Official Title of Study:

A Phase 3B/4, Multicenter, Randomized, Double-blind Placebo-controlled Study to Evaluate the Efficacy and Safety of Deucravacitinib in Participants With Moderate-to-severe Scalp Psoriasis (PSORIATYK SCALP)

NCT Number: NCT05478499

Document Date (Date in which document was last revised): 23 May 2023

CLINICAL PROTOCOL IM011220

A PHASE 3B/4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DEUCRAVACITINIB IN PARTICIPANTS WITH MODERATE-TO-SEVERE SCALP PSORIASIS (PSORIATYK SCALP)

Compound: BMS-986165

Brief Title: Efficacy and safety of deucravacitinib versus placebo in participants with moderate-to-severe scalp psoriasis

Protocol Amendment 03

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NCT Number: NCT05478499

UTN: U1111-1274-7417

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 03	23-May-2023	• The compound number was added to the title page. • The Sponsor contact information was updated from [redacted] • Text was revised to reflect approval of SOTYKTU™ (deucravacitinib) [redacted] in multiple countries at a dose of 6 mg QD. • s-PGA 0/1 at Week 16 was added as a key secondary endpoint. • [redacted] • The statistical methods were updated to include a description of the 2 populations of interest (Overall Population and the s-PGA Sub-Population [participants with s-PGA ≥ 3 at baseline]). • Added corresponding text on the null hypothesis, multiplicity assessment, sample size determination analysis set, definition of estimands, etc for s-PGA 0/1. • The following exclusion criterion: "Participants who are not fully vaccinated against SARS-CoV-2 as defined by the local and current national guidelines" was made "Not applicable per Protocol Amendment 03." • Additional details were added to clarify guidance for Investigators to check and provide counseling to the participants with regard to vaccinations. • [redacted] • [redacted] • Text was clarified to highlight that "Participants with a positive IGRA must obtain a chest x-ray." • [redacted]

Document	Date of Issue	Summary of Changes
		• [redacted] • Table 3.2.3-1 language was updated and streamlined. • Details of the external SSC were added. • Added the following footnote to Table 2-2: "The Week 1 visit should not be entered into the IRT system because study intervention is not dispensed at Week 1." • Added a footnote (similar to already included in Table 2-3) for the order of assessments. • [redacted] • [redacted] • The following exclusion criterion: "Has donated blood > 500 mL within 4 weeks prior to Day 1, or plans to donate blood during the course of the study" was made "Not applicable per Protocol Amendment 03." • Text was updated to clarify that any planned "major" surgery within the first 52 weeks will be exclusionary. • Removed 1,25-dihydroxy vitamin D_3 and analogues from the list of exclusionary systemic non-biologic medications. • The following text: "No concomitant medications (prescription, over-the-counter, or herbal) are to be administered during the study unless prescribed for intervention of specific clinical AEs. Any concomitant therapies must be recorded on the (e)CRF. The Investigator should contact and confirm agreement with the Medical Monitor or designee prior to the administration of any concomitant medications." was replaced with: "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." • Additional details were added to clarify which assessments are to be repeated during rescreening. • [redacted] • [redacted]
Protocol Amendment 02	05-Dec-2022	• [redacted] • The US FDA approval date was added for the study drug • Details about completed and ongoing studies were updated • Pregnant partner surveillance language was removed

Document	Date of Issue	Summary of Changes
		• [redacted] • Incorporated language from French specific protocol amendment • Clarifying additions/deletions were made throughout the protocol • Minor administrative changes were made throughout the protocol
Protocol Amendment 01	19-May-2022	• [redacted] • [redacted] • Updated language in the multiplicity adjustment section to reflect the primary endpoint is included in the hierarchal order. • Change of safety endpoint from exploratory to "other" secondary endpoint. • Update to the definition of estimands table for primary and key secondary endpoints per the estimand guidance document • APPENDIX 2 updated with Data Protection, Data Privacy, and Data Security and Diversity Sections • References to BMS-986165 were changed to deucravacitinib throughout the protocol and in the title • PSORIATYK SCALP added to the title • Clarifying additions/deletions were made throughout the protocol • Minor administrative changes were made throughout the protocol
Original Protocol	23-Mar-2022	Not applicable

(e)CRF, electronic case report form; AE, adverse event, [redacted]; BMS, Bristol-Myers Squibb Company; [redacted] FDA, Food and Drug Administration; [redacted] IP, investigational product; IRT, interactive response technology; PE, physical examination; [redacted]; QD, once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; s-PGA, static Physician Global Assessment; SSC, Study Steering Committee; TB, tuberculosis; TYK2, tyrosine kinase 2; US, United States; WHO, World Health Organization.

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

Overall Rationale for Protocol Amendment 03, 19-May-2023

This protocol has been revised to remove the serology testing requirement for HBV-DNA viral load from the screening procedures in the Schedule of Activity table (ie, Screening Procedural Outline), the Infectious/Immune-related Exclusions, and the Clinical Laboratory Assessments table.

Additionally, Protocol Amendment 03 defined an additional sub-population for the primary and secondary analyses to demonstrate deucravacitinib efficacy in the sub-population of participants with s-PGA ≥ 3.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	• The compound number was added to the title page.	• This change was made to reflect the Sponsor's protocol template.
Title Page	• The Sponsor contact information for the medical monitor was updated from [redacted]	• This change was made to reflect changes in the study personnel.
Section 1 Protocol Summary Section 3.1 Study Rationale Section 3.2.1 Clinical Development	• Text was revised to reflect approval of SOTYKTU™ (deucravacitinib) [redacted] in multiple countries.	• This revision was made to reflect approval of deucravacitinib [redacted] in additional countries beyond the US.
Section 3.2.5 Benefit Assessment Section 5.5 Justification for Dose	• Text was revised to reflect approval of SOTYKTU™ (deucravacitinib) [redacted] in multiple countries at a dose of 6 mg QD.	• To highlight that the 6 mg QD dose of deucravacitinib is now approved [redacted] in multiple countries.
Section 1 Protocol Summary Section 4 Objectives and Endpoints (Table 4-1)	• s-PGA 0/1 at Week 16 was added as a key secondary endpoint.	• [redacted]
Throughout	• The text was updated in multiple sections.	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
		• The text throughout the protocol was updated to reflect this change.
Section 10 Statistical Considerations	• An additional sub-population was defined for the primary and secondary analyses. Due to additional hypothesis tests within each endpoint using 2 analysis populations, new multiplicity adjustment method was employed. Sample sizes and their corresponding powers are reassessed. for each study endpoint for the additional population. • The statistical methods were updated to include a description of the 2 populations of interest (Overall Population and the s-PGA Sub-Population [participants with s-PGA ≥ 3 at baseline]). • Added corresponding text on the null hypothesis, multiplicity assessment, sample size determination analysis set, definition of estimands, etc for s-PGA 0/1.	• [redacted] • To provide additional description of the analyses that would be performed for sub-population of participants with s-PGA ≥ 3 at baseline
Throughout	• The text was updated in multiple sections.	• The text throughout the protocol was updated to reflect this change.
Section 6.2 Exclusion Criteria	• The following exclusion criterion: "Participants who are not fully vaccinated against SARS-CoV-2 as defined by the local and current national guidelines" was made "Not applicable per Protocol Amendment 03."	• To minimize barriers for participant enrollment, this exclusion criteria was made "Not applicable per Protocol Amendment 03.".
Section 2 Schedule of Activities (Table 2-1)	• Additional details were added to clarify guidance for Investigators to check and provide counseling to the participants with regard to vaccinations as follows: Investigators are encouraged to check whether participants have had preventive health measures such as cancer screening (eg, Pap smear, colonoscopy, mammograms) and are up-to-date with recommended vaccinations according to local guidelines (eg, influenza, herpes zoster, SARS-CoV-2).	• To clarify and provide guidance for Investigators to counsel participants with regard to vaccinations.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule of Activities (Table 2-2) Section 9.8 Biomarkers	• [redacted]	[redacted]
Section 2 Schedule of Activities (Table 2-1) [redacted] Section 12 [redacted]	• [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • To provide detailed information for Investigators to perform adequate assessment of participants' risk for TB.
Section 6.2 Exclusion Criteria	• Text was clarified to highlight that "Participants with a positive IGRA must obtain a chest x-ray."	• [redacted]
Section 2 Schedule of Activities (Table 2-1) Section 6.2	• HBV DNA viral load was removed as a required test at screening.	• [redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Exclusion Criteria [redacted] Section 12 Appendices APPENDIX 6 HEPATITIS B VIRUS (HBV) SCREENING	• Additionally, a new appendix (APPENDIX 6) providing detailed HBV screening approach was added.	[redacted] • To provide detailed instructions for HBV screening.
Section 1 Protocol Summary Section 4 Objectives and Endpoints (Table 4-1)	• [redacted] Similar changes were made to the text describing the safety analyses.	• Any abnormal PE finding during the study will be recorded as an AE/SAE, which is an already a safety endpoint
Section 3.2.3 Risk Assessment (Table 3.2.3-1)	• Table 3.2.3-1 language was updated and streamlined.	• Given the SOTYKTU™ FDA approval in the US and the updated IB version, this section was updated and streamlined for this Phase 4 study.
Section 1 Protocol Summary Section 5.1.6 Data Monitoring Committee and Other Committees	• Details of the external SSC were added.	• To provide the description and the roles of the SSC in the protocol.
Section 2 Schedule of Activities (Table 2-2)	• Added the following footnote: "The Week 1 visit should not be entered into the IRT system because study intervention is not dispensed at Week 1."	• This revision was made to clarify the IRT system procedures.
Section 2 Schedule of Activities (Table 2-2)	• Added a footnote (similar to already included in Table 2-3) for the order of assessments.	• This revision made for consistency throughout the document.
Section 2 Schedule of Activities (Table 2-2 and Table 2-3)	• All references to "health outcomes" were revised to "patient-reported outcomes" (PRO).	• To have consistent language throughout the protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Exclusion Criteria	• [redacted]	• [redacted]
Section 6.2 Exclusion Criteria	• The following exclusion criterion: "Has donated blood > 500 mL within 4 weeks prior to Day 1, or plans to donate blood during the course of the study" was made "Not applicable per Protocol Amendment 03."	• To minimize the participant burden in this Phase 3b/4 study this exclusion criteria was made "Not applicable per Protocol Amendment 03.".
Section 6.2 Exclusion Criteria	• Text was updated to clarify that any planned "major" surgery within the first 52 weeks will be exclusionary.	• To optimize participant enrollment and to minimize the participant burden in this Phase 3b/4 study.
Section 6.2 Exclusion Criteria	• Removed 1,25-dihydroxy vitamin D_3 and analogues from the list of exclusionary systemic non-biologic medications.	• To reduce participant burden and optimize enrollment this prohibited medication/exclusion criteria was removed.
Section 7.7.1 Prohibited and/or Restricted Interventions Section 7.7.2 Permitted Concomitant Medications	• The following text: "No concomitant medications (prescription, over-the-counter, or herbal) are to be administered during the study unless prescribed for intervention of specific clinical AEs. Any concomitant therapies must be recorded on the (e)CRF. The Investigator should contact and confirm agreement with the Medical Monitor or designee prior to the administration of any concomitant medications." was replaced with: "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."	• This requirement was removed from this Phase 4 study to minimize participant and Investigator burden. • Provided clarification to streamline administration and capturing concomitant medications during the study on the eCRF.
Section 6.4.1 Retesting During the Screening Period	• Additional details were added to clarify which assessments are to be repeated during rescreening.	• To minimize participant burden and optimize enrollment.
Section 7.8 Continued Access to Study Intervention	• The following paragraph was removed: "BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur:	• This paragraph was not applicable to this Phase 4 study.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
After the End of the Study	a) the study is terminated due to safety concerns; b) the development of deucravacitinib is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations."	
All	• Minor administrative changes and clarifying edits were made throughout the protocol.	• Minor edits were made to improve overall readability, consistency, and to streamline this phase 4 Study protocol following the FDA approval of SOTYKTU™.

(e)CRF, electronic case report form; AE, adverse event; BMS, Bristol-Myers Squibb Company; DNA, deoxyribonucleic acid; FDA, Food and Drug Administration; [redacted] IB, Investigator's Brochure; IGRA, interferon gamma release assay; IP, investigational product; IRT, interactive response technology; PE, physical examination; [redacted] QD, once daily; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; s-PGA, static Physician Global Assessment; SSC, Study Steering Committee; TB, tuberculosis; TYK2, tyrosine kinase 2; US, United States; WHO, World Health Organization.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 3b/4, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate The Efficacy and Safety of Deucravacitinib in Participants with Moderate-To-Severe Scalp Psoriasis (Psoriatyk Scalp)

Brief Title: Efficacy and safety of deucravacitinib versus placebo in participants with moderate-to-severe scalp 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. These approvals were based on the results of the 52-week, randomized, Phase 3, placebo-controlled studies of deucravacitinib 6 mg daily versus placebo and apremilast 30 mg twice daily (BID) (POETYK PSO-1 and PSO-2).

In these 2 studies, in addition to the co-primary endpoints, scalp psoriasis was assessed using the scalp-specific Physician Global Assessment (ss-PGA) 0/1 and Psoriasis Scalp Severity Index (PSSI) 90 scores. For the purposes of the analyses in both of these studies, the scalp response assessment only included participants with a ss-PGA score ≥ 3 (moderate-to-severe scalp psoriasis) at baseline. Approximately 64% of participants in the Phase 3 studies met this criterion. Significantly higher ss-PGA 0/1 responses were seen in participants in the deucravacitinib arm as compared to those in the placebo and apremilast arms at Week 16 in POETYK PSO-1 (70.8% vs 17.4% vs 39.1% respectively) and POETYK PSO-2 (60.3% vs 17.3% vs 37.3% respectively). 66.5% of participants on deucravacitinib maintained a ss-PGA 0/1 response at Week 52 in POETYK PSO-1. Additionally, significantly higher PSSI 90 responses were seen in the deucravacitinib arm compared with apremilast arm through Week 24 both in POETYK PSO-1 (61.2% vs 29.1% respectively) and POETYK PSO-2 (48.9% vs 28.9% respectively). [redacted]

[redacted]. Additional analyses, including formal statistical hypothesis testing, will also be performed in the participant sub-population with static Physician Global Assessment (s-PGA) ≥ 3 at baseline for s-PGA 0/1 response at Week 16 to demonstrate [redacted]

[redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by ss-PGA 0/1, of deucravacitinib versus placebo at Week 16: o in participants with moderate-to-severe scalp plaque psoriasis o in the sub-population of participants with a s-PGA ≥ 3 at baseline	• ss-PGA 0/1 response as a proportion of participants with an ss-PGA 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 PSSI 90 response, of deucravacitinib versus placebo at Week 16: o in participants with moderate-to-severe scalp plaque psoriasis o in the sub-population of participants with a s-PGA ≥ 3 at baseline	• PSSI 90 response as a proportion of participants who achieve at least 90% improvement from baseline in the PSSI score at Week 16
• To compare the efficacy, as measured by scalp-specific itch NRS score, of deucravacitinib versus placebo at Week 16: o in participants with moderate-to-severe scalp plaque psoriasis o in the sub-population of participants with a s-PGA ≥ 3 at baseline	• Change from baseline in scalp-specific 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 the sub-population of participants with a s-PGA ≥ 3 at baseline	• s-PGA 0/1 response as a proportion of participants with an 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 moderate-to-severe scalp plaque psoriasis between Week 0 and Week 16	• AEs, SAEs, laboratory parameters, and VS between Week 0 and Week 16

Objectives	Endpoints
Selected Exploratory	
[redacted]	

AE, adverse event; [redacted] PE, physical examination; [redacted] SAE, serious adverse event; Scalpdex, scalp dermatitis-specific quality of life instrument; [redacted] VS, vital signs.

Overall Design:

This is a 52-week, Phase 3b/4, multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of deucravacitinib versus placebo in participants with moderate-to-severe scalp psoriasis. Participants will undergo screening evaluations within 28 days prior to administration of study intervention to determine eligibility. Following the screening process, approximately 150 participants will be randomized in a 2:1 ratio to either deucravacitinib 6 mg once daily (QD) or placebo, respectively.

[redacted]

[redacted] It is anticipated that 95% (n=143) of the 150 randomized participants will have s-PGA ≥ 3 at baseline.

The duration of study participation is approximately 60 weeks and will be divided into the following periods: Screening (up to 4 weeks), Intervention (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 and Investigators remain blinded to double-blind, placebo-controlled period study intervention until the end of the study.

[redacted]

Participants will be followed up for safety for 4 additional weeks, from Week 52 through Week 56. 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 serious adverse events or adverse events experienced during this time.

Number of Participants:

It is estimated that approximately 220 enrolled participants will be required to achieve 150 randomized. Approximately 150 participants will be randomized in a 2:1 ratio to deucravacitinib 6 mg QD or placebo matching deucravacitinib QD, respectively. Sample size considerations are described in the Sample Size Determination section.

Study Population:

Men and women ≥ 18 years of age diagnosed with stable plaque psoriasis ≥ 6 months (defined as no morphology changes or significant flares of disease activity in the opinion of the Investigator) with moderate-to-severe scalp psoriasis (ss-PGA ≥ 3, PSSI ≥ 12, and SSA ≥ 20%), BSA ≥ 3%, and who are candidates for phototherapy or systemic therapy will be eligible to participate in the study.

Intervention Groups and Duration:

Participants in both intervention groups will take oral doses of one of the investigational [medicinal] product (IP/IMP), 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.

Study Intervention:

Study Intervention for IM011220		
Arm Name	**Deucravacitinib (BMS-986165)**	**Placebo**
Intervention Name	Deucravacitinib (BMS-986165)	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Placebo tablet
Unit Dose Strength	6 mg	n/a
Dosage Level(s)	1 active tablet QD in the morning	1 placebo tablet 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.

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

Statistical Methods:

There are 2 population groups of interest in this study. The Overall Population consists of all participants who were randomized to any treatment arm. The s-PGA ≥ 3 Sub-Population consists of all participants who were randomized to any treatment arm in the study with s-PGA ≥ 3 at baseline.

Two types of multiplicity adjustment are implemented to ensure that the family-wise Type I error rate is controlled to be no more than 2-sided 5% in the study.

- Union-Intersection principle between the 2 populations and corresponding hypotheses within each endpoint.
- Hierarchical gatekeeping procedure for the primary and secondary endpoints and associated hypotheses.

The 2 primary hypotheses will be tested simultaneously with a significance level (alpha) of 0.05 (2-sided). If either of the test results is not statistically significant (ie, at least one of null hypotheses is not rejected), then it is deemed that the study objective is not met. Key secondary endpoints will be tested in a hierarchical order only if the primary endpoint achieved statistical significance at the 2-sided 0.05 level on both the Overall Population and the s-PGA ≥ 3 Sub-Population. A hierarchical test may proceed to the next key secondary endpoint only if both null hypotheses within a key secondary endpoint are rejected.

The analysis model for the primary efficacy endpoint and secondary binary endpoint will use stratified Cochran-Mantel-Haenszel tests [redacted] to compare the response rates of deucravacitinib 6 mg QD to placebo. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for the analysis. Non-responder imputation will be used for binary endpoints for participants who discontinue early or who have otherwise missing endpoint data at the specified timepoint.

The analysis model for the continuous secondary endpoint will use analysis of covariance (ANCOVA) with study intervention and [redacted] The baseline value will be added into the model as a covariate. Intervention differences based on least-squares means and the corresponding 2-sided 95% confidence intervals 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.

The primary analysis at Week 16 will occur once all randomized participants have completed their Week 16 visit or have discontinued prior to Week 16. Analyses of the collected efficacy and safety data through Week 16 will be performed. A final analysis will be performed after all participants complete the final safety follow-up visit at Week 56 or post-discontinuation follow-up visit.

Data Monitoring Committee and Other Committees:

A Data Monitoring Committee will not be used in the study. This study will use an external Study Steering Committee.

Brief Summary:

The purpose of this study is to compare the efficacy and safety of deucravacitinib to placebo in participants with moderate-to-severe scalp psoriasis. The study will also compare the efficacy and safety of deucravacitinib to placebo in participants with moderate-to-severe plaque psoriasis [redacted]. This will be a multicenter, randomized, double-blind, placebo-controlled study.

The study will compare improvement in scalp psoriasis in participants treated with deucravacitinib to those treated with placebo during the first 16 weeks. This improvement is defined as ss-PGA 0/1 score and will be assessed at Week 16. The primary hypotheses are that the odds of achieving a ss-PGA 0/1 score with at least a 2-point reduction from baseline at Week 16 in participants receiving deucravacitinib 6 mg QD are improved compared to participants receiving placebo in both the Overall Population and the s-PGA ≥ 3 Sub-Population. In addition, PSSI 90 response, improvement in scalp itching, and the proportion of participants with s-PGA ≥ 3 at baseline who achieve s-PGA 0/1 at Week 16 will also be assessed. Similar assessments for improvement and maintenance of scalp psoriasis treatment response will be performed at Week 52.

The duration of study participation is approximately 60 weeks and will be divided into the following periods: Screening (up to 4 weeks), Intervention (52 weeks), and Follow-up (4 weeks). Following the initial Screening 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 will be randomized on Day 1 in a 2:1 ratio to receive either deucravacitinib 6 mg QD or placebo, respectively, for the first 16 weeks. [redacted]. 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 until the end of the study.

At Week 20 and at any of the subsequent study visits, a participant with insufficient treatment response may be treated with rescue topical medications/shampoos at the discretion of the Investigator, which may be continued through the end of study.

2 SCHEDULE OF ACTIVITIES

Schedules of activities and procedures are documented in Table 2-1 for the Screening Visit, Table 2-2 for Day 1 through Week 20, and Table 2-3 for Week 24 through Week 52.

Table 2-1: Screening Procedural Outline (IM011220)

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 and documentation of presence of plaque psoriasis with scalp involvement by the Investigator.
Medical History	X	[redacted]
History of Tobacco Use	X	Include description of current tobacco use.
Psoriasis-Related History	X	Includes scalp symptoms, PsA, history of other forms of psoriasis.
Psoriasis-Related Systemic Intervention	X	History of conventional systemic (eg, methotrexate), biologic, and/or phototherapy. For each therapy, include length of time on intervention and reason(s) for discontinuation (eg, lack of efficacy, intolerance, side effects, loss of access to intervention), if applicable.
Other Prior and Concomitant Interventions	X	Includes topical interventions and shampoos for psoriasis and all medications for other conditions such as cardiovascular disorders and mood disorder.

Table 2-1: Screening Procedural Outline (IM011220)

Procedure	Screening Visit (Day –28 to Day –1)	Notes
Safety Assessments		
PE	X	Complete PE
Physical Measurements	X	Includes height, weight, and BMI.
VS	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 would be collected.
[redacted]		
Laboratory Tests		
[redacted]		

Table 2-1: Screening Procedural Outline (IM011220)

Procedure	Screening Visit (Day –28 to Day –1)	Notes
[redacted]		
TSH	X	Abnormal TSH will be exclusionary. If TSH above normal reference range, test free T4; if TSH below normal range, test free T4 and T3 (see Section 6.2).
Pregnancy test (serum)	X	For WOCBP only; see APPENDIX 4 Serum (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) to be done at Screening Visit. The participant must be excluded from participation if the serum pregnancy result is positive.
FSH	X	If needed to document post-menopausal status, as defined in Section 9.4. Females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause.
AE Reporting		
Monitor for SAEs	X	All 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. All AE (SAEs or nonserious AE) related to SARS-CoV-2 infection collected from time of consent.
Clinical Efficacy Assessments		
ss-PGA	X	
SSA	X	
PSSI	X	
BSA	X	

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; ECG, electrocardiogram; FSH, follicle-stimulating hormone; [redacted]; [redacted]; hCG, human

chorionic gonadotropin; [redacted]; [redacted]; IRT, interactive response technology; LDH, lactate dehydrogenase; MDR/RR-TB, multidrug/rifampicin-resistant tuberculosis; PASI, Psoriasis Area and Severity Index; PE, physical examination; PHQ-8, 8-item Patient Health Questionnaire; PsA, psoriatic arthritis; PSSI, Psoriasis Scalp Severity Index; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ss-PGA, scalp-specific Physician Global Assessment; SSA, scalp surface area; T3, triiodothyronine; T4, thyroxine; [redacted] TSH, thyroid-stimulating hormone; ULN, upper limit of normal; V, visit; VS, vital signs; WHO, World Health Organization; WOCBP, women of childbearing potential.

* - WHO global lists of high burden countries for TB, TB/HIV, and MDR/RR-TB, 2021–2025; APPENDIX 5.

Table 2-2: On-Intervention Procedural Outline (IM011220), Day 1 through Week 20

Procedure	Visit 1 (Day 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	
Body Weight	X								
VS	X	X	X	X	X	X	X	X	
[redacted]									
Concomitant Medication Use	X	X	X	X	X	X	X	X	
AE Reporting									
Monitor for AEs and SAEs	X	X	X	X	X	X	X	X	
Laboratory Tests									
Hematology	X			X	X	X	X	X	
Chemistry Panel	X			X	X	X	X	X	

Table 2-2: On-Intervention Procedural Outline (IM011220), Day 1 through Week 20

Procedure	Visit 1 (Day 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]									
Urinalysis	X						X		
Pregnancy Test (Urine)	X			X	X	X	X	X	WOCBP only
[redacted]									
Clinical Efficacy Assessments									
ss-PGA	X	X	X	X	X	X	X	X	
SSA	X								
PSSI	X	X	X	X	X	X	X	X	
BSA	X	X	X	X	X	X	X	X	
s-PGA	X	X	X	X	X	X	X	X	
PASI	X	X	X	X	X	X	X	X	
[redacted]									

Table 2-2: On-Intervention Procedural Outline (IM011220), Day 1 through Week 20

Procedure	Visit 1 (Day 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[a]	X		X	X	X	X	X	X	
Study Intervention Compliance		X	X	X	X	X	X	X	

AE, adverse event; BSA, body surface area; d, days; D, day; [redacted] IP, investigational product; IRT, interactive response technology; [redacted]; PASI, Psoriasis Area and Severity Index; PE, physical examination; PHQ-8, 8-item Patient Health Questionnaire; PRO, patient-reported outcome; [redacted]

[redacted] PSSI, Psoriasis Scalp Severity Index; SAE, serious adverse event; Scalpdex, Scalp dermatitis-specific quality of life instrument; s-PGA, static Physician Global Assessment; ss-PGA, scalp-specific Physician Global Assessment; SSA, scalp surface area; V, visit; WOCBP, women of childbearing potential.

[a] The Week 1 visit should not be entered into the IRT system because study intervention is not dispensed at Week 1.

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

1) [redacted]
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests (eg, safety laboratory tests). The dose of the IP on a visit day is to be taken after blood draws for laboratory tests.

Table 2-3: On-Intervention Procedural Outline, (IM011220) Week 24 through Week 52

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		
VS	X	X	X	X	X	X	
Concomitant Medication Use	X	X	X	X	X	X	
AE Reporting							
Monitor for AEs and SAEs	X	X	X	X	X	X	
Laboratory Tests							
Hematology	X	X	X	X	X	X	
Chemistry Panel	X	X	X	X	X	X	
Pregnancy Test (Urine)	X	X	X	X	X	X	WOCBP only French participants only: WOCBP only Between visit windows, at weeks

Table 2-3: On-Intervention Procedural Outline, (IM011220) Week 24 through Week 52

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
							36, 44, and 48, an at home urine pregnancy test will be performed. Participants will provide the results by phone. See Section 9.2.6.
[redacted]	[redacted]				[redacted]		[redacted]
[redacted]	[redacted]				[redacted]		[redacted]
Clinical Efficacy Assessments							
ss-PGA	X	X	X	X	X		
PSSI	X	X	X	X	X		
BSA	X	X	X	X	X		
s-PGA	X	X	X	X	X		
PASI	X	X	X	X	X		
[redacted]							

Table 2-3: On-Intervention Procedural Outline, (IM011220) Week 24 through Week 52

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 2-3: On-Intervention Procedural Outline, (IM011220) Week 24 through Week 52

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		

AE, adverse event; BSA, body surface area; d, days; D, Day; [redacted] EOT, End of Treatment; ET, early termination; [redacted] IP, investigational product; IRT, interactive response technology; PASI, Psoriasis Area and Severity Index; PE, physical examination; PRO, patient-reported outcome; [redacted] PSSI, Psoriasis Scalp Severity Index; SAE, serious adverse event; Scalpdex, Scalp dermatitis-specific quality of life instrument; s-PGA, static Physician Global Assessment; ss-PGA, scalp-specific Physician Global Assessment; WOCBP, women of childbearing potential.

[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 days ± 3 days after the last dose of study treatment.

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

1) [redacted]
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests (eg, safety laboratory tests). The dose of the IP on a visit day is to be taken after blood draws for laboratory tests.

3 INTRODUCTION

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.[1,2] 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.[3,4,5] 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.[3] Psoriasis can involve skin in any part of the body; particularly disabling is the involvement of specific anatomic regions, such as hands and feet (palmoplantar), face, scalp, and nails. The scalp is the most commonly affected region of the body in psoriasis, involved in about 80% of psoriasis cases.[6] Scalp psoriasis represents one of the "special sites," given its difficult-to-treat nature and disproportionate impact on quality of life (QoL). Psoriasis in general has a profound impact on QoL and can lead to psychological, social, and economic consequences, especially in moderate-to-severe disease.[7,8] Additionally, scalp disease in particular is associated with pain, itching, and bleeding. It has been shown to be associated with a disproportionate impact on QoL with significant impact on psychosocial impairment. Effective management of scalp psoriasis is essential to improving a participant's QoL.[6] The presence of hair and unacceptable cosmetic appeal of topical therapy are barriers to compliance and satisfaction with the currently available topical interventions. Topical regimens can be complex and are highly dependent on participant preference. Additionally, some participants with severe scalp disease may have minimal body involvement and, hence, may not receive systemic therapy indicated for moderate-to-severe chronic plaque psoriasis.[6,9,10]

Interventions 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; and systemic therapies. In moderate-to-severe disease, systemic interventions 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-interleukin (IL)-12/23p40 antibody (ustekinumab), IL-17 antagonists (secukinumab, ixekizumab, and brodalumab), and anti-IL-23p19 antibody (guselkumab, tildrakizumab and risankizumab). Many of these interventions are associated with increased risk of adverse events (AEs) such as hepatotoxicity and neutropenia (methotrexate);[11] nephrotoxicity (cyclosporine);[12] depression and weight loss (apremilast);[13] serious infections (cytokine inhibitors);[14,15,16,17] candidiasis and Crohn's disease (IL-17 antagonists).[17,18,19]

Although effective therapeutic options are available, undertreatment or nontreatment of psoriasis has been reported in up to half of surveyed participants (based on absence of intervention and/or dissatisfaction with intervention).[20] Only guselkumab, secukinumab, and apremilast have efficacy data for scalp psoriasis included in their Food and Drug Administration (FDA) label.[13,17,21] Scalp psoriasis presents considerable intervention challenges for the patient and practitioner. Psoriasis of this site also contributes to a significant burden on patient QoL.[6]

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. These approvals were based on the results of completed 52-week, randomized, Phase 3, placebo-controlled studies of deucravacitinib 6 mg daily (BMS-986165) versus placebo and apremilast 30 mg twice daily (BID) (POETYK PSO-1 and PSO-2).

In these 2 studies, in addition to the co-primary endpoints, scalp psoriasis was assessed using the scalp-specific Physician Global Assessment (ss-PGA) 0/1 and Psoriasis Scalp Severity Index (PSSI) 90 scores. For the purposes of the analyses in both studies, the scalp response assessment only included participants with a [redacted] (moderate-to-severe scalp psoriasis) [redacted]. Approximately 64% of participants in the Phase 3 studies met this criterion. Significantly higher ss-PGA 0/1 responses were seen in participants in the deucravacitinib arm as compared to those in the placebo and apremilast arms at Week 16 in both POETYK PSO-1 (70.8% vs 17.4% vs 39.1%, respectively) and POETYK PSO-2 (60.3% vs 17.3% vs 37.3%, respectively). Furthermore, deucravacitinib was also superior to apremilast at Week 24 in both studies (72.2% vs 42.7% and 59.7% vs 41.6%, respectively). 66.5% of participants on deucravacitinib maintained a ss-PGA 0/1 response at Week 52 in POETYK PSO-1. Additionally, significantly higher PSSI 90 responses were seen in the deucravacitinib arm as compared to apremilast through Week 24 in both POETYK PSO-1 (61.2% vs 29.1% respectively) and POETYK PSO-2 (48.9% vs 28.9%, respectively).

[redacted]

This Phase 3b/4 study is designed to evaluate the efficacy and safety of deucravacitinib in participants with moderate-to-severe scalp psoriasis. The primary hypothesis for the study is that the odds of achieving ss-PGA 0/1 with at least a 2-point reduction from baseline at Week 16 in participants receiving deucravacitinib 6 mg QD are improved compared to participants receiving placebo. The ss-PGA 0/1 is a standard measure in clinical trials of demonstrating efficacy of systemic psoriasis interventions. Additional analyses, including formal statistical hypothesis testing, will also be performed in the participant sub-population with static Physician Global Assessment (s-PGA) ≥ 3 at baseline for s-PGA 0/1 response at Week 16 to [redacted]

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.

Deucravacitinib is a potent, highly selective, oral, small molecule inhibitor of TYK2. A comprehensive in vitro and in vivo characterization of deucravacitinib has been established and supports the development of this compound in humans. Inhibition of TYK2 is expected to provide therapeutic benefit for participants with psoriasis for multiple reasons: 1) Many of the pathways in the TYK2 signaling cascade (IL-23 and the downstream mediators IL-17 and IL-22; IFNα) have been implicated in pathogenesis of psoriasis).[8] Biologic agents targeting the IL-17, IL-23p19, and IL-12/23 p40 pathways have been approved for and are highly efficacious in the intervention of psoriasis. Further, it is conceivable that participants with psoriasis could sustain a durable therapeutic response after repeated dosing with deucravacitinib. A recent trial using only a single

dose of a monoclonal antibody targeting the IL-23p19 subunit resulted in a rapid and sustained response for up to 66 weeks in participants with moderate-to-severe psoriasis.[25]

A detailed description of the chemistry, pharmacology, efficacy, and safety of deucravacitinib is provided in the Investigator's Brochure (IB).[26]

3.2.1 Clinical Development

The clinical development program for deucravacitinib consists of 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, 1 Phase 2 study (IM011011) and 2 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 QD. Studies IM011046 and IM011047 were pivotal, double-blind, placebo- and active-controlled 52-week, Phase 3 studies. Based on these studies, SOTYKTU™ (deucravacitinib), a first-in-class, oral, selective, allosteric TYK2 inhibitor was approved in multiple countries 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.

A detailed description is provided in the deucravacitinib IB.[26]

3.2.2 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of deucravacitinib may be found in the IB.[26]

3.2.3 Risk Assessment

Table 3.2.3-1: Risk Assessments

[redacted]

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.

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

3.2.4 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 Company (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 IB 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 IP (Section 8.1.1 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 AEs (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.

3.2.5 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 (IM011046 and IM011047) 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. Significantly higher ss-PGA 0/1 responses were seen with deucravacitinib versus placebo and apremilast arms at Week 16 in POETYK PSO-and POETYK PSO-2. Furthermore, deucravacitinib was also superior to apremilast at Week 24 in both studies. Additionally, significantly higher PSSI 90 responses were seen with deucravacitinib versus apremilast through Week 24 in POETYK PSO-1 and POETYK PSO-2. 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-glucoronosyltransferase (UGT) enzymes, cytochrome P450s (CYPs), or drug transporters. Details are described in the deucravacitinib IB.[26]

3.2.6 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 scalp plaque psoriasis.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by ss-PGA 0/1, of deucravacitinib versus placebo at Week 16: ○ in participants with moderate-to-severe scalp plaque psoriasis ○ in the sub-population of participants with a s-PGA ≥ 3 at baseline	• ss-PGA 0/1 response as a proportion of participants with an ss-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Key Secondary	
• To compare the efficacy, as measured by PSSI 90 response, of deucravacitinib versus placebo at Week 16: o in participants with moderate-to-severe scalp plaque psoriasis o in the sub-population of participants with a s-PGA ≥ 3 at baseline	• PSSI 90 response as a proportion of participants who achieve at least 90% improvement from baseline in the PSSI score at Week 16
• To compare the efficacy, as measured by scalp-specific itch NRS score, of deucravacitinib versus placebo at Week 16: o in participants with moderate-to-severe scalp plaque psoriasis o in the sub-population of participants with a s-PGA ≥ 3 at baseline	• Change from baseline in scalp-specific 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 the sub-population of participants with a s-PGA ≥ 3 at baseline	• s-PGA 0/1 response as a proportion of participants with an 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 moderate-to-severe scalp plaque psoriasis between Week 0 and Week 16	• AEs, SAEs, laboratory parameters, and VS between Week 0 and Week 16
Selected Exploratory	
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

AE, adverse event; NRS, Numerical Rating Scale; s-PGA, static Physician Global Assessment; VS, vital signs.

5 STUDY DESIGN

5.1 Overall Design

This study (IM011220) is a 52-week, Phase 3b/4, multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of deucravacitinib versus placebo in participants with moderate-to-severe scalp psoriasis. A total of approximately 150 qualified participants with moderate-to-severe scalp plaque psoriasis will be randomized (see Section 10.2). It is anticipated that 95% (n=143) of the 150 randomized participants will have s-PGA ≥ 3 at baseline.

The duration of study participation is approximately 60 weeks and will be divided into the following periods: Screening (up to 4 weeks), Intervention (52 weeks), and Safety follow-up (4 weeks).

Physical examination (PE), clinical laboratory evaluations, and other assessments will be done at select visits during the study. Participants in this study will be monitored for AEs.

5.1.1 Screening Period

Participants will be evaluated during the screening period (up to 4 weeks/ 28 days) to ensure they meet eligibility criteria. A detailed medical history will be done at this time, as well as a complete PE. Psoriasis-related history, which will include length of diagnosis, BSA involvement, scalp involvement, SSA involvement, and history of systemic intervention, will be assessed at Screening. [redacted] An evaluation for TB will be done based on medical history, recent chest imaging [redacted]

If a participant exceeds the 28-day screening period due to a study-related procedure (eg, waiting for a study-related laboratory value), the participant must be reconsented. A new participant identification number will be assigned by interactive response technology (IRT) at the time of re-enrollment. In this situation, 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).

5.1.2 Intervention Period

Participants who have completed the screening procedures and have met the inclusion/exclusion criteria will be randomized on Day 1 in a 2:1 ratio to either deucravacitinib 6 mg QD or placebo, respectively.

Dummy tablets (placebo to deucravacitinib 6 mg tablets) will be administered to participants to maintain blinding. Additional details are provided in Section 7.1.

[redacted]

5.1.3 Week 16

All efficacy endpoints and safety will be assessed at Week 16. At Week 16, all participants, regardless of their blinded intervention, will be switched to open-label deucravacitinib 6 mg QD bottles through Week 52.

5.1.4 Week 20

[redacted]

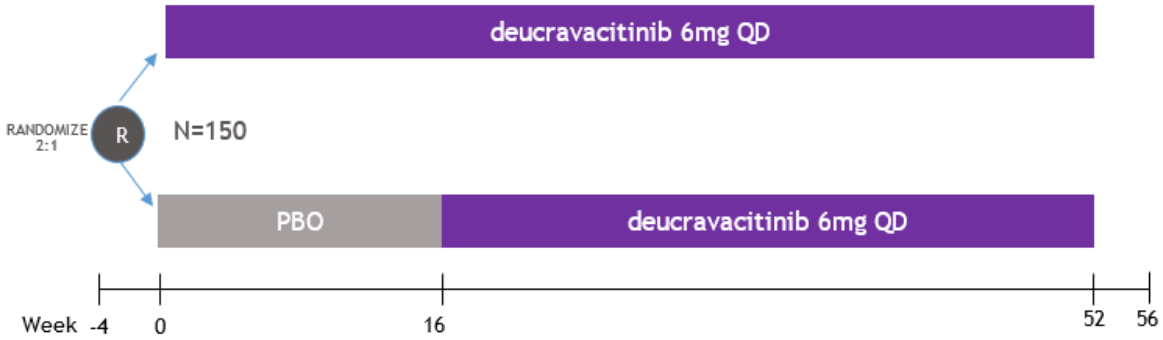
5.1.5 Week 52 and Safety Follow-up Period

The safety follow-up period is a 28-day window after the Week 52 visit. The participant will be encouraged to report any SAEs or AEs experienced during this time.

The End of Treatment (EOT) visit will be completed for participants who discontinue study intervention early. The participant will be asked to return to the clinic to complete the 28-day safety follow-up visit.

The study design schematic is presented in Figure 5.1.5-1.

Figure 5.1.5-1: Study Design Schema



PBO, placebo; QD, once daily.

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 External Study Steering Committee (SSC)

The 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.

5.2 Number of Participants

It is estimated that approximately 220 enrolled participants will be required to achieve 150 randomized. Approximately 150 participants will be randomized in a 2:1 ratio to deucravacitinib 6 mg QD or placebo matching deucravacitinib QD, respectively. [redacted] Sample size considerations are described in Section 10.2. It is anticipated that 95% (n=143) of the 150 randomized participants will have s-PGA ≥ 3 at baseline.

5.3 End of Study Definition

The duration of study participation for individual participants is expected to be up to 60 weeks (420 days), which includes Screening (up to 4 weeks), intervention (52 weeks), and follow-up (up to 4 weeks) periods.

The start of the study is defined as the first visit for the first participant screened.

The end of study is defined as the last participant last visit or scheduled procedure shown in the Schedule of Activities (Section 2) for the last participant.

Study completion is defined as the final date on which data were or are expected to be collected if this is not the same.

5.4 Scientific Rationale for Study Design

This Phase 3b/4 study will be conducted in a population of participants with stable moderate -to -severe scalp plaque psoriasis who are candidates for systemic psoriasis therapy. The study is designed to compare the efficacy and safety of deucravacitinib to placebo in achieving ss-PGA of 0/1 at Week 16. The ss-PGA 0/1 is a standard measure in clinical trials of demonstrating efficacy of systemic psoriasis interventions. Additional analyses, including formal statistical hypothesis testing, will also be performed in the participant sub-population with s-PGA ≥ 3 at baseline for s-PGA 0/1 response at Week 16 to [redacted]. s-PGA 0/1 is a standard measure in clinical trials of demonstrating efficacy of systemic psoriasis interventions. A placebo arm is included in this study 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 will be switched to deucravacitinib at Week 16 to provide them with psoriasis intervention 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 is the endpoint used in preceding psoriasis Phase 3 studies. The purpose of doing a 52-week study is to demonstrate the maintenance of improvement in PROs and clinical response.

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 the current study 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 2 Phase 3 studies demonstrated that deucravacitinib at 6 mg QD achieved significantly higher PASI 75 responses compared with placebo at Week 16 and significantly higher ss-PGA 0/1 and PSSI 90 responses in a subset of participants with moderate-to-severe scalp psoriasis.

6 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure: 1) selection of appropriate participants with scalp psoriasis, 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

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

a) Men and women diagnosed with stable plaque psoriasis with scalp involvement for 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) Deemed by the Investigator to be a candidate for phototherapy or systemic therapy

c) Moderate-to-severe scalp psoriasis as defined by ss-PGA ≥ 3; ≥ 20% SSA; PSSI ≥ 12 at the Screening Visit and Day 1

d) ≥ 3% of BSA involvement at the Screening Visit and Day 1

e) Evidence of plaque psoriasis in a non-scalp area

f) Failed to respond to, or intolerant of ≥ 1 topical therapy for scalp psoriasis

3) Age of Participant

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 relationship 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) 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 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 located in Section 2 (Schedule of Activities).

- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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

iv) WOCBP are permitted to use hormonal contraception methods (as described in APPENDIX 4)

v) 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 with regard to contraception (if any); however, no specific 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 nonplaque psoriasis (ie, guttate, inverse, pustular, erythrodermic or drug-induced psoriasis) at Screening or Day 1

2) Reproductive Status

a) Women who are pregnant

b) Women who are breastfeeding

c) Women who are lactating

d) Women who are 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 intervention 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) **Not applicable per Protocol Amendment 03:** Participants who are not fully vaccinated against SARS-CoV-2 as defined by the local and current national guidelines

g) 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 intervention

h) Receipt of any non-live vaccine within 30 days prior to Day 1 including any COVID-19 vaccine (first, second or booster dose)

i) Presence of herpes zoster lesions at Screening or Day 1

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

k) Evidence of, or test positive for, hepatitis B virus 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) **Not applicable per Protocol Amendment 03:** Presence of hepatitis B virus deoxyribonucleic acid

   OR

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

l) Evidence of, or test positive for, hepatitis C virus (HCV) at Screening. A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCVAb) AND 2) positive via a confirmatory test for HCV (eg, HCV polymerase chain reaction)

m) Positive for human immunodeficiency virus by antibody testing (HIV-1 and -2 antibody) at Screening

n) 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)

o) 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 trial physician, there are no sequelae that would place the participant at a higher risk of receiving investigational intervention.

4) Any of the following tuberculosis (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]

5) Medical History and Concurrent Diseases

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

b) **Not applicable per Protocol Amendment 03:** Has donated blood > 500 mL within 4 weeks prior to Day1, or plans to donate blood during the course of the study

c) Drug or alcohol abuse, as determined by the Investigator, within 6 months prior to Day 1

d) Medical marijuana or prescription marijuana taken for medicinal reasons

e) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, psychiatric, neurologic, immunologic, or local active infection/infectious illness) that, in the Investigator's judgment or after consultation with the Medical Monitor or designee, will substantially increase the risk to the participant if he or she participates in the study

f) 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

g) Has uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) > 160 mm Hg or diastolic BP > 100 mm Hg

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

h) Class III or IV congestive heart failure by New York Heart Association criteria

i) 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 cervix in situ that has been treated with no evidence of recurrence)

j) [redacted]

k) [redacted]

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

   i) Antibodies to IL-12, IL-17, or IL-23 (eg, ustekinumab, secukinumab, tildrakizumab, ixekizumab, or 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

m) Has received systemic non-biologic 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

n) Has used leflunomide within 6 months prior to Day 1

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

p) Has received lithium, antimalarials, or intramuscular (IM) gold within 4 weeks of the first administration of any study medication

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

r) Has used topical medications/interventions that could affect psoriasis evaluation (including, but not limited to, high potency corticosteroids (World Health Organization [WHO] Classes I to V), > 3% salicylic acid, urea, alpha- or beta-hydroxyl acids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, and tacrolimus) and intralesional corticosteroids within 2 weeks prior to Day 1

[redacted]

s) Use of shampoos that contain corticosteroids, coal tar, > 3% salicylic acid, or vitamin D_3 analogues within 2 weeks prior to Day 1

t) 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

u) 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 < $3000/mm^3$

ii) Absolute lymphocyte count < $500/mm^3$

iii) Absolute neutrophil count < $1000/mm^3$

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

v) Hemoglobin < 9 g/dL

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

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

viii) Thyroid-stimulating hormone (TSH) outside the normal range

AND

Free T4 (thyroxine) or T3 (triiodothyronine) outside the normal reference range

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

c) Inability to be venipunctured and/or tolerate venous access

d) 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 Reaction

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 and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)

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

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

d) Participation in another clinical trial concurrent with this study.

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; [redacted]

6.3.2 Caffeine, Alcohol, and Tobacco

No restrictions are required; however, extensive use of caffeine, 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 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 AEs.

6.4.1 Retesting During the Screening Period

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, 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 rescreening, 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 chest imaging, if performed during screening, may not be required. Duration of existing interventions and required discontinuation periods shall be considered relative to the new Screening Visit and/or randomization. [redacted]

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 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, or 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 as non-IP.

7.1 Study Interventions Administered

The selection and timing of dose for each participant is presented in Table 7.1-1.

Table 7.1-1: Study Interventions

Arm Name	Deucravacitinib (BMS-986165)	Placebo
Intervention name	Deucravacitinib (BMS-986165)	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.

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

7.2 Method of Study Intervention Assignment

Before the study is initiated, each user (at investigative sites) will receive log-in 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.

At Day 1, participants who meet all criteria for enrollment 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]

After all inclusion/exclusion criteria have been met for a participant, the investigative site will access the IRT on Day 1 for the purpose of randomizing a participant. An intervention group will be assigned by IRT based on the above-described randomization schedule. In addition, a unique kit number will be assigned to the participant corresponding to the intervention assignment.

Study intervention will be dispensed at study visits as shown in the Schedule of Activities (Section 2). When new intervention 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, 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 intervention 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 intervention, as shown in Table 7.1-1. Investigative site staff, Sponsor and designee personnel, and participants and their families will remain blinded to intervention 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. The primary analysis database lock will occur after all randomized participants completed their Week 16 visit or discontinued prior to Week 16. The study participants and Investigators will remain blinded to the initial treatment assignment throughout the study.

7.3.2 Circumstances for Unblinding

Blinding of study treatment 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 if 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 or designee, 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 call in for 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 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.

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

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

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 intervention. If a participant interrupts intervention due to an AE, study intervention can be restarted in consultation with the Medical Monitor or designee.

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 the 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 BMS. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

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

IP documentation (whether supplied by BMS or not) must be maintained that includes 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 the appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

7.6 Treatment Compliance

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

A record of the quantity of deucravacitinib/placebo 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 eCRF.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Interventions

Prohibited and/or restricted medications taken during the study are described below.

- Exposure to any investigational drug, investigational vaccine, or placebo outside of the current study. Specifically, participants currently in other interventional trials for COVID-19, including investigational COVID-19 vaccination trials that are not authorized or approved by relevant Health Authorities, should not participate in BMS clinical trials.
- Use of any medications/therapies that would aggravate psoriasis. These include agents such as lithium, antimalarials (quinacrine, chloroquine, and hydroxychloroquine), propranolol, indomethacin, and quinidine unless it is considered necessary for the participant's welfare and/or intervention of an AE/SAE
- Use of opioid analgesics unless it is considered necessary for the participant's welfare and/or treatment of an AE/SAE
- Phototherapy; use of tanning booths or therapeutic sunbathing
- Any use of biologic medications (eg, adalimumab, etanercept, infliximab, ustekinumab).
- Any use of oral psoriasis medications (eg, apremilast, methotrexate, cyclosporine, retinoids, fumaric acid derivatives) for any indication.
- Any use of oral or injectable corticosteroids (prednisone, methylprednisolone, etc), unless it is considered necessary for the participant's welfare and/or intervention of an AE/SAE.

  Note: optic, ophthalmic, nasal, and inhaled corticosteroids within recommended doses and with no systemic effects are permitted.
- Any topical medications/interventions, which are used for any indication, that could affect psoriasis evaluation (including, but not limited to, high potency corticosteroids [WHO Classes I to V], > 3% salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, calcipotriene, vitamin

D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, and tacrolimus) and intralesional corticosteroids.

Exception: The following topical interventions may be initiated at Week 20 and at any of the subsequent study visits per Investigator's discretion in participants who have ss-PGA ≥ 3 or s-PGA ≥ 3 (see Section 7.7): High potency corticosteroids (Classes I to V)

[redacted]

- Any medicated shampoos that contain corticosteroids, coal tar, > 3% salicylic acid, or vitamin D_3 analogues

  Exception: The shampoos that contain corticosteroids may be initiated at Week 20 and at any of the subsequent study visits per Investigator's discretion in participants who have ss-PGA scores ≥ 3 (Section 7.7).
- Live attenuated vaccines (including, but not limited to, any live attenuated COVID-19 vaccines) should not be used during the study, including the safety follow-up period of 60 days following last dose of IP (see Section 7.7.4 for permitted vaccines).

7.7.2 Permitted Concomitant Medications

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 meet 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. 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.

[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 is 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 enrollment. 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 concomitant medication page. For COVID-19 vaccines administered prior to enrollment, the types, details, and dates should be also recorded on the appropriate eCRF page.

Please contact the Medical Monitor or designee with any questions related to COVID-19 vaccines.

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

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Intervention

Participants MUST discontinue IP/IMP 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 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 BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (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 BMS approval is required.)

- Abnormal liver tests suggestive of drug-induced liver injury (DILI), as defined in Section 9.2.8 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 non-melanoma 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 9.2.6).
- 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.
- Participant reports suicidal ideation, suicidal behavior, or suicide attempts at any time after inclusion. The participant should then be immediately referred to a mental health professional for evaluation of suicide risk.

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

In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. The study treatment will be permanently discontinued. See Section 8.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2. 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 intervention 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 eCRF 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 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. In order to facilitate reporting of SARS-CoV-2 events that occur during the study, all AEs and SAEs related to SARS-CoV-2 must be reported from the time of consent. In addition, AEs or SAEs will trigger additional data collection through dedicated eCRF pages, which will allow the Sponsor to further evaluate these events.

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 8.2 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 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 intervention with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate eCRF 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 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 both from the study intervention and from 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 one (1) registered mail letter. All attempts should be 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.
- If the Investigator's use of 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 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, in order 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.

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.

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 Investigator-Administered Assessments

9.1.1.1 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.[27] 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.

9.1.1.2 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).[28] 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.

9.1.1.3 Body Surface Area (BSA)

Measurement of psoriasis BSA involvement is estimated using the handprint method with the size of a participant's handprint (including fingers and thumb) representing 1% of BSA involved.[29,30,31] The total BSA = 100% with breakdown by body region as follows: head and neck = 10% (10 handprints), upper extremities = 20% (20 handprints), trunk including axillae and groin = 30% (30 handprints), lower extremities including buttocks = 40% (40 handprints). All BSA assessments should be performed by a dermatologist or appropriately trained Investigator who is experienced in the assessment of psoriasis patients.

9.1.1.4 Scalp-Specific Physician's Global Assessment (ss-PGA)

For this assessment in participants with scalp involvement,[32] scalp lesions are evaluated in terms of clinical signs of redness, thickness, and scaliness and scored on the following 5-point ss-PGA scale: 0 = absence of disease, 1 = very mild disease, 2 = mild disease, 3 = moderate disease, 4 = severe disease.

The ss-PGA should be performed by a dermatologist or appropriately trained Investigator who is experienced in the assessment of psoriasis patients.

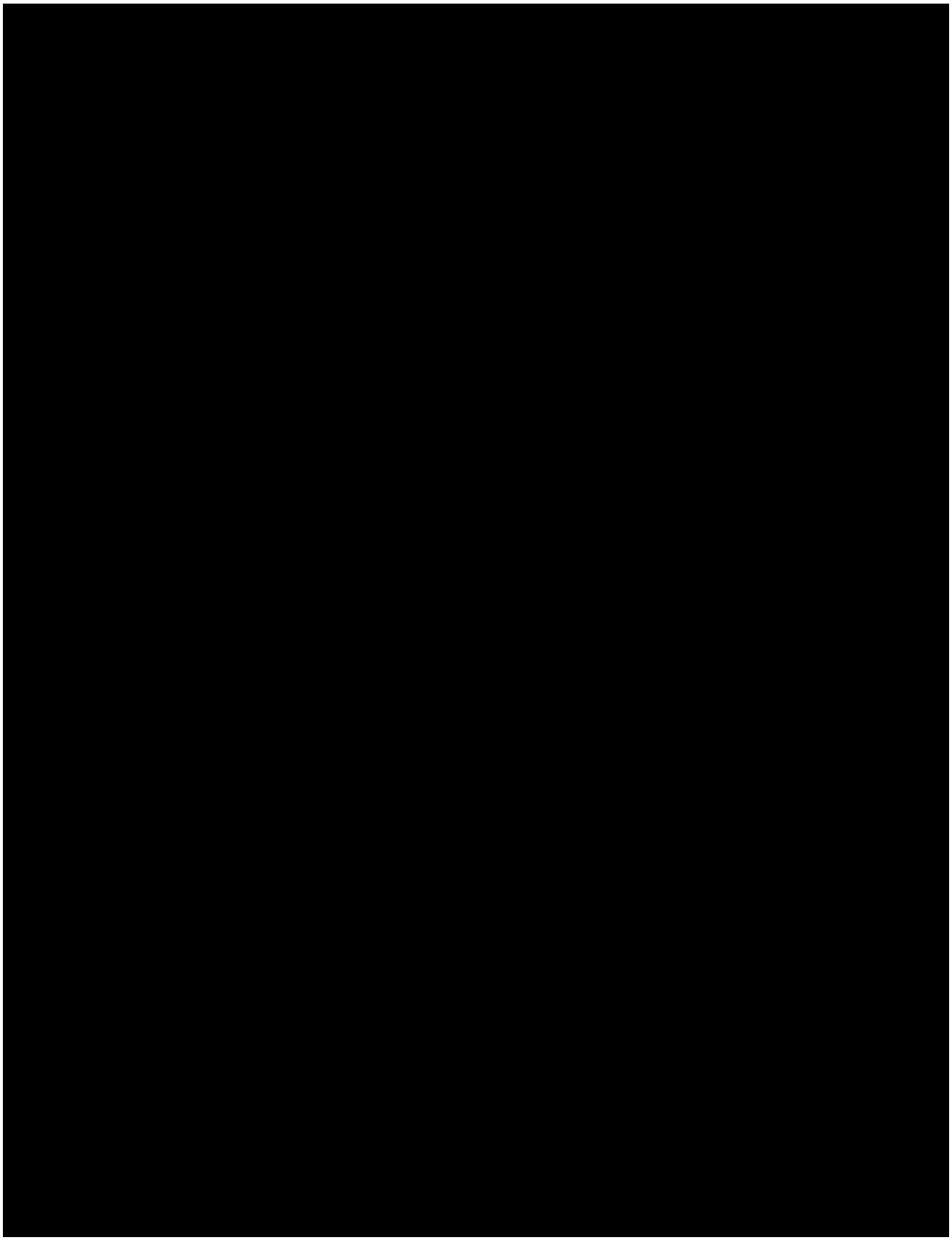
9.1.1.5 Psoriasis Scalp Severity Index (PSSI)

The PSSI assesses severity of scalp disease in participants with scalp involvement with a 5-point Likert-type scale on the clinical parameters of erythema, induration, and desquamation.[33] The scores are summed and multiplied by an integer (0 to 6) that represents the area of affected scalp. The PSSI score ranges from 0 to 72. The PSSI should be performed by a dermatologist or appropriately trained Investigator who is experienced in the assessment of psoriasis patients.

9.1.1.6 Scalp Surface Area (SSA)

Assessment of psoriasis SSA involvement will be estimated by an Investigator at each of the study visit as listed in the Schedule of Activities (Section 2). SSA assessment should be performed by a dermatologist or appropriately trained Investigator who is experienced in the assessment of psoriasis patients.

[redacted]



[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, or 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.

[redacted]

9.2.2 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study intervention until discharge from the study (ie, final study visit for a given participant), at the timepoints specified in the Schedule of Activities (Section 2).

Appendix 1 of the IB[26] represents the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 30 days following discontinuation of dosing.

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

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, 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.

9.2.3 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.

9.2.4 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 nonserious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the eCRF. Completion of supplemental eCRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious [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).

Further information on follow-up procedures is given in APPENDIX 3.

9.2.5 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 SUSAR (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.

9.2.6 Pregnancy

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome 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 on the participant.

In the event a participant becomes pregnant during the study, the study intervention must be discontinued immediately.

French specific study participants who are WOCBP will utilize urine pregnancy kits so they can conduct pregnancy tests at home at Weeks 36, 44, and 48. At-home pregnancy urine hCG test testing (WOCBP only) must be done per protocol schedule. Study participants will be instructed to communicate the results of the pregnancy tests to the site, with reminders and follow-up from the site study team, and pregnancy test results will be documented by the site in study participants' eCRFs. Sites need to obtain and document that the pregnancy test is negative. If at-home urine pregnancy test is ambiguous, a serum pregnancy test must be performed and participants should be asked to immediately pause taking study intervention until pregnancy status is confirmed. If at-home urine pregnancy test is positive, the study participant will be discontinued from the study as per the protocol discontinuation criteria. If pregnancy testing is not done per protocol schedule, the Investigator must contact the Medical Monitor as soon as feasible to discuss the participant's further participation in the study.

9.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE eCRF page or SAE eCRF, as appropriate. 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 required the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

9.2.8 Potential Drug-induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory 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 9.2.5 and APPENDIX 3 for reporting details).

A potential DILI is defined as:

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

AND

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

AND

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

9.2.9 Other Safety Considerations

Any significant worsening of conditions noted during interim or final PEs, ECG, x-ray filming, 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.

9.3 Overdose

For this study, any dose of deucravacitinib greater than 24 mg within a 24-hour time period will be considered an overdose. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (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 the Schedule of Activities (Section 2).

9.4.1 Physical Examinations

A complete PE will include general appearance, VS, eyes, ears, nose, mouth, throat, neck, respiratory, cardiovascular, respiratory, gastrointestinal/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.

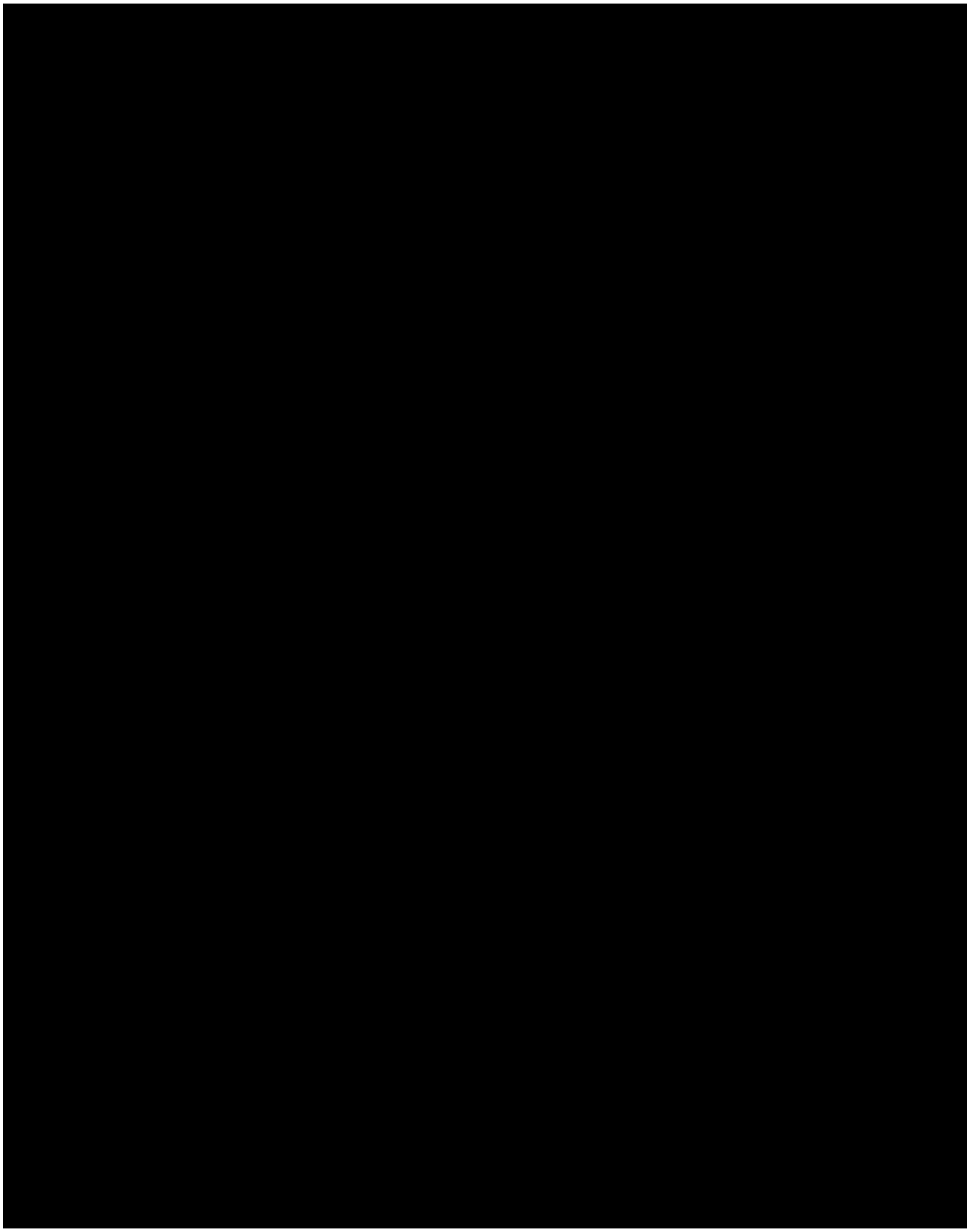
9.4.2 Vital Signs

VS includes (ear or oral) body temperature, respiratory rate, and seated BP and heart rate and will be recorded at each visit based on the 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 indicated in the Schedule of Activities (Section 2). 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]



[redacted]

9.5 Pharmacokinetics

PK parameters will not be evaluated in this study.

[redacted]

9.6 Immunogenicity Assessments

Not applicable.

9.7 Genetics

Not applicable.

9.8 Biomarkers

Biomarkers will not be evaluated in this study.

9.9 Additional Research

This protocol will not include sample collection and/or residual sample storage for additional research.

9.10 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

There are 2 population groups of interest in this study:

- Overall Population: All participants who were randomized to any treatment arm in the study.
- s-PGA ≥ 3 Sub-Population: All participants who were randomized to any treatment arm in the study with s-PGA ≥ 3 at baseline.

The statistical hypotheses associated with the primary endpoint (ss-PGA 0/1) and the secondary endpoints (PSSI 90, scalp-specific itch NRS [ss-NRS], and s-PGA 0/1 [s-PGA ≥ 3 Sub-population only]), will be formally tested in each population group using the multiplicity adjustment methods described in Section 10.1.1.

10.1 Statistical Hypotheses

The primary hypotheses for this study are that the odds of achieving ss-PGA 0/1 with at least a 2-point reduction from baseline at Week 16 in participants receiving deucravacitinib 6 mg QD are improved compared to participants receiving placebo on both the Overall Population and the s-PGA ≥ 3 Sub-Population.

The null hypotheses to be tested for the primary endpoint are the following:

- The odds of achieving ss-PGA 0/1 with at least a 2-point reduction from baseline at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo on the Overall Population.
- The odds of achieving ss-PGA 0/1 with at least a 2-point reduction from baseline at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo on the s-PGA ≥ 3 Sub-Population.

Key secondary endpoints and associated hypotheses will be tested in a hierarchical order only if both primary hypotheses achieved statistical significance. The null hypotheses corresponding to the key secondary endpoints are described below by population.

Overall Population:

- The odds of achieving at least a 90% improvement from baseline in the PSSI score at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.
- The mean change from baseline in scalp-specific itch NRS at Week 16 in participants receiving deucravacitinib 6 mg QD is not different from participants receiving placebo.

s-PGA ≥ 3 Sub-Population:

- The odds of achieving at least a 90% improvement from baseline in the PSSI score at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.
- The mean change from baseline in scalp-specific itch NRS at Week 16 in participants receiving deucravacitinib 6 mg QD is not different from participants receiving placebo.
- The odds of achieving s-PGA 0/1 with at least a 2-point reduction from baseline at Week 16 in participants receiving deucravacitinib 6 mg QD are the same as participants receiving placebo.

10.1.1 Multiplicity Adjustment

Two types of multiplicity adjustment are implemented to ensure that the family-wise Type I error rate is controlled to be no more than 2-sided 5% in the study 10.1.

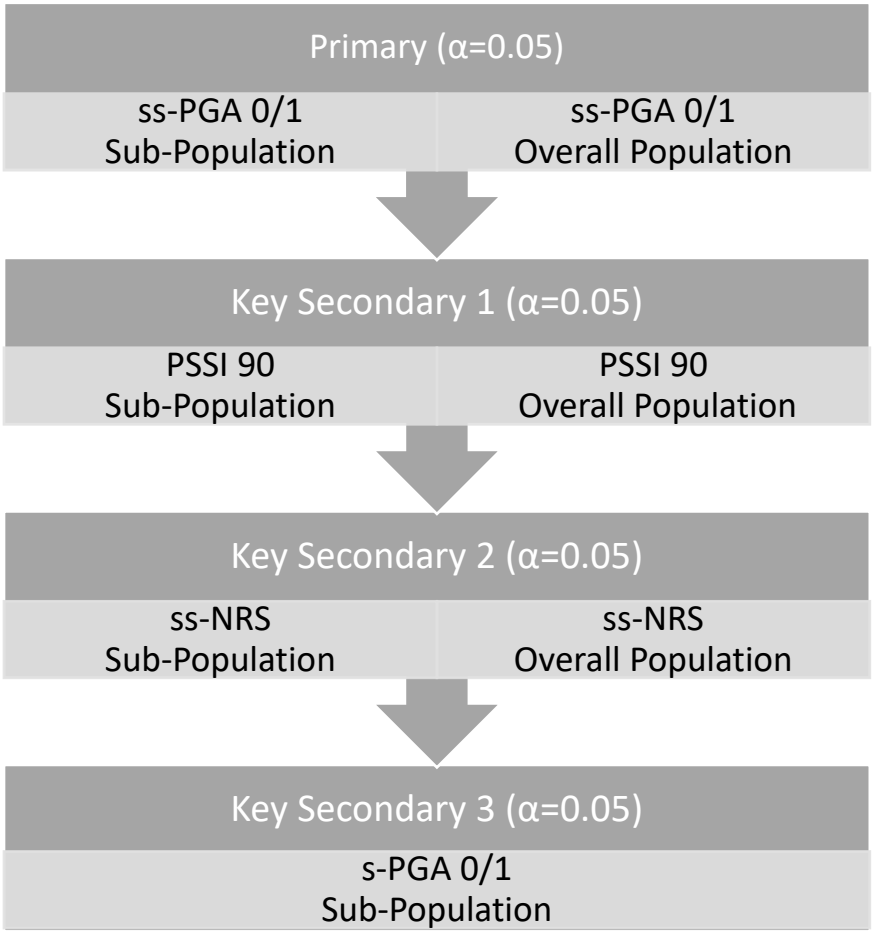
- Union-Intersection principle [41] between the 2 populations and corresponding hypotheses within each endpoint.
- Hierarchical gatekeeping procedure for the primary and secondary endpoints and associated hypotheses.

The 2 primary hypotheses will be tested simultaneously with a significance level (alpha) of 0.05 (2-sided). If either of the test results is not statistically significant (ie, at least one of null hypotheses is not rejected), then it is deemed that the study objective is not met. To proceed to the secondary hypothesis tests, both primary hypotheses must be met.

Secondary Family – Key secondary endpoints will be tested in a hierarchical order that presented in Figure 10.1.1-1, only if the primary endpoint achieved statistical significance at the 2-sided 0.05 level on both the Overall Population and the s-PGA ≥ 3 Sub-Population.

Figure 10.1.1-1 depicts the hierarchical order of hypothesis tests for the primary and secondary endpoints implementing the union-intersection principal and hierarchical gatekeeping procedure for the secondary hypothesis tests. If both primary hypotheses are satisfied, testing will proceed for the key secondary endpoints in a hierarchical order at an alpha level of 0.05. A hierarchical test may proceed to the next key secondary endpoint only if both null hypotheses within a key secondary endpoint are rejected. If a secondary endpoint fails at any step, then all subsequent p-values will be considered descriptive.

Figure 10.1.1-1: Hierarchical Order of Primary and Secondary Hypothesis Testing



PASI, Psoriasis Area and Severity Index; s-PGA, static Physician Global Assessment; ss-NRS, scalp-specific itch numerical rating scale; ss-PGA, scalp-specific Physician Global Assessment.

There will be no multiplicity adjustment for other additional endpoints; however, nominal P-values will be provided as descriptive statistics.

10.2 Sample Size Determination

It is estimated that approximately 220 enrolled participants will be required to achieve 150 randomized. Approximately 150 participants will be randomized in a 2:1 fashion to deucravacitinib 6 mg QD or placebo matching deucravacitinib 6 mg QD, respectively. Additionally, it is estimated that approximately 95% of randomized subjects (ie, approximately 143 subjects) would have baseline s-PGA scores ≥ 3. All assumed response rates and averages used for the sample size calculation were derived from the Phase 3 BMS studies IM011046 and IM011047 data. All sample size estimates were performed using nQuery Advisor version 7.0.

A total sample size of 150 participants randomized in a blinded fashion in a 2:1 ratio to deucravacitinib 6 mg QD and placebo, will provide approximately 95% power based on a chi-squared test with Type I error = 0.05, to compare deucravacitinib 6 mg QD to placebo for the

primary endpoint, proportion of participants that achieve ss-PGA 0/1 with at least a 2-point reduction from baseline at Week 16. Also, a sample size of 143 (sub-population with baseline s-PGA ≥ 3) provides approximately 94% power with Type I error = 0.05. This power estimate assumes ss-PGA 0/1 response rates of 55% and 25% for deucravacitinib 6 mg QD and placebo, respectively.

The assumed ss-PGA 0/1 response rates of 55% and 25% for deucravacitinib 6 mg QD and placebo, respectively, were derived based on a weighted average of response rates such that mild plaque psoriasis attributed 30% and moderate/severe plaque psoriasis attributed 70% of the population per the study design. The ss-PGA 0/1 response rates at Week 16 (deucravacitinib 6 mg QD: 65%, placebo: 20%) from the pooled Phase 3 studies (IM011047 and IM011046) were used for the moderate/severe plaque psoriasis and an assumed response rate of 25% in each arm for the mild population. With a total of 150 randomized participants (100 deucravacitinib 6 mg QD participants and 50 placebo participants), the weighted ss-PGA 0/1 response rates were approximately 55% and 25% for deucravacitinib 6 mg QD and placebo, respectively. Given the uncertainty in the assumed ss-PGA 0/1 response rates, Table 10.2-1 presents the impact on power for other possible response rates; eg, if the placebo rate was as high as 30%, there is still 83% power to detect a difference of 25% (OR: 2.852) between deucravacitinib 6 mg QD and placebo at an alpha level of 0.05.

Table 10.2-1: Power Calculation for Assumed ss-PGA 0/1 Response Rates with Sample Size of 150

Deucravacitinib 6 mg QD	Placebo	Difference	Odds Ratio	Power at α=0.05
55%	25%	30%	3.667	95%
55%	30%	25%	2.852	83%
50%	25%	25%	3.00	85%
50%	30%	20%	2.33	65%

QD, once daily; ss-PGA, scalp-specific Physician Global Assessment.

The sample size for the study is driven primarily to ensure there is a nominal power of approximately 90% for each endpoint including the 3 key secondary endpoints on the Overall Population. It is anticipated that 95% (n=143) of the 150 randomized participants will have s-PGA ≥ 3 at baseline, and therefore the statistical power is still adequate for the sub-population. Table 10.2-2 presents the powers for each endpoint by population at a Type I error rate of 0.05.

Table 10.2-2: Power Calculation for Each Endpoint by Population

Variable of Interest	Assumption: Deucravacitinib vs. Placebo	Sub-Population (Baseline s-PGA ≥ 3)		Overall Population	
		n	Power at α=0.05	n	Power at α=0.05
Primary					
ss-PGA 0/1	Response rate of 55% vs. 25%	143	94%	150	95%
Key Secondary					
PSSI 90	Response rate of 40% vs.15%	143	88%	150	90%
ss-NRS	Mean CFB -2.0 vs. -0.5 (σ=2.7)	143	87%	150	89%
s-PGA 0/1	50% vs. 10%	143	99%	N/A	

CFB, Change from BL, PSSI, Psoriasis Scalp Severity Index; s-PGA, static Physician Global Assessment; ss-NRS, scalp-specific itch numerical rating scale; ss-PGA, scalp-specific Physician Global Assessment

10.3 Analysis Sets

For purposes of analysis, the populations and analysis data sets are defined in Table 10.3-1.

Table 10.3-1: Populations and Analysis Data Sets

Population	Description
Enrolled	All participants who sign informed consent.
Randomized (FAS)	All participants who were randomized to any treatment arm in the study.
Full Analysis Subgroup	All participants who were randomized to any treatment arm in the study and baseline s-PGA ≥ 3.
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 ss-PGA 0/1	All randomized participants with baseline s-PGA ≥ 3; 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.
	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.

Table 10.3-1: Populations and Analysis Data Sets

Population	Description
Analysis set for secondary estimand of PSSI 90	All randomized participants with baseline s-PGA ≥ 3; 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.
	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 Scalp-specific itch NRS	All randomized participants with baseline s-PGA ≥ 3; 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.
	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 secondary estimand of s-PGA 0/1	All randomized participants with baseline s-PGA ≥ 3; 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.

NRS, numerical rating scale; PSSI, Psoriasis Scalp Severity Index; s-PGA, static Physician Global Assessment; ss-PGA, scalp-specific Physician Global Assessment.

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before the primary analysis database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. 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, 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 clinical study report.

10.4.1 General Considerations

Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy values will be summarized for all visits in which the variable is assessed. Baseline values are defined as the last non-missing value prior to the first dose of study drug unless otherwise indicated.

During the first 16 weeks of treatment, data will be presented for the following interventions:

- Deucravacitinib 6 mg QD
- Placebo

After Week 16, data will be presented for the following interventions:

- Deucravacitinib 6 mg QD
- Placebo – Deucravacitinib 6 mg QD (starting at Week 20 through Week 52)

The primary endpoint, ss-PGA 0/1 response, is defined as a proportion of participants with an ss-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16. The key secondary endpoints assessed at Week 16 are PSSI 90 response, change from baseline in scalp-specific itch NRS score, and s-PGA 0/1 response (sub-population only). PSSI 90 is defined as a proportion of participants who achieve at least a 90% improvement from baseline in the PSSI score, and s-PGA 0/1 is defined as a proportion of participants with a s-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16.

[redacted]

Table 10.4.1-1: Definition of Estimands for Primary and Key Secondary Endpoints

Primary Endpoint			
Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus placebo		
Population	FAS population and FAS sub-population		
Variable	ss-PGA 0/1		
ICEs	**Event**	**Strategy**	**Description**
	Discontinuation of intervention or study early prior to Week 16 assessment	Composite variable	Participant will be counted as a non-responder

Table 10.4.1-1: Definition of Estimands for Primary and Key Secondary Endpoints

	Lost to follow-up prior to Week 16 or otherwise missing endpoint data at Week 16 assessment	Composite variable	Participant will be counted as a non-responder
	Start a protocol prohibited medication/therapy	Treatment policy	Participants will be included in the primary analysis regardless of the occurrence of the ICE according to the respective endpoint definition.
	Missing assessment at Week 16 due to SARS-CoV-2	While on treatment	Participants will be excluded from the primary analysis if the Week 16 assessment was not completed due to SARS-CoV-2
Population-level Summary	Odds ratio of achieving ss-PGA 0/1		
Key Secondary Endpoints			
Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus placebo		
Population	FAS population and FAS sub-population		
Variable	PSSI 90		
ICEs	**Event**	**Strategy**	**Description**
	Discontinuation of intervention or 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 missing endpoint data at Week 16 assessment	Composite variable	Participant will be counted as a non-responder
	Start a protocol prohibited medication/therapy	Treatment policy	Participants will be included in the analysis regardless of the occurrence of the ICE according to the respective endpoint definition.
	Missing assessment at Week 16 due to SARS-CoV-2	While on treatment	Participants will be excluded from the analysis if the Week 16 assessment was not completed due to SARS-CoV-2
Population-level Summary	Odds ratio of achieving PSSI 90		

Table 10.4.1-1: Definition of Estimands for Primary and Key Secondary Endpoints

Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus placebo		
Population	FAS population and FAS sub-population		
Variable	Change from baseline in Scalp-specific itch Numeric Rating Scale (NRS)		
ICEs	**Event**	**Strategy**	**Description**
	Discontinuation of intervention or study early prior to Week 16 assessment	Composite variable	Missing data will be imputed using multiple imputation
	Lost to follow-up prior to Week 16 or otherwise missing endpoint data at Week 16 assessment	Composite variable	Missing data will be imputed using multiple imputation
	Start a protocol prohibited medication/therapy	Treatment policy	Participants will be included in the analysis regardless of the occurrence of the ICE according to the respective endpoint definition.
	Missing assessment at Week 16 due to SARS-CoV-2	While on treatment	Participants will be excluded from the analysis if the Week 16 assessment was not completed due to SARS-CoV-2
Population-level Summary	Adjusted mean difference between deucravacitinib 6 mg QD and placebo		
Estimand Attribute	**Definition**		
Treatment	Deucravacitinib 6 mg QD versus placebo		
Population	FAS sub-population		
Variable	s-PGA 0/1		
ICEs	**Event**	**Strategy**	**Description**
	Discontinuation of intervention or 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 missing endpoint data at Week 16 assessment	Composite variable	Participant will be counted as a non-responder
	Start a protocol prohibited medication/therapy	Treatment policy	Participants will be included in the primary analysis regardless of the occurrence of the ICE according to the

Table 10.4.1-1: Definition of Estimands for Primary and Key Secondary Endpoints

			respective endpoint definition.
	Missing assessment at Week 16 due to SARS-CoV-2	While on treatment	Participants will be excluded from the primary analysis if the Week 16 assessment was not completed due to SARS-CoV-2
Population-level Summary	Odds ratio of achieving s-PGA 0/1		

FAS, Full Analysis Set; ICE, intercurrent event; NRS, numerical rating scale; PSSI, Psoriasis Scalp Severity Index; QD, once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ss-PGA, scalp-specific Physician Global Assessment; s-PGA, static Physician Global Assessment.

10.4.2 Primary Endpoints

Table 10.4.2-1: Summary of Primary Endpoints

Primary Endpoint	Description of Analysis	Time Frame
ss-PGA 0/1 response rate is defined as a proportion of participants with an ss-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.	The analysis model for the primary endpoint, ss-PGA 0/1 (responder/non-responder) at Week 16, will use a stratified CMH test stratified [redacted] to compare the response rates of deucravacitinib 6 mg QD to placebo using the Week 16 data of the FAS as well as the FAS subgroup where baseline s-PGA ≥ 3. If expected cell counts are not sufficient for each strata level, then strata level will be combined for the analysis. The odds ratio (ratio of odds in deucravacitinib 6 mg QD to the odds in placebo group) and the corresponding 2-sided 95% CI will be provided. Estimates of proportions and their 2-sided 95% CIs will be provided. 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

CI, confidence interval; CMH, Cochran-Mantel-Haenszel; NRI, non-responder imputation; QD, once daily; SAP, statistical analysis plan; s-PGA, static Physician Global Assessment; ss-PGA, scalp-specific Physician Global Assessment.

10.4.3 Secondary Endpoints

Table 10.4.3-1: Summary of Key Secondary Endpoints

Secondary Endpoint	Description of Analysis	Time Frame
PSSI 90 response rate is defined as a proportion of participants who achieve at least a 90% improvement from baseline in the PSSI score.	The analysis model for PSSI 90 (responder/non-responder) at Week 16, will use stratified CMH tests [redacted] to compare the response rates of deucravacitinib 6 mg QD to placebo for the FAS population as well as the FAS sub-population where baseline s-PGA ≥ 3. The odds ratio (ratio of odds in deucravacitinib 6 mg QD to the odds in placebo group) and the corresponding 2-sided 95% 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
Change from baseline in Scalp-specific itch NRS	The analysis model for the continuous secondary endpoint, change from baseline in Scalp-specific itch NRS at Week 16, will use ANCOVA with intervention and [redacted] The baseline value will be added into the model as a covariate. Intervention differences based on LS means and the corresponding 2-sided 95% CIs will be provided for the difference between deucravacitinib 6 mg QD and placebo for the FAS population as well as the FAS sub-population where baseline s-PGA ≥ 3. For the continuous secondary efficacy endpoint, multiple imputation will be used for missing data.	Week 16
s-PGA 0/1 response rate is defined as a proportion of participants with an s-PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.	The analysis model for s-PGA 0/1 (responder/non-responder) at Week 16, will use stratified CMH tests [redacted] to compare the response rates of deucravacitinib 6 mg QD to placebo for the FAS sub-population where baseline s-PGA ≥ 3. The odds ratio (ratio of odds in deucravacitinib 6 mg QD to the odds in placebo group) and the corresponding 2-sided 95% 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

CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, Full Analysis Set; PSSI, Psoriasis Scalp Severity Index; QD, once daily; ANCOVA, analysis of covariance; NRI, non-responder imputation; NRS, numerical rating scale; LS, least-squares; s-PGA, static Physician Global Assessment.

[redacted]

10.4.5 Safety Analysis

Safety data will be analyzed for AEs, SAEs, laboratory parameters, and VS. Safety will be summarized using the Safety population. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Safety will be analyzed through Week 16 and then up to end of study.

10.4.5.1 Adverse Events

Treatment-emergent AEs (TEAEs), SAEs, deaths, AEs leading to study intervention discontinuation, and [redacted] will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

10.4.5.2 Vital Signs

VS will be summarized as raw, change from baseline, including the maximum post-baseline value. Baseline values are defined as the last non-missing value prior to the first dose of study drug. The number and proportion of participants with vital sign abnormalities will be summarized at each scheduled visit.

10.4.5.3 Clinical Laboratory Tests

Laboratory parameters will be summarized as raw, change from baseline, including the maximum post-baseline value. Incidence of abnormal, high, or low values will be summarized. Shift tables will also be provided. Baseline values are defined as the last non-missing value prior to the first dose of study drug. The number and proportion of participants with clinical laboratory abnormalities will be summarized at each scheduled visit.

10.4.6 Other Analyses

Not applicable.

10.4.7 Interim Analyses

Not applicable.

10.5 Week 16 Primary Analysis

A 16-week primary analysis will occur once all randomized participants have completed their Week 16 visit or have discontinued prior to Week 16. Analyses of the collected efficacy and safety data will be performed. The study participants and Investigators will remain blinded to the initial treatment assignment 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 final safety follow-up visit at Week 56 or post-discontinuation follow-up visit.

11 REFERENCES

1 Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-385.

2 Kupetsky EA, Keller M. Psoriasis vulgaris: an evidence-based guide for primary care. J Am Board Fam Med. 2013;26(6):787-801.

3 World Health Organization. Global Report on psoriasis. WHO 2016

4 Langely RG, Kruger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005;64(Suppl II): ii18-ii23.

5 Quiero R, Tejon P, Alonso S, Coto P. Age at disease onset: a key factor for understanding psoriatic disease. Rheumatology (Oxford). 2014;53(7):1178-1185.

6 Mosca M, Hong J, Hadeler E, et al. Scalp psoriasis: a literature review of effective therapies and updated recommendations for practical management. Dermatol Ther (Heidelb). 2021;11:769-797.

7 Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41:401-407.

8 Nestle FO, Kaplan DH, Barker J. Mechanisms of disease: psoriasis. N Engl J Med. 2009;361:496-509.

9 van de Kerkhof PC, Franssen ME. Psoriasis of the scalp. Diagnosis and management. Am J Clin Dermatol. 2001;2(3):159-165.

10 Merola JF, Qureshi A, Husni ME. Underdiagnosed and undertreated psoriasis: nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails. Dermatol Ther. 2018;31(3):e12589.

11 Novartis. Rheumatrex® (methotrexate). United States Prescribing Information. 2016.

12 Novartis. Neoral® (cyclosporine). United States Prescribing Information. 2009.

13 Celgene. Otezla® (apremilast). United States Prescribing Information. 2017.

14 AbbVie. Humira® (adalimumab). United States Prescribing Information. 2017.

15 Janssen Biotech. Remicade® (infliximab). United States Prescribing Information. 2013.

16 Janssen Biotech. Stelara® (ustekinumab). United States Prescribing Information. 2016.

17 Novartis. Cosentyx® (secukinumab). United States Prescribing Information. 2015.

18 Eli Lilly. Taltz® (ixekizumab). United States Prescribing Information. 2017.

19 Valeant. Siliq® (brodalumab). United States Prescribing Information. 2017.

[20] Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among subjects with psoriasis and psoriatic arthritis in the United States. Findings from the National Psoriasis Foundation Surveys, 2003-2011. JAMA Dermatol. 2013;149(10):1180-1185.

[21] Janssen Biotech. TREMFYA® (guselkumab). United States Prescribing Information. 2017.

[22] Tokarski JS, Zupa-Fernandez A, Tredup JA, et al. Tyrosine kinase 2-mediated signal transduction in T lymphocytes is blocked by pharmacological stabilization of its pseudokinase domain. J Biol Chem. 2015;290:11061-11074.

[23] Watford WT, Hissong BD, Bream JH, et al. Signaling by IL-12 and IL-23 and the immunoregulatory roles of STAT4. Immunol Rev. 2004;202:139-156.

[24] Shaw MH, Boyartchuk V, Wong S, et al. A natural mutation in the Tyk2 pseudokinase domain underlies altered susceptibility of B10.Q/J mice to infection and autoimmunity. Proc Natl Acad Sci U S A. 2003;100:11594-11599.

[25] Krueger JG, Ferris LK, Menter A, Wagner F, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2015;136(1):116-124.

[26] BMS-986165 Deucravacitinib Investigator Brochure Version 09. Bristol-Myers Squibb Company; 2022. Document Control No. 930090873.

[27] Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis. 2005;64:ii65-ii68.

[28] Fredriksson T, Pettersson U. Severe psoriasis-oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-244.

[29] Rossiter ND, Chapman P, Haywood IA. How big is a hand. Burns.1996;22:230-231.

[30] Long CC, Finlay AY, Averill RW. The rule of hand: 4 hand areas = 2 FTU = 1 g. Arch Dermatol. 1992;128:1129-1130.

[31] Thomas CL, Finlay AY. The 'handprint' approximates to 1% of the total body surface area whereas the 'palm minus the fingers' does not. Br J Dermatol. 2007;157(5):1080-1081.

[32] Kragballe K, Menter A, Lebwohl M, et al. Long-term management of scalp psoriasis: perspectives from the international psoriasis council. J Dermatol Treat. 2013;24:188-192.

[33] Thaçi D, Daiber W, Boehncke WH, Kaufmann R. Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety and acceptance in 3,396 patients. Dermatology. 2001;203(2):153-156.

[redacted]

[redacted]

39 Kroenke K, Strine TW, Spitzer RL, et al. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009;114(1-3):163-173.

[redacted]

41 Sen PK. Union-intersection principle and constrained statistical inference. Journal of Statistical Planning and Inference. 2007;137(11):3741-3752.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AAD-NPF	American Academy of Dermatology–National Psoriasis Foundation
AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBc total	hepatitis B core antibody total
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AxMP	auxiliary medicinal product
BID	twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb Company
BP	blood pressure
BSA	body surface area
CES2	carboxylesterase 2
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DILI	drug-induced liver injury
[redacted]	[redacted]
DNA	deoxyribonucleic acid
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EE	ethinyl estradiol
[redacted]	[redacted]
EOT	End of Treatment

Term	Definition
ET	early termination
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
[redacted]	[redacted]
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN	interferon
IGRA	interferon gamma release assay
IL	interleukin
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
IUS	Intrauterine hormone-releasing system
IV	intravenous

Term	Definition
JAK	Janus kinase
LAM	lactational amenorrhea method
LS	least squares
LTBI	latent tuberculosis infection
MDR/RR-TB	multidrug/rifampicin-resistant tuberculosis
[redacted]	[redacted]
n/a	not applicable
[redacted]	[redacted]
NIMP	non-investigational medicinal product
NMSC	non-melanoma skin cancer
NRI	non-responder imputation
NRS	numerical rating scale
PASI	Psoriasis Area and Severity Index
PE	physical examination
PHQ-8	8-Item Patient Health Questionnaire
PK	Pharmacokinetics
[redacted]	[redacted]
[redacted]	[redacted]
PsA	psoriatic arthritis
PSSI	Psoriasis Scalp Severity Index
p-y	patient-years
QD	once daily
QoL	quality of life
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	[redacted]
SIR	standardized incidence ratio
s-PGA	static Physician Global Assessment
SSA	scalp surface area
SSC	Study Steering Committee
ss-PGA	scalp-specific Physician Global Assessment
STAT	signal transducer and activator of transcription

Term	Definition
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
TYK2	tyrosine kinase 2
UGT	UDP-glucoronosyltransferase
ULN	upper limit of normal
US	United States
VS	vital signs
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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 Electronic Case Report Form (eCRF).

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 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, one 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, IB, 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 Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and 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, also 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:

- IRB/IEC
- Regulatory authority(ies), if applicable by 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, also by the local Health Authority, must be sent to Bristol-Myers Squibb (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 course of 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 or his/her legally acceptable representative and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 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 participant or his/her legally acceptable representative to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant or his/her legally acceptable representative and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before 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 participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

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 or his/her legally acceptable representative 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.

In situations where consent cannot be given by participants, their legally acceptable representatives (as per country regulation) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

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.

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[1]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 or entered in the electronic CRF (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.
- Definitions of what constitutes source data can be found in the monitoring plan.

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: • 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, as per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply or a specialty pharmacy)	The Investigator or designee accepts responsibility for documenting traceability and study treatment 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

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 eCRF 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. eCRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of 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 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 eCRFs.

The completed eCRF and SAE/pregnancy eCRFs 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 eCRF approval task. The Investigator must retain a copy of the eCRFs, 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 noncompliance 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.

Certain eCRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to eCRFs, 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.

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments 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 treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments 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 treatments provided by BMS (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the Investigator or designee.

STUDY AND SITE START AND 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:

- 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 recruitment of participants by the Investigator
- Discontinuation of further study intervention development

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 assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare 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 as 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 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 their 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 time 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 BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon 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); AND
2) Drafting the work or revising it critically for important intellectual content; AND

3) Final approval of the version to be published; AND
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 BMS 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 AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, VS measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. Note that abnormal lab tests or other safety assessments 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 it 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 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 NOT 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 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 which 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 Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as 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 entry into 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 result 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 room 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 9.2.8 for the definition of potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 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 IB 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 one 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 predefined 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 treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 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 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 designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile 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 facsimile transmission.

SAE Email Address: [redacted]

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

US: [redacted]

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 Woman of Childbearing Potential 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 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman 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
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 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 in order 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 timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be 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 IMP to pass.

METHODS OF CONTRACEPTION

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

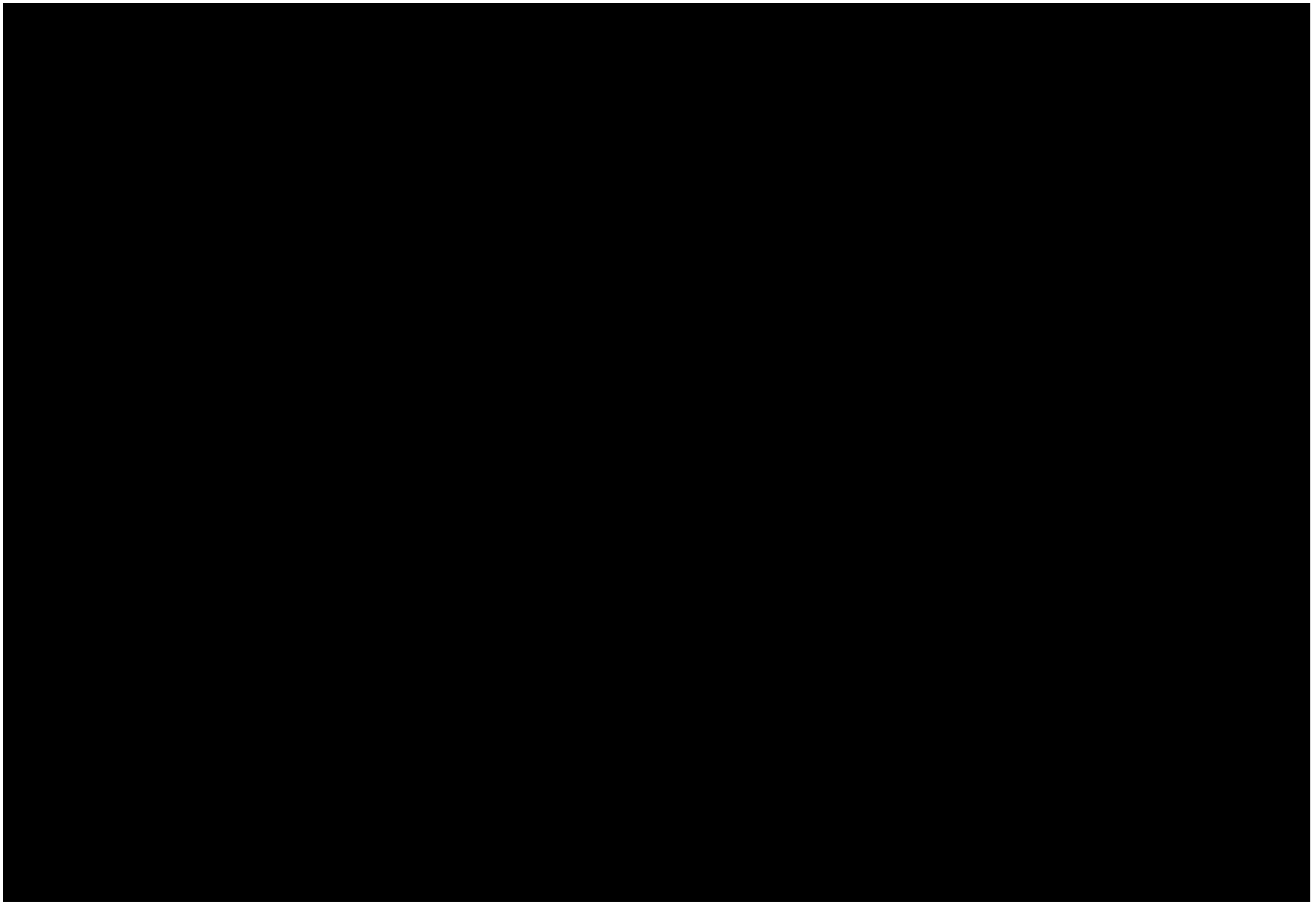
Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where 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 where 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 where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device. • Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where 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. • 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, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational 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 IMP 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. Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED INTERVENTIONS of the protocol. [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. Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED INTERVENTIONS of the protocol.

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 where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation 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 9.2.6 and APPENDIX 3.



APPENDIX 6 HEPATITIS B VIRUS (HBV) SCREENING

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

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

Table 1: Eligibility Based on Hepatitis B Virus Test Results

	HBV Test Results		
Action	**Hepatitis B Surface Antigen (HBsAg)**	**Hepatitis B Surface Antibody (anti-HBs)**	**Hepatitis B Core Antibody Total (anti-HBc total)**
Include	-	-	-
	-	+	-
	-	+	+
Exclude	+	**- or +**	**- or +**
	-	-	+

anti-HBs, hepatitis B surface antibody; anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

APPENDIX 7 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 05-Dec-2022

This protocol has been revised to add fasting lipid collection at Week 24 and Week 52.

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Correction of phone number and zip code for [redacted] address and correction of phone number [redacted]	Updated contact information
Schedule of Activities (Table 2-3)	[redacted]	[redacted]
Schedule of Activities (Table 2-3) On-Intervention Procedural Outline, (IM011220) Week 24 through 52	Added French specific language: Between visit windows, at weeks 36, 44, and 48, an at home urine pregnancy test will be performed Participants will provide the results by phone. See Section 9.2.6	This French specific change is to add pregnancy testing collection in the active treatment period between visits [redacted].
Schedule of Activities (Table 2-3)	[redacted]	Minor correction
Section 3.1 Study Rationale	The following text was added to reflect FDA approval: "The US FDA approved SOTYKTU™ (deucravacitinib), a first-in-class, oral, selective, allosteric tyrosine kinase 2 (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."	To reflect FDA approval of deucravacitinib in the United States
Section 3.2.1 Clinical Development	The following text was added to reflect FDA approval: Based on these studies, the US 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.	To reflect FDA approval of deucravacitinib in the United States
Section 3.2.1 Clinical Development	Updated details regarding completed and ongoing studies.	To include the most up-to-date information in the protocol
Section 3.2.5 Benefit Assessment Section 5.5 Justification for Dose	The following text was added: "The dose of 6 mg QD is also the FDA-approved dose."	To clarify the FDA-approved dose of deucravacitinib

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.6 Pregnancy	The following language was deleted: "Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form."	To align with current protocol model document language
Section 9.2.6 Pregnancy	The following French specific text was added: Study participants who are WOCBP will use urine pregnancy kits so they can conduct pregnancy tests at home at Weeks 36, 44, and 48. At-home pregnancy urine hCG test testing (WOCBP only) must be done per protocol schedule. Study participants will be instructed to communicate the results of the pregnancy tests to the site, with reminders and follow-up from the site study team, and pregnancy test results will be documented by the site in study participants' eCRFs. Sites need to obtain and document that the pregnancy test is negative. If at-home urine pregnancy test is ambiguous, a serum pregnancy test must be performed, and participants should be asked to immediately pause taking study intervention until pregnancy status is confirmed. If at-home urine pregnancy test is positive, the study participant will be discontinued from the study as per the protocol discontinuation criteria. If pregnancy testing is not done per protocol schedule, the Investigator must contact the Medical Monitor as soon as feasible to discuss the participant's further participation in the study.	This French specific change is to add pregnancy testing collection in the active treatment period between visits [redacted]
[redacted]		

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
All	Minor formatting and typographical corrections	Minor edits made to improve overall readability, consistency, etc

Overall Rationale for the Protocol Amendment 01, 19-May-2022

The primary reason for Protocol Amendment 01 is to clarify medical photography language and to update the [redacted] section. Additionally, there was an update to the language in the multiplicity adjustment section to reflect that the primary endpoint is included in the hierarchical order. Change of safety endpoint from exploratory to "other" secondary endpoint. Updated the definition of estimands table for primary and key secondary endpoints as per estimand guidance. Updated APPENDIX 2 with the current BMS language. References to BMS-986165 were changed to deucravacitinib throughout the protocol and in the title. Addition of PSORIATYK SCALP to the title. Clarifying information and administrative changes were made.

These changes pertain to all participants.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Addition of PSORIATYK SCALP to the title	To be consistent with the clinicaltrials.gov listing
All	Replaced references to BMS-986165 to deucravacitinib after being described as "also known as" throughout the protocol including protocol title change	Updated product number to the product name
Title Page	Deletion of Syneos Medical Monitor contact info	Updated contact information
Section 1 Overall Design	Added that participant will be followed for safety for 4 additional weeks from week 52 through week 56	Provides details for follow up period
Sections 1 and 4, Table 4A Objectives and Endpoints	"To assess the safety of deucravacitinib vs placebo in participants with moderate-to-severe scalp plaque psoriasis" The endpoint was changed from an exploratory endpoint to an "other secondary endpoint." Modified language for clarity as to how the response will be measured	Safety is an important other secondary endpoint Provides details as to how objectives will be measured

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1 Statistical Methods	Clarified the timepoints to be analyzed for the primary analysis will occur after the last participant completes Week 16 and the final analysis will occur after all participants complete their final safety visit at Week 56 or their post-discontinuation follow-up visit	Provides a specific timepoint of reference
Section 3.3.1-1 Risk Assessment	Added this sentence for clarification "Because deucravacitinib is a potential immunosuppressant and in line with standard practice for immunosuppressive therapies, the studies have been designed with inclusion/exclusion criteria aimed at minimizing the [redacted]"	Provides greater clarity in describing risk minimization
Section 5.5 Justification for Dose	Updated the justification for the dose	Provides greater clarity
Section 7.2 Method of Study Intervention Assignment	Removed "each participant will be assigned a unique randomization number	Per IRT manager
Section 7.3.1 Unblinding section Maintaining the Blind	Added that the Sponsor and site-facing study team will be unblinded after the Week 16 database lock but the study participants and Investigators will remain blinded throughout the study.	Clarification of who will be unblinded at Week 16 and at the completion of the study
Section 8.1.2 Post Study Intervention Study Follow-Up	Removed the term "until death" for one of the follow-up intervals	To clarify that the follow-up interval is until the conclusion of the study (Week 56)
[redacted]		

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.1.1.1 Static Physician's Global Assessment (s-PGA)	Assessment term # 1 changed from "minimal" to "almost clear",	Align with standard scales
Section 10.1.1 Multiplicity Adjustment	Updated language of hierarchical order since the primary endpoint was inadvertently not included	Clarification of hierarchical order
Section 10.4.1-1 Table 10.4.1-1	Updated Estimand table	As per the Estimand Guidance document
Section 10.4.5	Included timing of safety analyses	Provides clarity
Appendix 2: Addition of BMS Commitment to Diversity in Clinical Trials	Addition of BMS Commitment to Diversity in Clinical Trials	As per the Protocol Model Document
Appendix 2: Data Protection, Data Privacy, and Data Security	Updated language to the Data Protection, Data Privacy, and Data Security	As per the Protocol Model Document
All	The term "subjects" was changed to "participants" throughout	Preferred term
All	Administrative changes, ie, for further clarification, spelling, spacing, typographical errors.	Administrative changes as applicable