class III or IV congestive heart failure by New York Heart Association Criteria.

h) Has cancer or history of cancer (solid organ or hematologic including myelodysplastic syndrome) or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell or squamous cell carcinoma, or carcinoma of the cervix in situ that has been treated with no evidence of recurrence).

[redacted]

j) If the participant has received biologics previously, the following exclusion criteria for washout will apply:

i) Antibodies to IL-12/23, IL-17, or IL-23 (eg, ustekinumab, secukinumab, tildrakizumab, ixekizumab, guselkumab, tildrakizumab, and risankizumab) within 6 months of Day 1.

ii) TNF inhibitor(s) (eg, etanercept, adalimumab, infliximab, certolizumab) within 2 months of Day 1.

iii) Agents that modulate integrin pathways to impact lymphocyte trafficking (eg, natalizumab), or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, or visilizumab) within 3 months of Day 1.

iv) Rituximab within 6 months of Day 1.

k) Has received systemic nonbiologic psoriasis medications and/or any systemic immunosuppressants (including, but not limited to, methotrexate, azathioprine, cyclosporine, JAK inhibitors, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus, oral or injectable corticosteroids, retinoids, psoralens, sulfasalazine, or fumaric acid derivatives and apremilast) within 4 weeks prior to Day 1.

l) Has used leflunomide within 6 months prior to Day 1.

m) Has used opioid analgesics within 4 weeks prior to Day 1.

n) Has received lithium, antimalarials, or intramuscular gold within 4 weeks of the first administration of any study medication.

o) Has received phototherapy (including either oral and topical psoralen plus ultraviolet A light therapy, UVB, or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to Day 1.

p) Has used topical medications/treatments that could affect psoriasis evaluation (including, but not limited to, high potency corticosteroids (WHO Classes IV), > 3% salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, and tacrolimus) and intralesional corticosteroids within 2 weeks prior to Day 1.

Note: Low potency topical steroids (WHO Class VI and VII) are permitted on the palms, soles, face (in the GenPs sub-protocol), and on the face and intertriginous areas (in the PP psoriasis sub-protocol) but should not be used within 24 hours prior to any study visit. Bland emollients (defined as emollients without urea or alpha or beta-hydroxy acids or other ingredients which are pharmacologically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit.

q) Use of shampoos that contain corticosteroids, coal tar, > 3% salicylic acid, or vitamin D3 analogues within 2 weeks prior to Day 1.

r) Has received an experimental antibody or experimental biologic therapy within the previous 6 months OR received any other experimental therapy or new investigational agent, including those for SARS-CoV-2, within 30 days or 5 half-lives (whichever is longer) prior to Day 1 OR is currently enrolled in an investigational study.

s) Any other sound medical, psychiatric, and/or social reasons as determined by the investigator.

6) Physical and Laboratory Test Findings

a) At screening

i) Absolute white blood cell count < 3,000/mm^3

ii) Absolute lymphocyte count < 500/mm^3

iii) Absolute neutrophil count < 1,000/mm^3

iv) Platelet count < 100,000/mm^3

v) Hemoglobin < 9 g/dL

vi) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3× upper limit of normal (ULN)

vii) Total, unconjugated, and/or conjugated bilirubin > 2× ULN

viii) ECG abnormalities that are considered clinically significant and would pose an unacceptable risk to the participant if participating in the study.

ix) Inability to undergo venipuncture and/or tolerate venous access.

x) Any other significant laboratory abnormalities that, in the opinion of the investigator, might place the participant at unacceptable risk for participation in this study.

7) Allergies and Adverse Drug Reactions

a) History of any significant drug allergy (such as anaphylaxis).

8) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

c) Inability to comply with restrictions and prohibited activities/treatments as listed in the study protocol.

d) Site personnel or their immediate family.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

General skin care measures (with above restrictions for topical interventions) are recommended that are standard for participants with plaque psoriasis. Participants should avoid excessive sun exposure or use of tanning booths or other ultraviolet light sources and avoid risks that are known to provoke flare of psoriasis.

6.3.1 Meals and Dietary Restrictions

Study intervention may be taken without regard to meals; however, participants are required to fast for a minimum of 10 hours before visits during which fasting lipid samples will be drawn.

6.3.2 Caffeine, Alcohol, and Tobacco

No restrictions are required; however, extensive use of alcohol, tobacco, and vaping should be avoided.

6.3.3 Activity

No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) that occurred following consent.

6.4.1 Re-testing During Screening or Re-screening

For laboratory parameters that initially do not meet eligibility requirements, a single retest within the 28-day screening period is permitted before participant is declared a screen failure. This is an effort to find all possible well-qualified participants. Consultation with the Medical Monitor or designee may be needed to identify whether repeat testing of any particular parameter would be clinically relevant.

The study permits the rescreening (after the end of the initial 28-day screening period) of a participant who discontinues the study as a pretreatment failure (ie, the participant fails to meet eligibility criteria and has not been treated). If re-enrolled, the participant must be reconsented, assigned a new identification number by interactive response technology (IRT), and a full screening visit must be performed again. A participant can only be rescreened 1 time (ie, if the participant fails 1 rescreening attempt, no additional rescreening is allowed). Depending on the timing of re-screening, repetition of some assessments may not be required. The fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility. In these cases, the site should consult with the BMS Medical Monitor (or designee). Similarly, repeat [redacted], if performed during screening, may not be required. The study also permits the re-screening of a participant to a second sub-protocol if they fail to meet eligibility criteria for the first sub-protocol. The participant must be assigned a new identification number by IRT.

Duration of existing interventions and required discontinuation periods shall be considered relative to the new screening visit and/or randomization.

The most current result(s) prior to randomization is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s), or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) as indicated in Table 7.1-1.

An IP, also known as an IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently from the authorized form, used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis may be considered Non-IMPs.

7.1 Study Interventions Administered

The selection and timing of dose for each participant are as follows in Table 7.1-1.

Table 7.1-1: Study Interventions

ARM Name	Deucravacitinib (BMS-986165)	Placebo
Intervention name	Deucravacitinib	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Placebo tablet
Unit Dose Strength(s)	6 mg	n/a
Dosage Level(s)	1 active tablet QD in the morning	1 placebo QD in the morning
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in a bottle. Each bottle will be labeled as per country requirement.

Abbreviations: AxMP, auxiliary medicinal products; n/a, not applicable; IMP, investigational medicinal product; NIMP, non-investigational medicinal product; QD, once daily.

7.2 Assignment to Study Intervention

Before the study is initiated, each user (at investigative sites) will receive login information and directions on how to access the IRT system. At the time of the screening visit, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a participant number for all participants, including participants not subsequently randomized or treated. The participant number is assigned sequentially by the system and will be unique across

all sites. All enrolled participants will be assigned sequential participant numbers. The participant number will not be used for any other participant. If a participant is rescreened, they will be given a new identification number. Participants with both PP and genital involvement can only be enrolled to 1 of the sub-protocols, and this decision is at the discretion of the investigator.

At Week 0 (Day 1), participants who meet all criteria for enrollment for PP sub-protocol at screening and Day 1 will be centrally randomized in a 2:1 ratio to deucravacitinib 6 mg QD or placebo as determined by a computer-generated randomization schedule using IRT. The randomization lists will be generated by the IRT vendor using a permuted block design within each stratum level. [redacted] Participants with the presence of pustules (see Section 6.1) would be limited to a maximum of 10% of all randomized participants.

At Week 0 (Day 1), participants who meet all criteria for enrollment for genital sub-protocol at screening and Day 1 will be centrally randomized in a 2:1 ratio to deucravacitinib 6 mg QD or placebo as determined by a computer-generated randomization schedule using IRT. The randomization lists will be generated by the IRT vendor using a permuted block design within each stratum level. [redacted] The study will aim to enroll at least 40% of female participants into the study.

After all eligibility criteria have been met for a participant (ie, all inclusion criteria met, and all exclusion criteria not met), the investigative site will access the IRT on Day 1 for the purpose of randomizing a participant for each sub-protocol. A treatment group will be assigned by IRT based on the above-described randomization schedule, and each participant will be assigned a unique randomization number. In addition, a unique kit number will be assigned to the participant corresponding to the treatment assignment.

Study treatment for each sub-protocol will be dispensed at study visits as shown in the Schedule of Activities (Section 2). When new treatment kits need to be provided, the investigative site will access the IRT to obtain the kit number to assign to the participant.

At Week 16 in both sub-protocols, all participants regardless of their blinded intervention, will be switched to open-label deucravacitinib 6 mg QD bottles through Week 52.

7.3 Blinding

This is a randomized, double-blind, placebo-controlled study.

7.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT. IP supply will be controlled by IRT at each visit.

All tablets are identical in appearance and will be supplied in bottles with each daily dose made up of the appropriate combination of active and/or placebo tablets to provide the correct treatment, as shown in Table 7.1-1. Investigative site staff, Sponsor and designated personnel, and participants and their families will remain blinded to treatment assignments.

The Sponsor and site-facing study team will be unblinded to the individual treatment assignments at the primary endpoint database lock after the last participant has completed the Week 16 visit independently for each sub-protocol. The primary analysis database lock will occur after all randomized participants completed their Week 16 visit or discontinued prior to Week 16 independently for each sub-protocol. The study participants and investigators will remain blinded to the initial treatment assignment received from Day 1 to Week 16 throughout the study.

7.3.2 Circumstances for Unblinding

Blinding of study intervention assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining whether a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving the IP. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The principal investigator or appointed designee should only perform the emergency unblinding after the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is described in the IRT manual.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to minimize additional disclosure and the impact of unblinding.

Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor.

In case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. After the unblinding, the investigator shall notify the Medical Monitor or designee and/or study director. Participant and unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the eCRF. After unblinding via IRT, the investigator shall notify the Medical Monitor or designee.

If a participant is unblinded for any reason, the participant will be discontinued from treatment.

7.4 Dosage Modification

There is no provision for dose modification of study treatment. If a participant interrupts treatment due to an AE, study treatment can be restarted in consultation with the Medical Monitor.

7.5 Preparation/Handling/Storage/Accountability

The IP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and the Sponsor should be contacted immediately.

Study intervention not supplied by the Sponsor will be stored in accordance with the package insert.

IP documentation (whether supplied by the Sponsor or not) must be maintained and must include all processes required to ensure the drug is accurately administered. This includes documentation of drug storage, administration, and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before the use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

7.6 Study Intervention Compliance

When participants self-administer study interventions at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, and counting returned tablets, etc. during the site visits and documented in the source documents and relevant form. Deviations from the prescribed dosage regimen should be recorded in the eCRF.

A record of the quantity of Deucravacitinib and Placebo for Deucravacitinib dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

7.7 Concomitant Therapy

[redacted]

7.7.2 Permitted Concomitant Medication

Participants may take any medication that is not restricted by the protocol, is not expected to interfere with the conduct of the study, and will not affect study assessments. Stable doses of concomitant medication for chronic medical conditions are permitted as long as neither the medication nor the medical condition meets exclusion criteria as detailed in Section 6. Dose adjustments of these medications should be avoided during the study unless clinically indicated. If a dose adjustment of these medications should occur, they must be recorded on the Concomitant Medications eCRF. Any concomitant therapies must be recorded on the (e)CRF. The investigator should instruct the participant to notify the study site about any new treatment he/she takes after the start of the study intervention. All medications and significant nondrug therapies (including physical therapy and blood transfusions) administered after the participant starts study intervention must be listed on the Concomitant Medications eCRF.

Concomitant medications (prescription, over the counter, or herbal) should be administered during the study only if they are to be used for treatment of specific medical reasons.

Low potency topical steroids (WHO Class VI and VII) are permitted on the palms, soles, face (in the GenPs sub-protocol), and on the face and intertriginous areas (in the PP psoriasis sub-protocol) but should not be used within 24 hours prior to any study visit. Bland emollients (defined as emollients without urea or alpha- or beta-hydroxy acids or other ingredients which are pharmacologically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit.

[redacted]

7.7.4 Permitted Vaccines (including COVID-19 Vaccine)

- Administration of a non-live vaccine is allowed during the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving deucravacitinib are unknown. The following are examples of non-live vaccines: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines (eg, influenza and

pneumococcal vaccines), toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (eg, Pfizer/BioNTech and Moderna COVID-19 vaccines) and replication-incompetent recombinant vector vaccines (eg, AstraZeneca/University of Oxford COVID-19 vaccine).

- For COVID-19 vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed 30 days prior to Day 1. Ideally, AEs attributable to a vaccine should have resolved prior to enrollment.
- If a participant receives a COVID-19 vaccination during the study, details such as type and date of vaccine received should be recorded on the COVID-19 vaccination eCRF page. For COVID-19 vaccines administered prior to enrollment, the types, details, and dates should be also recorded on the appropriate COVID-19 vaccination eCRF page.
- Please contact the Medical Monitor or designee with any questions related to COVID-19 vaccines.

7.7.5 Other Restrictions and Precautions

Participants are prohibited from joining another clinical trial while they are participating in this study.

7.8 Continued Access to Study Intervention After the End of the Study

At the end of the study, the Sponsor will not continue to provide Sponsor-supplied study intervention to participants/investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 2.

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Any clinical AE, laboratory test result abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)

- Abnormal liver tests suggestive of drug-induced liver injury (DILI), as defined in Section 9.2.7 or if the investigator believes that it is in the best interest of the participant.
- The participant develops a malignancy, with the exception of a participant who develops nonmelanoma skin cancer who may continue in the study at the discretion of the investigator.
- Pregnancy, positive pregnancy test or participant expresses an interest in becoming pregnant (refer to Section 9.2.5).
- Participant develops active TB during the study or prematurely discontinues intervention for LTBI, or participant is noncompliant with LTBI therapy (Section 6.2).
- Unblinding of a participant's intervention assignment for any reason (emergency or nonemergency).
- Inability or failure to comply with protocol requirements in the opinion of the investigator (eg, procedures, assessments, medications, etc.). The investigator should discuss such issues with the Medical Monitor.

Refer to Section 2 Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2: Schedule of Activities. The only exception to this requirement is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Temporary Discontinuation From Study Intervention

Temporary study intervention discontinuation is only allowed if the participant develops an AE which, in the opinion of the investigator, indicates that it is in the participant's best interest that the study intervention be placed on hold. Study intervention in this situation should be stopped until the AE is medically treated and has resolved per the principal investigator's judgment.

Temporary interruption of study treatment should be implemented in the context of clinical suspicion for SARS-CoV-2 or a positive diagnostic test for SARS-CoV-2. When study treatment is interrupted in a confirmed case of SARS-CoV-2, the investigator, in consultation with the Medical Monitor, should determine whether the resolution of symptoms alone (ie, without repeat diagnostic testing for SARS-CoV-2) is sufficient to resume study treatment.

Temporary interruption of study intervention may be considered in the event of SARS-CoV-2 vaccination according to local guidelines.

Any temporary study intervention discontinuation, as well as restart, must be documented in the corresponding eCRF.

8.1.2 Post-study Intervention Study Follow-up

In this study, efficacy is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed in this study for collection of outcome data as required and in line with Section 5 until the conclusion of the study.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities (Section 2). See the Schedule of Activities (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from both the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails, as well as lack of response by participant to **1** registered mail letter. All attempts should be documented in the participant's medical records.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data, such as public health registries and databases, necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).
- For several assessments, appropriate training will be provided to investigators and designated personnel at sites. Only those individuals trained and certified to perform these assessments will be performing them during the study.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

- As part of the online questionnaire (eCOA), the study Sponsor may collect and use information about the gender that participants identify with, sexual orientation, and intersex status. At the conclusion of the study, summaries of this information, including information already collected about race, ethnicity, and gender, across all study participants will be developed to understand the populations that participated in the study. In addition, in the future, this data may be combined with data from other BMS studies to conduct subsequent research on how the disease or treatments impacts certain populations. Answering the questions about the gender you identify with, sexual orientation, and intersex status is voluntary, and participants are not required to answer these questions in the questionnaire to take part in this clinical study.

9.1 Efficacy Assessments

Every effort must be made to ensure that the same evaluator(s) complete the assessment for each participant. If the evaluator(s) is/are unable to complete the evaluation, then a qualified individual with overlapping experience may perform the evaluation. Documentation of who performed the evaluation is to be recorded in source documents. Assessments are to be performed at approximately the same time of day throughout the duration of the study.

Baseline assessments must be performed per protocol (standard-of-care assessments may not be used for baseline). Procedures not specified in the protocol that are part of standard care may be performed if they do not interfere with study procedures; any data arising from such procedures are not to be reported in the eCRF.

[redacted]

9.1.1 Assessments used in both sub-protocols

9.1.1.1 Investigator-administered Assessments

9.1.1.1.1 Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the average redness, thickness, and scaliness of psoriatic skin lesions (each graded on a 0 to 4 scale), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks).[26] The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. The PASI can also be used to assess response to treatment. The PASI-50 is the proportion of participants who experience at least a 50% improvement in PASI score as compared with the baseline value. The PASI-75, PASI-90, and PASI-100 are defined similarly. BMS will host a training session prior to initiation of the study to demonstrate proper PASI scoring. All PASI assessments should be performed by a trained physician (dermatologist) or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

[redacted]

9.1.1.1.3 Static Physician's Global Assessment (s-PGA)

The s-PGA is a 5-point scale of an average assessment of all psoriatic lesions based on erythema, scale, and induration.[30] The s-PGA measure determines psoriasis severity at a single point in time (without taking into account the baseline disease condition) as clear (0), almost clear (1), mild (2), moderate (3), or severe (4). All s-PGA assessments should be performed by a trained physician (eg, dermatologist) or appropriately trained investigator who is experienced in the assessment of psoriasis patients. Every effort should be made to ensure that the physician or designee who performed the s-PGA evaluations for a participant at randomization performs the s-PGA for that participant at all subsequent visits.

[redacted]

9.1.2 Palmoplantar Sub-protocol Specific Assessments

9.1.2.1 Investigator-administered Assessments

9.1.2.1.1 Palmoplantar Physician's Global Assessment (pp-PGA)

The pp-PGA is a 5-point scale of an average assessment of PP involvement.[34] The pp-PGA measure determines psoriasis severity at a single point in time (without taking into account the baseline disease condition) as clear (0), almost clear (1), mild (2), moderate (3), or severe (4). All pp-PGA assessments should be performed by a trained physician (eg, dermatologist) or appropriately trained investigator who is experienced in the assessment of psoriasis patients. Every effort should be made to ensure that the physician or designee who performed the pp-PGA evaluations for a participant at randomization performs the pp-PGA for that participant at all subsequent visits.

9.1.2.1.2 Palmoplantar-Psoriasis Area and Severity Index (pp-PASI)

The pp-PASI is an adaptation of the PASI grading system to evaluate the severity of PP (including the finger and toe surfaces) psoriatic lesions and their response to treatment. [35] The pp-PASI produces a numeric score that can range from 0 to 72.

The pp-PASI is divided into 4 regions: the right palm, the left palm, the right sole, and the left sole. Each palm contributes 20% and each sole contributes 30% to the total PP surface area. Each of these areas are evaluated for erythema, induration, and scaling, which are rated on a scale from 0-4. Each of these areas are evaluated for percent involvement and assigned a score based on a 0-6 scale. The pp-PASI should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

[redacted]

9.1.3 Genital Psoriasis Sub-protocol Specific Assessments

9.1.3.1 Investigator-administered Assessments

[redacted]

9.1.3.1.2 s-PGA of Genitalia (s-PGA-G)

The s-PGA-G is the clinician's determination of the participant's psoriasis lesions' overall severity in the genital area (labia majora, labia minora, and perineum in females; penis, scrotum, and perineum in males) at a given timepoint. Overall, lesions are categorized by descriptions for

elevation, erythema, and scaling.[39] It is not necessary that all 3 criteria be fulfilled. The s-PGA-G score is based on a combination of erythema and the secondary features (plaque elevation and/or scale). Since erythema is the most robust finding, it should be the dominant feature influencing the s-PGA-G rating in the majority of cases. For the analysis of responses, the patient's psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). All s-PGA-G assessments should be performed by a trained physician (eg, dermatologist) or appropriately trained investigator who is experienced in the assessment of psoriasis patients. Every effort should be made to ensure that the physician or designee who performed the s-PGA-G evaluations for a participant at randomization performs the s-PGA-G for that participant at all subsequent visits.

[redacted]

9.1.3.1.4 Comprehensive Assessment of Psoriasis Patient (CAPP)– Genital Subindex Objective

Comprehensive Assessment of the Psoriasis Patient (CAPP) is a disease severity measure to assess the full burden of plaque psoriasis and subtypes, including inverse, scalp, nail, PP, and GenPs.[43] Only the genital subindex will be utilized for this study. Severity of genital areas involved by psoriasis (suprapubic area, perineum and in male: scrotum, penis; in female: labia major and/or minora) will be graded as 0 = clear; 2 = erythema, no raised plaques, no scale; 4 = erythema, mildly thick plaques, mild scale; 6 = erythema, moderately thick plaques, mild scale; 8 = prominent erythema, moderately thick plaques, moderate scale OR fissuring present; 10 = prominent erythema, thick plaques, hypertrophic scale with/without excoriations, irrespective of area involved OR skin tearing present. (For severity scores 2 to 8: +2 if labia minora or glans penis involvement). PROs of pain and intimacy would be evaluated using VAS (minimal score 0, maximum score 10). The final genital severity score = measured genital severity plus the higher of the 2 PRO VAS scores (minimal score 0, maximum score 20).

[redacted]

[redacted]

9.1.4 Additional Assessments

[redacted]

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, a surrogate, or the participant's legally acceptable representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

Refer to Appendix 3 for SAE reporting.

9.2.1 Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and until 30 days following discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

The investigator must report any SAE that occurs after these periods and that is believed to be related to a study intervention or protocol-specified procedure.

- All SAEs will be recorded and reported to the Sponsor or designee, promptly and not to exceed 24 hours of awareness of the event, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified non-serious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported/identified during the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, [redacted], will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A suspected, unexpected serious adverse reaction is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

This section is not applicable for Women Not of Childbearing Potential.

If, following initiation of the study intervention, it is discovered that a participant is pregnant or may have been pregnant at the time of study intervention exposure, including at least 30 days after study product administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In all cases, the study intervention will be discontinued immediately.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcomes and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the Adverse Events – Nonserious and Serious Events CRF page. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE.
- Any laboratory test result abnormality that requires the participant to have study intervention discontinued or interrupted.
- Any laboratory test result abnormality that requires the participant to receive specific corrective therapy.

It is expected that, wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory test result abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

A potential DILI is defined as follows:

- Aminotransferase (ALT or AST) elevation > 3× ULN

  AND

- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

  AND

- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, radiographic imaging, or any other potential safety assessment required or not required by the protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

[redacted]

[redacted]

9.3 Overdose

For this study, any dose of deucravacitinib greater than [redacted] within a 24-hour period will be considered an overdose. Overdoses that meet the regulatory definition of an SAE will be reported as SAEs (see Appendix 3).

In the event of an overdose, the investigator should:

1) Contact the Medical Monitor or designee immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities for at least 5 half-lives of deucravacitinib, approximately 3 days.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor or designee based on the clinical evaluation of the participant.

9.4 Safety

Planned timepoints for all safety assessments are listed in Section 2: Schedule of Activities.

9.4.1 Physical Examinations

A complete PE will include general appearance, vital signs, eyes, ears, nose, mouth, throat, neck, respiratory, cardiovascular, respiratory, GI/abdomen, lymphatic, musculoskeletal, skin, psychiatric, and neurologic exams. A targeted PE will include any organ system associated with an AE or a laboratory abnormality.

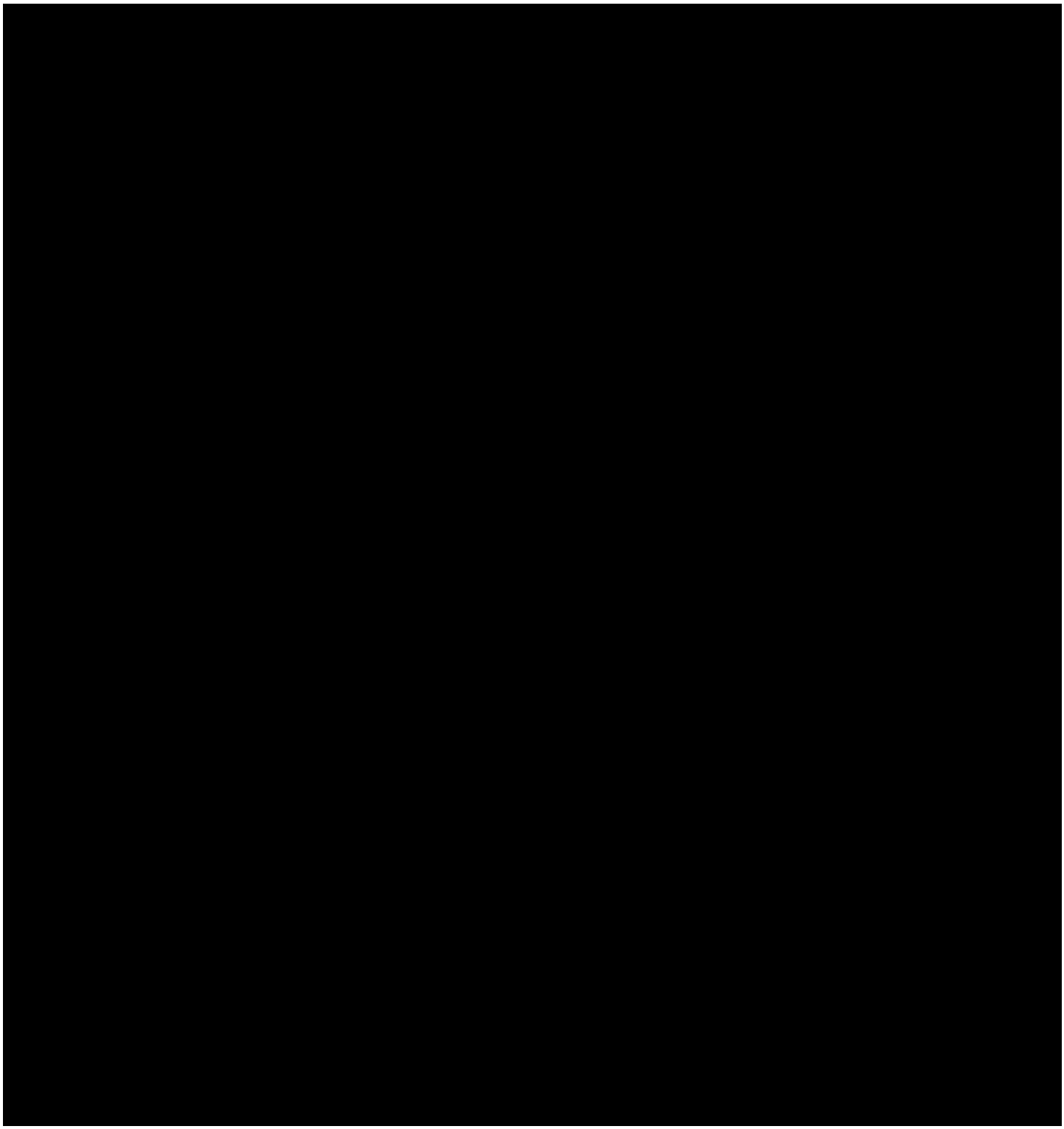
While the targeted PE may not be as comprehensive as the initial full examination, key aspects should evaluate important body systems as clinically indicated. These body systems can include lymph nodes, liver, spleen, and breast at the discretion of the examiner. A targeted examination may note any changes in the participant's condition (body systems) since the last assessment and does not preclude examination of any of the other body systems as clinically indicated. Every effort should be made to ensure the same evaluator will complete the examination for each participant at all visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

9.4.2 Vital Signs

Vital signs include (ear or oral) body temperature, respiratory rate, and seated BP and heart rate and will be recorded at each visit based on Schedule of Activities (Section 2). BP and heart rate should be measured after the participant has been seated quietly for at least 5 minutes.

9.4.3 Electrocardiograms

A 12-lead ECG will be performed at the screening visit. The participant will remain supine for 5 to 10 minutes prior to the ECG and must have their lab work done after the tracing so that the ECG results remain as accurate as possible. The ECG results will be read by the primary study investigator or a designee.



[redacted]

9.5 Pharmacokinetics

Not applicable.

9.6 Immunogenicity Assessments

Not applicable.

[redacted]

[redacted]

9.8 Optional Future Research

This protocol will include residual sample storage for optional future research.

Samples kept for future research will be stored at the Sponsor-designated storage facility.

The manager of these samples will ensure that they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 25 years after the end of the study or the maximum period allowed by applicable law.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key will be securely held by the investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the laboratory/procedure manual.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

For the non-pustular PP psoriasis sub-protocol, the primary hypothesis is that the odds of achieving pp-PASI-75 at Week 16 in participants receiving deucravacitinib 6 mg QD are improved compared to participants receiving placebo.

The null hypothesis to be tested for the primary endpoint is the following:

- The odds of achieving pp-PASI-75 at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

The null hypothesis corresponding to the key secondary endpoint is:

- The odds of achieving pp-PGA 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

For the GenPs sub-protocol, the primary hypothesis is that the odds of achieving s-PGA-G 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are improved compared to participants receiving placebo.

The null hypothesis to be tested for the primary endpoint is the following:

- The odds of achieving s-PGA-G 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

The null hypothesis corresponding to the key secondary endpoint is:

- The mean change from baseline in GenPs Itch NRS score at Week 16 in participants receiving deucravacitinib 6 mg QD is not different from participants receiving placebo.

The null hypothesis corresponding to the second key secondary endpoint is:

- The odds of achieving s-PGA 0/1 at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

Multiplicity Adjustment

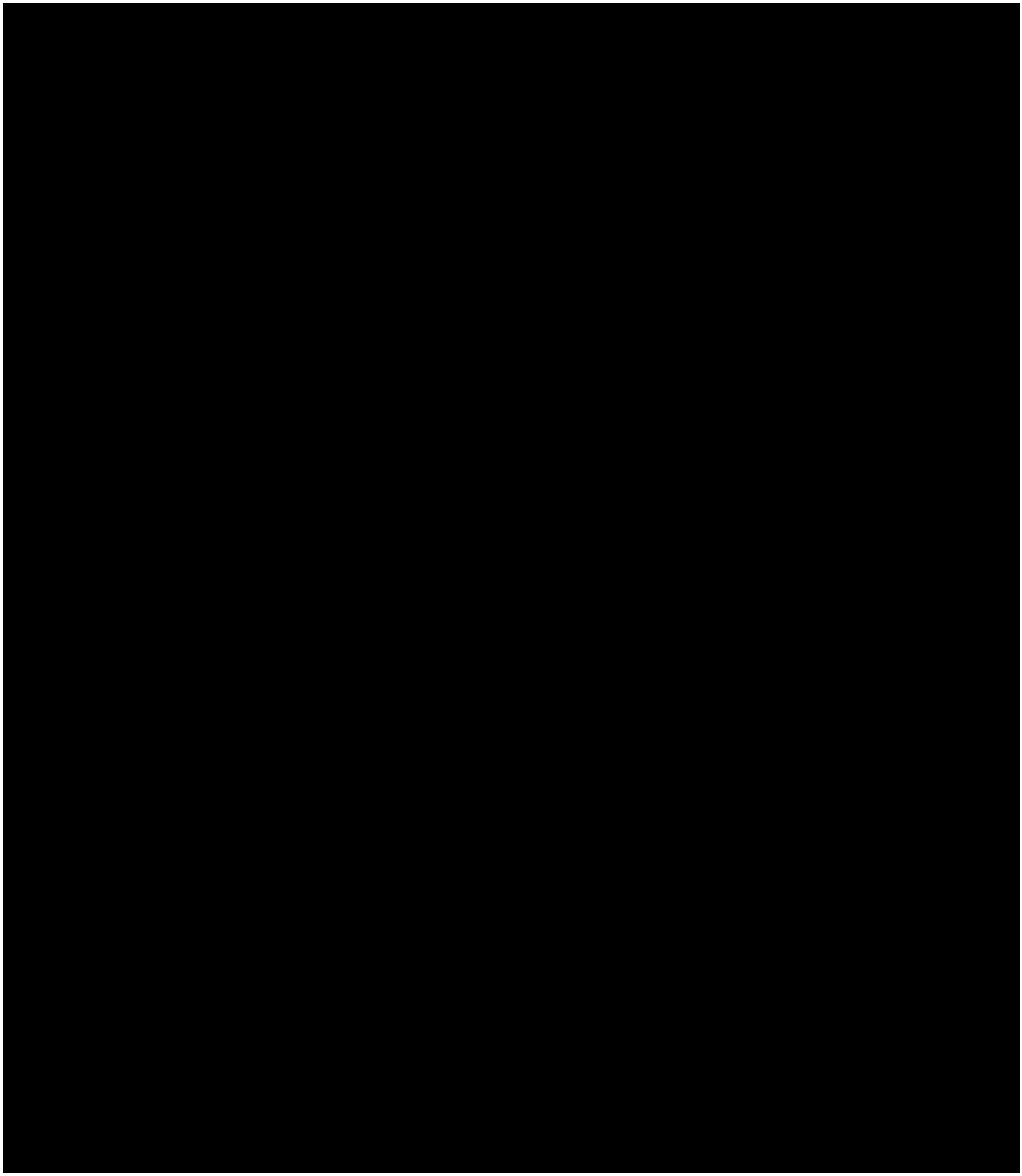
The statistical comparisons for the primary efficacy endpoint and the key secondary endpoint will be carried out in a hierarchical order for each sub-protocol. The hierarchical testing will preserve the overall Type I error at 0.05 for each sub-protocol.

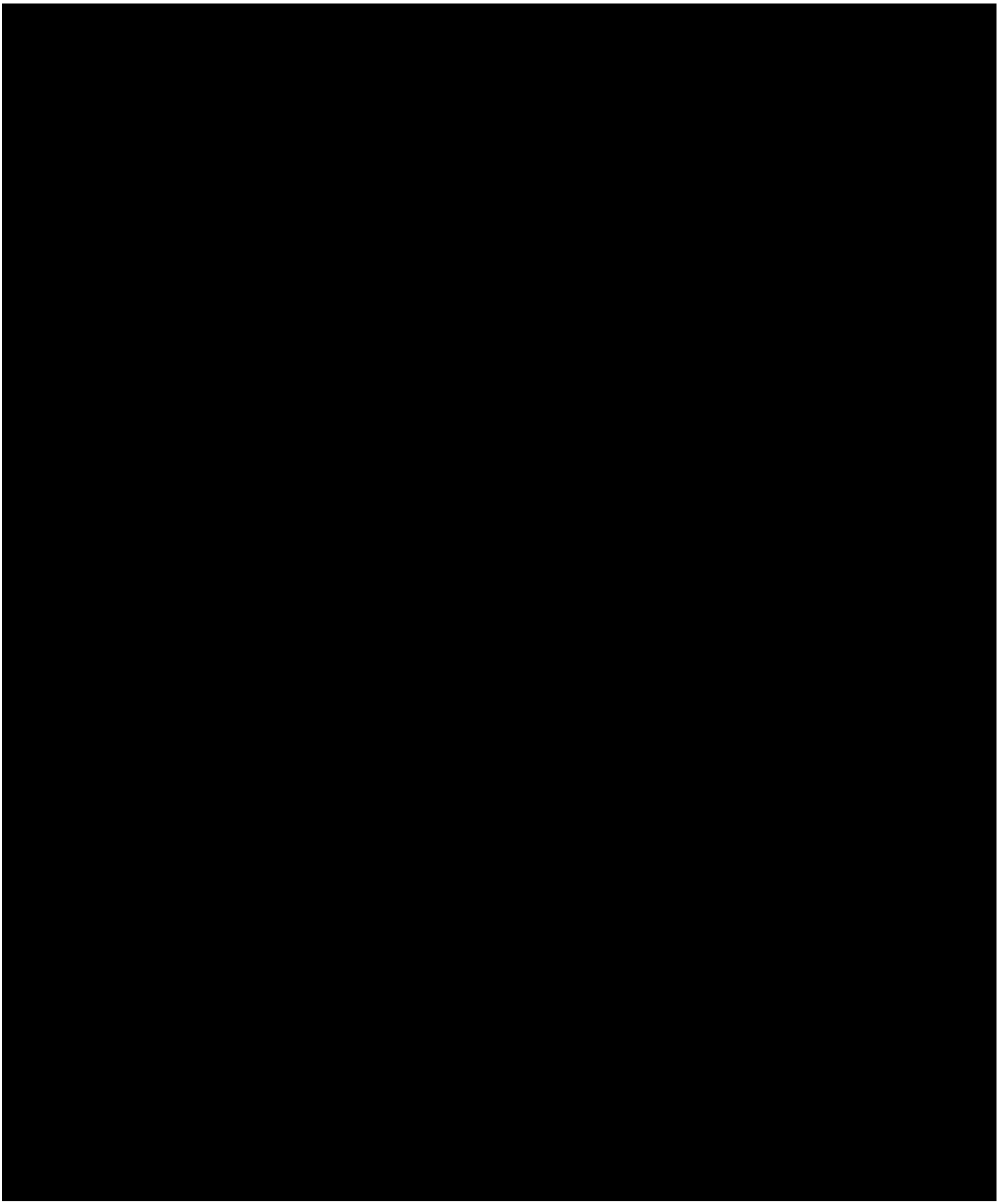
The primary endpoint for each sub-protocol will be tested with a 2-sided Type 1 error (α) of 0.05, and if statistical significance is met for the primary endpoint, testing will proceed with the 2-sided α of 0.05 passed down to each respective key secondary endpoint.

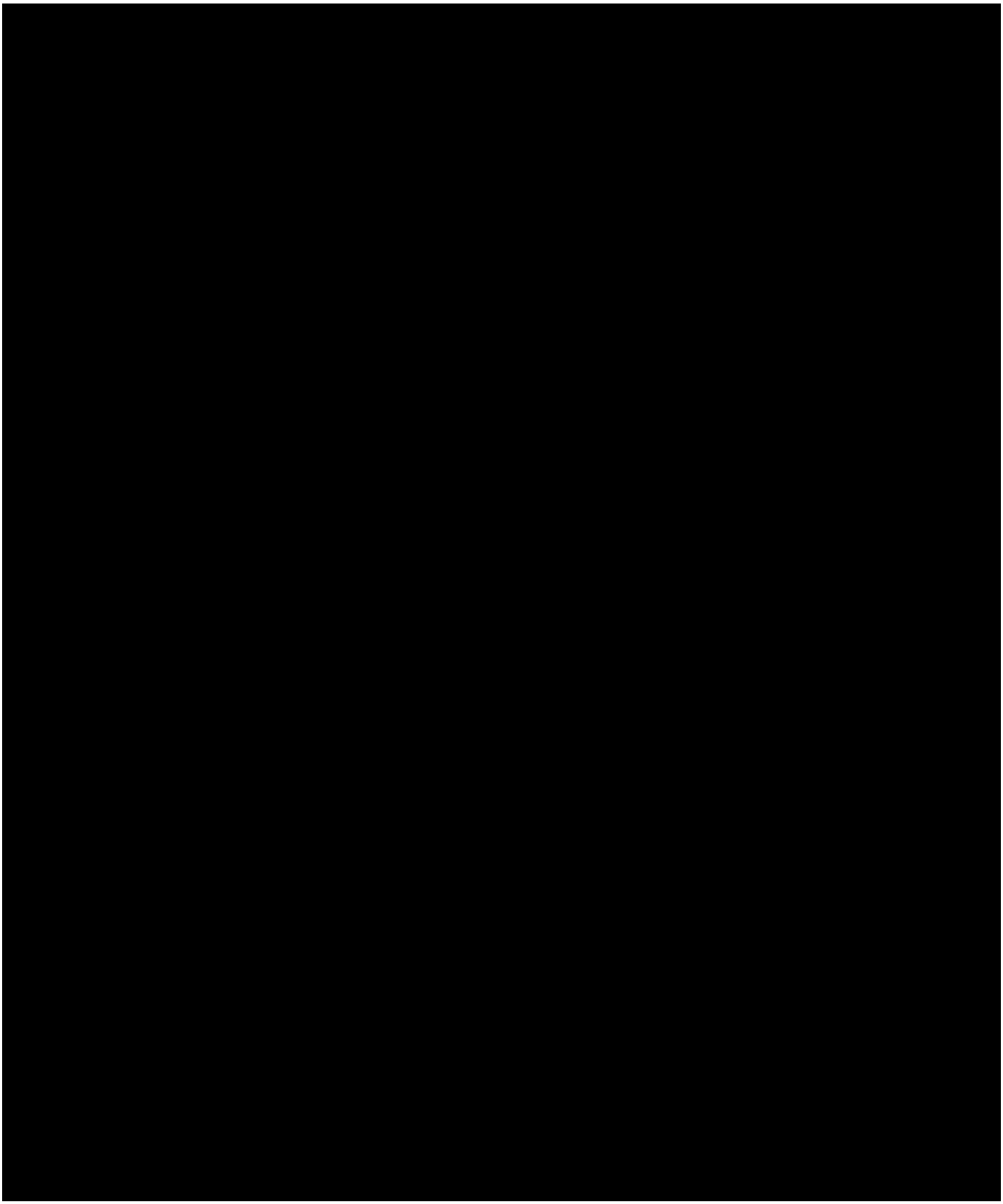
If statistical significance is not met for the primary endpoint, then subsequent p-values will be considered descriptive for that sub-protocol.

There will be no multiplicity adjustment for other additional endpoints in either sub-protocol; however, nominal p-values will be provided as descriptive statistics.

[redacted]







10.3 Analysis Sets

For the purposes of analysis, the following analysis sets will be used for each sub-protocol in this trial:

Table 10.3-1: Palmoplantar Psoriasis Sub-Protocol Analysis Sets

Population	Description
Enrolled	All participants who sign informed consent.
Randomized (Full Analysis Set [FAS])	All participants who were randomized to any treatment arm in the study.
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to intervention received.
Defined Analysis Data Sets	**Description**
Analysis set for primary estimand of pp-PASI-75	All randomized participants; all available data up to Week 16 database lock. Participants who discontinued prior to Week 16 will be imputed as non-responders in the analysis dataset. Following the intent-to-treat principle, participants will be analyzed according to the intervention group assigned at randomization.
Analysis set for secondary estimand of pp-PGA 0/1	All randomized participants; all available data up to Week 16 database lock. Participants who discontinued prior to Week 16 will be imputed as non-responders in the analysis dataset. Following the intent-to-treat principle, participants will be analyzed according to the intervention group assigned at randomization.
Analysis set for safety	All safety events reported for all randomized participants who are exposed to study intervention. For participants who discontinue study intervention all post discontinuation up to Day 28 post last dose of study intervention will be included in the safety summaries. Participants will be analyzed according to intervention received.

Abbreviations: pp-PASI, palmoplantar Psoriasis Area and Severity Index; pp-PGA, palmoplantar physician global assessment.

Table 10.3-2: Genital Psoriasis Sub-Protocol Analysis Sets

Population	Description
Enrolled	All participants who sign informed consent.
Randomized (Full Analysis Set [FAS])	All participants who were randomized to any treatment arm in the study.
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be included in the treatment group to which they were randomized.
Defined Analysis Data Sets	**Description**
Analysis set for primary estimand of s-PGA-G 0/1	All randomized participants; all available data up to Week 16 database lock. Participants who discontinued prior to Week 16 will be imputed as non-responders in the analysis dataset. Following the intent-to-treat principle, participants will be analyzed according to the intervention group assigned at randomization.
Analysis set for secondary estimand of GenPs itch NRS	All randomized participants; all available data up to Week 16 database lock. Participants who discontinued prior to Week 16 will be imputed using multiple imputation in the analysis dataset. Following the intent-to-treat principle, participants will be analyzed according to the intervention group assigned at randomization.
Analysis set for safety	All safety events reported for all randomized participants who are exposed to study intervention. For participants who discontinue study intervention all post discontinuation up to Day 28 post last dose of study intervention will be included in the safety summaries. Participants will be analyzed according to intervention received.

Abbreviations: GenPs, genital psoriasis; NRS, numerical rating scale; s-PGA-G, static Physician's Global Assessment of Genitalia.

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock at week 16 and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data for each sub-protocol. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

A description of the participant population will be included in the clinical study report (CSR), including subgroups of age, gender, race, and other study-specific populations and demographic characteristics. A description of participant disposition will also be included in the CSR.

Participant characteristics and/or demographic data may be pooled across studies for future analysis.

10.4.1 General Considerations

Efficacy Analyses

Descriptive statistics will be presented by the treatment group. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation (SD), median, minimum, and maximum unless otherwise specified. Efficacy values will be summarized for all visits in which the variable is assessed. Details of the planned analyses of endpoints during the 16-week double-blinded placebo-controlled period will be documented in the SAP and finalized before the primary analysis database lock for each sub-protocol.

During the first 16 weeks of treatment, data will be presented for the following treatments for each sub-protocol:

- deucravacitinib 6 mg QD
- placebo

After Week 16, data for each sub-protocol will be presented for the following treatments:

- deucravacitinib 6 mg QD
- placebo → deucravacitinib 6 mg QD (starting at Weeks 16 through 52)

[redacted]

The main estimands for the primary and key secondary objectives are summarized below in Table 10.4.1-1 for non-pustular PP psoriasis and in Table 10.4.1-2 for GenPs, respectively.

Table 10.4.1-1: Summary of the Attributes of the Main Estimand for the Primary and Key Secondary Objectives of Palmoplantar Psoriasis Sub-protocol

Primary Objective			
Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus Placebo		
Population	Participants with moderate-to-severe non-pustular palmoplantar psoriasis		
Variable	pp-PASI-75: Individual patient's binary outcome (Yes or No) of achieving 75% improvement at Week 16 in pp-PASI score from baseline.		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Discontinuation of intervention and study early prior to Week 16 assessment	Composite variable	Participant will be counted as a non-responder
	Lost to follow-up prior to Week 16 or otherwise missed assessment at Week 16	Composite variable	Participant will be counted as a non-responder
Population-level Summary	Odds ratio of achieving 75% improvement in pp-PASI score from baseline between treatment groups.		
Key Secondary Objective			
Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus Placebo		
Population	Participants with moderate-to-severe non-pustular palmoplantar psoriasis		
Variable	pp-PGA 0/1: Individual patient's binary outcome (Yes or No) of achieving pp-PGA 0/1 at Week 16		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Discontinuation of intervention and study early prior to Week 16 assessment	Composite variable	Participant will be counted as a non-responder
	Lost to follow-up prior to Week 16 or otherwise missed assessment at Week 16	Composite variable	Participant will be counted as a non-responder
Population-level Summary	Odds ratio of achieving pp-PGA 0/1 at Week 16 between treatment groups.		

Abbreviations: pp-PASI, palmoplantar Psoriasis Area and Severity Index; pp-PGA, palmoplantar Physician Global Assessment; QD, once daily.

Table 10.4.1-2: Summary of the Attributes of the Main Estimand for the Primary and Key Secondary Objectives of Genital Psoriasis Sub-protocol

Primary Objective			
Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus Placebo		
Population	Participants with Moderate-to-severe genital psoriasis		
Variable	s-PGA-G 0/1: Individual patient's binary outcome (Yes or No) of achieving s-PGA-G score of 0 or 1 at Week 16		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Discontinuation of intervention and study early prior to Week 16 assessment	Composite variable	Participant will be counted as a non-responder
	Lost to follow-up prior to Week 16 or otherwise missed assessment at Week 16	Composite variable	Participant will be counted as a non-responder
Population-level Summary	Odds ratio of achieving s-PGA-G score of 0 or 1 at Week 16 between treatment groups.		
Key Secondary Objective			
Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus Placebo		
Variable	Change from baseline GenPs itch numerical rating scale (NRS)		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Discontinuation of intervention and study early prior to Week 16 assessment	Composite variable	Baseline Observation Carried Forward (BOCF) will be applied.
	Lost to follow-up prior to Week 16 or otherwise missed assessment at Week 16	Composite variable	Last Observation Carried Forward (LOCF) will be applied (including the baseline value if necessary).
Population-level Summary	Adjusted mean difference between treatment groups.		
Second Key Secondary Objective			
Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus Placebo		
Variable	s-PGA 0/1: Proportion of participants achieving s-PGA score of 0 or 1 at Week 16		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Discontinuation of intervention and study early prior to Week 16 assessment	Composite variable	Participant will be counted as a non-responder
	Lost to follow-up or otherwise missing	Composite variable	Participant will be counted as a non-responder

Table 10.4.1-2: Summary of the Attributes of the Main Estimand for the Primary and Key Secondary Objectives of Genital Psoriasis Sub-protocol

	endpoint data at or prior to Week 16 assessment		
Population-level Summary	Odds ratio of achieving s-PGA score of 0 or 1 at Week 16 between treatment groups.		

Abbreviations: QD, once daily; s-PGA, static Physician's Global Assessment; s-PGA-G, static Physician Global Assessment Genitals; NRS, Numerical Rating Scale.

10.4.2 Primary Endpoint(s)

Table 10.4.2-1: Primary Endpoint for Palmoplantar Psoriasis Sub-protocol

Primary Endpoint	Description of Analysis	Time Frame
pp-PASI-75 response rate is defined as a proportion of participants achieving 75% improvement in pp-PASI score	The analysis model for the primary endpoint, pp-PASI-75 (responder/non-responder) at Week 16, [redacted] to compare the response rates of deucravacitinib 6 mg QD to placebo using the Week 16 data of the Full Analysis Set population. The odds ratio (ratio of odds in deucravacitinib 6 mg QD to the odds in placebo group) and the corresponding 2-sided 95% confidence interval (CI) will be provided. Estimates of proportions and their 2-sided 95% CIs will be provided. Non-responder imputation (NRI) will be used for the primary efficacy endpoint for participants who discontinue intervention or study prior to Week 16 or who have otherwise missing endpoint data at Week 16. NRI will be the primary method of imputation for the primary efficacy endpoint. Sensitivity and supportive analyses to be performed for the primary endpoint will be described in the SAP.	Week 16

Abbreviations: pp-PASI, palmoplantar Psoriasis Area and Severity Index; SAP, statistical analysis plan; QD, once daily.

Table 10.4.2-2: Primary Endpoint for Genital Psoriasis Sub-protocol

Primary Endpoint	Description of Analysis	Time Frame
s-PGA-G response rate is defined as a proportion of participants achieving participants achieving s-PGA-G score of 0 or 1 with at least a 2-point reduction from baseline at Week 16	The analysis model for the primary endpoint, s-PGA-G (responder/non-responder) at Week 16, [redacted]) to compare the response rates of deucravacitinib 6 mg QD to placebo using the Week 16 data of the Full Analysis Set population. The odds ratio (ratio of odds in deucravacitinib 6 mg QD to the odds in placebo group) and the corresponding 2-sided 95% confidence interval (CI) will be provided. Estimates of proportions and their 2-sided 95% CIs will be provided. Non-responder imputation (NRI) will be used for the primary efficacy endpoint for participants who discontinue intervention or study prior to Week 16 or who have otherwise missing endpoint data at the specified timepoint. NRI will be the primary method of imputation for the primary efficacy endpoint. Sensitivity and supportive analyses to be performed for the primary endpoint will be described in the SAP.	Week 16

Abbreviations: SAP, statistical analysis plan; s-PGA-G, static physician global assessment genitals; QD, once daily.

10.4.3 Secondary Endpoint(s)

Key Secondary Endpoints

Table 10.4.3-1: Key Secondary Endpoint for Palmoplantar Psoriasis Sub-protocol

Key Secondary Endpoint	Description of Analysis	Time Frame
pp-PGA 0/1 is defined as a proportion of participants achieving pp-PGA 0/1 at Week 16	The analysis model for pp-PGA 0/1 (responder/non-responder) at Week 16, will use [redacted] to compare the response rates of deucravacitinib 6 mg QD to placebo for the FAS population. The odds ratio (ratio of odds in deucravacitinib 6 mg QD to the odds in placebo group) and the corresponding 2-sided 95% confidence interval (CI) will be provided. Estimates of proportions and their 2-sided 95% CIs will be provided. The NRI method will be applied to the analysis of the binary secondary efficacy endpoint for participants who discontinue early or who have otherwise missing endpoint data at the specified timepoint.	Week 16

Abbreviations: [redacted]; FAS, full analysis set; pp-PGA, palmoplantar physician global assessment; QD, once daily.

Table 10.4.3-2: Key Secondary Endpoints for Genital Psoriasis Sub-protocol

Key Secondary Endpoint	Description of Analysis	Time Frame
Change from baseline in GenPs itch NRS score	The analysis model for the continuous secondary endpoint, change from baseline in GenPs itch NRS at Week 16, will use analysis of covariance (ANCOVA) with intervention [redacted]. The baseline value will be added into the model as a covariate. Intervention differences based on least-squares (LS) means and the corresponding 2-sided 95% CIs will be provided for the difference between deucravacitinib 6 mg QD and placebo. For the continuous secondary efficacy endpoint, multiple imputation will be used for missing data.	Week 16
s-PGA response is defined as a proportion of participants achieving s-PGA score of 0 or 1 with at least a 2-point reduction from baseline at Week 16	The analysis model for the primary endpoint, s-PGA (responder/non-responder) at Week 16, will use a [redacted] to compare the response rates of deucravacitinib 6 mg QD to placebo using the Week 16 data of the Full Analysis Set population. The odds ratio (ratio of odds in deucravacitinib 6 mg QD to the odds in placebo group) and the corresponding 2-sided 95% confidence interval (CI) will be provided. Estimates of proportions and their 2-sided 95% CIs will be provided. Non-responder imputation (NRI) will be used for the primary efficacy endpoint for participants who discontinue intervention or study prior to Week 16 or who have otherwise missing endpoint data at the specified timepoint. NRI will be the primary method of imputation for the primary efficacy endpoint. Sensitivity and supportive analyses to be performed for the primary endpoint will be described in the SAP.	Week 16

Abbreviations: GenPs, genital psoriasis; NRS, numerical rating scale; QD, once daily; SAP, statistical analysis plan.

[redacted]

10.4.5 Safety Analyses

Safety data will be analyzed for AEs, SAEs, laboratory analytes, vital signs. Safety will be summarized using the as-treated population for each sub-protocol. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, SD, median, minimum, and maximum unless otherwise specified. Safety will be analyzed through Week 16 and then up to end of study.

10.4.6 Other Analyses

Not applicable.

10.5 Interim Analyses

No interim is currently planned.

Week 16 Primary Analysis

A 16-week primary analysis will occur once all randomized participants have completed through Week 16 or have discontinued prior to Week 16 in each sub-protocol independently. Analyses of the collected efficacy and safety data will be performed independently also. The study participants and investigators will remain blinded to the initial treatment assignment received from Day 1 to Week 16 and the results of this analysis throughout the study. The Sponsor and site-facing study team will be unblinded to the individual treatment assignments following the last Week 16 visit.

Additional details of these analyses will be described in the SAP. A final analysis will be performed after all participants complete the Week 52 visit or discontinue prior to the Week 52 visit.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS

Term	Definition
ADD	American Academy of Dermatology
AE	Adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminase
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
BID	twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb Company
BP	blood pressure
[redacted]	[redacted]
C	Celsius
CAPP	Comprehensive Assessment of the Psoriasis Patient
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cmax	maximum observed concentration
COVID-19	Coronavirus disease 2019
CRF	Case Report Form, paper or electronic (eCRF)
CRO	Contract Research Organization
CSR	Clinical Study Report
DILI	Drug induced liver injury
[redacted]	
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessments
eCRF	electronic Case Report Form
EE	Ethinyl estradiol
EOT	End of treatment
[redacted]	

Term	Definition
ET	Early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GenPs	genital psoriasis
[redacted]	
GI	Gastrointestinal
[redacted]	
HBsAg/HBsAb	hepatitis B surface antigen/antibody
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
[redacted]	
IU	international unit
IV	intravenous(ly)
(J)AAD	Joint American Academy of Dermatology
LTBI	latent TB infection

Term	Definition
[redacted]	
mm Hg	millimeters of mercury
[redacted]	
N	number of participants or observations
N/A	not applicable
NCT (number)	National Clinical Trial number
Non-IMP	Non-investigational Medicinal Product
NPF	National Psoriasis Foundation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
pp-PASI	palmoplantar Psoriasis Area and Severity Index
PBO	Placebo
PE	physical examination
pp-PGA	palmoplantar physician global assessment
[redacted]	
PK	pharmacokinetic(s)
PP	palmoplantar
PRO	patient-reported outcomes
PSA	psoriatic arthritis
PSO	psoriasis
QD	once daily
QoL	quality of life
SAE	serious adverse event
SD	standard deviation
s-PGA	static Physician Global Assessment
s-PGA-G	static physician global assessment genitals
SSC	Study Steering Committee
[redacted]	
ULN	upper limit of normal
US	United States
UV	ultraviolet
VAS	visual analog scale
WHO	World Health Organization

Term	Definition
WOCBP	women of childbearing potential

[redacted]

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a quality issue (eg, protocol deviation) that is likely to affect, to a significant degree, 1 or more of the following: (1) the rights, physical safety, or mental integrity of 1 or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)

- European Union (EU) Directive 2001/20/EC
- European Regulation 536/2014 for clinical studies (if applicable)
- European Medical Device Regulation 2017/745 for clinical device research (if applicable)
- the IRB/IEC
- all other applicable local regulations

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to the following:

- IRB/IEC
- Regulatory authority(ies), if applicable according to local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, by the local Health Authority must be sent to Bristol-Myers Squibb Company (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with regulations, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for the participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

RECRUITMENT STRATEGY

A patient engagement and recruitment program will be developed and implemented to assist sites with patient recruitment efforts. Tactics will support patient education and awareness, and HCP outreach. This program will also include solutions to address anticipated recruitment challenges.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber-attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors)	Records or logs must comply with applicable regulations and guidelines and should include the following: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include Investigational Product sourced from the site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study intervention integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported or identified during the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

Each individual electronically signing eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or its designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or its designee.

Records collected throughout the study will be stored in the BMS clinical data management system for a duration of the life of the product plus 25 years.

RETURN OF STUDY INTERVENTION

For this study, study interventions (those supplied by BMS or a vendor or sourced by the investigator), such as partially used study intervention containers, vials, and syringes, may be destroyed on site.

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/clinical research associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible study monitor.
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study interventions provided by BMS (or its vendors). Destruction of non-study interventions sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE CLOSURE

The Sponsor/designee reserves the right to close the study site or to 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, the following:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care providers, and researchers and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public per regulatory and BMS requirements. BMS will post study information on local, national, or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in the EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the Clinical Trial Agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the period set forth in the CTAg.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at the Sponsor is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based on significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion)
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published
4) Agreement 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.

Those who make the most significant contributions, as defined above, will be considered by the Sponsor for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition occurring in a clinical investigation participant after signing of informed consent, whether or not considered related to the study intervention.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration, even though the condition may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify “intentional overdose” as the verbatim term.
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per the definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life threatening (defined as an event in which 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 causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • A visit to the emergency department or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery that was planned prior to signing consent. • Admissions per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to enrollment in the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life threatening or results in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency department or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7: Potential Drug-induced Liver Injury of the protocol for the definition of a potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as those used for SAEs. (See Section 9.2.5: Pregnancy of the protocol for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.) If an ongoing SAE changes in its intensity or relationship to study intervention or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or the designee) using the same procedure used for transmitting the initial SAE report. All AEs/SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic Case Report Form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or the designee).
    - In this case, the paper form is transmitted via email or confirmed fax transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed fax transmission.

SAE Email Address: worldwide.safety@BMS.com

SAE Fax Number: Will be provided by local site monitor.

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Women of Childbearing Potential (WOCBP) and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1: Inclusion Criteria of the protocol. Only the contraceptive methods as described in Section 6.1: Inclusion Criteria of the protocol are acceptable for this study.

DEFINITIONS

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Pre-menopausal female with 1 of the following:
  - Hysterectomy
  - Bilateral salpingectomy
  - Bilateral oophorectomy
- Post-menopausal female
  - A post-menopausal state is defined as 12 months of amenorrhea in a woman over the age of 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgment in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point at which the study intervention (Investigational Medicinal Product [IP/IMP] and other study interventions ie, Non-IMP/AxMP

required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of < 1% per year when used consistently and correctly.[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b]
  - Oral (birth control pills)
  - Intravaginal (rings)
  - Transdermal
- Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.

- Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b]
  - Oral
  - Injectable
- Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b]
- Intrauterine device.
- Intrauterine system (IUS). (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b,c]
- Bilateral tubal occlusion.

- Vasectomized partner.

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

A vasectomy is a highly effective contraception method provided that the participant is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- 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.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 of the protocol.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are 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. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria [redacted]

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria [redacted]

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of > 1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide.
- Cervical cap with spermicide.
- Vaginal sponge with spermicide.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies in which hormonal contraception is prohibited.)

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods).

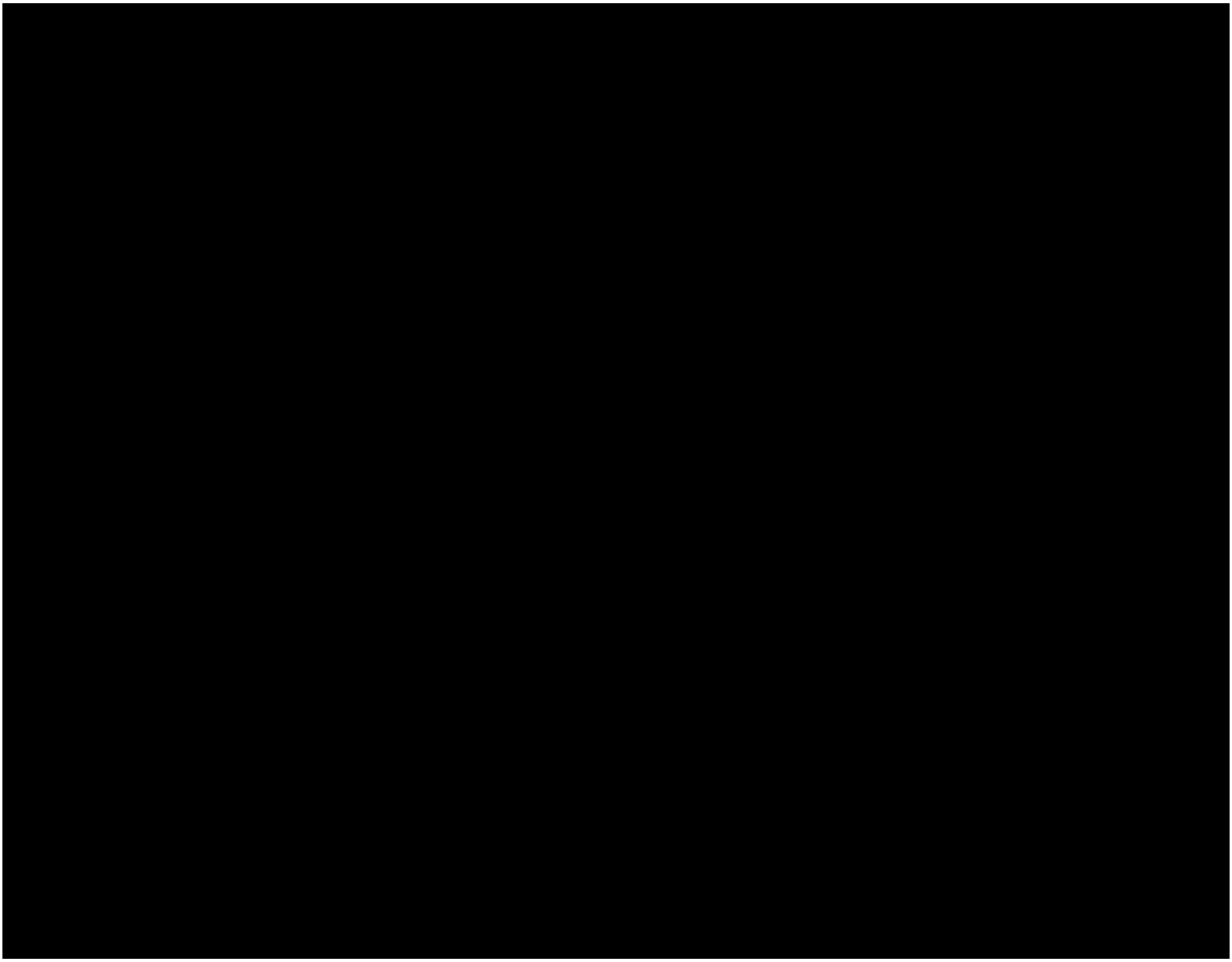
- Withdrawal (coitus interruptus).
- Spermicide only.
- LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5: Pregnancy of the protocol and Appendix 3.

[redacted]

[redacted]



APPENDIX 6 HEPATITIS B VIRUS (HBV) SCREENING

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (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 study.
- Participants who test **negative** for surface antigens (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study regardless of results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) ***are NOT eligible*** for this study.

Participants who **are not eligible for this study due to HBV results**, consultation with a physician with expertise in the treatment of hepatitis B virus is recommended.

Table 2: Eligibility Based on Hepatitis B Virus Test Results

	Hepatitis B Test Result		
Action	Hepatitis B Surface Antigen (HBsAg)	Hepatitis B Surface Antibody (anti-HSs)	Hepatitis B Core Antibody (anti-HBC total)
	-	-	-
Include	-	+	-
	-	+	+
Exclude	+	- Or +	- or +
	-	-	+