Official Title of Study:

A Phase IV, Open-label, Single-group, Single-dose Study
Evaluating Deucravacitinib Concentrations in the Breast Milk and Plasma of Healthy Lactating Female Participants

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CLINICAL PROTOCOL IM0111123

A Phase IV, Open-label, Single-group, Single-dose Study
Evaluating Deucravacitinib Concentrations in the Breast Milk and Plasma of Healthy Lactating Female Participants

Compound: BMS-986165

Brief Title: Deucravacitinib Concentrations in the Breast Milk and Plasma of Lactating Females

Medical Monitor Name and Contact Information:

[redacted]
Clinical Trial Physician – Medical Monitor
Bristol-Myers Squibb Company
1000 Sierra Point Parkway
Brisbane, CA 94005
Phone: [redacted]
Email: [redacted]

24-hr Emergency Telephone Number
USA: 1-866-470-2267
International: +1-248-844-7390

Sponsor Name and Legal Registered Address:

Bristol-Myers Squibb Company
Route 206 & Province Line Road
Princeton, NJ 08543

REGULATORY AGENCY IDENTIFIER NUMBER

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Original Protocol	03-May-2024	Not applicable.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Phase IV, Open-label, Single-group, Single-dose Study Evaluating Deucravacitinib Concentrations in the Breast Milk and Plasma of Healthy Lactating Female Participants

Brief Title:

Deucravacitinib Concentrations in the Breast Milk and Plasma of Females

Rationale:

A milk-only clinical study for deucravacitinib in lactating females [redacted] to assess the concentrations of deucravacitinib in breast milk.

To date, no data are available on the presence of deucravacitinib in human milk.

The purpose of this study is to determine the pharmacokinetics (PK) of deucravacitinib and its major active metabolite, BMT-153261, in the breast milk of healthy lactating female participants following a single oral administration of deucravacitinib. Knowledge of the PK of deucravacitinib and BMT-153261 in breast milk is relevant for potential exposure to breast fed infants and the appropriate labeling of the product for the treatment of plaque psoriasis and future approved indications.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the PK of deucravacitinib and its major active metabolite (BMT-153261) in breast milk of healthy lactating females	• Milk Cmax • Milk Tmax • Milk AUC(0-24) • Milk AUC(INF) • Milk Cavg • Milk AR(24) • Milk AR • M/P
To estimate dose in infants	• Estimated daily infant dose • Relative infant dose
Secondary	
To assess the PK of deucravacitinib and its major active metabolite (BMT-153261) in plasma of healthy lactating females	• Plasma Cmax • Plasma AUC(INF) • Plasma AUC(0-24) • Plasma AUC(0-T) • Plasma Tmax • Plasma Cavg

Objectives	Endpoints
To evaluate the safety and tolerability of deucravacitinib and its major active metabolite (BMT-153261) in healthy lactating females	• Incidence, severity, and relationship of treatment-emergent adverse events; and clinically significant changes in clinical laboratory tests (hematology and chemistry), vital signs, physical examinations, and electrocardiograms

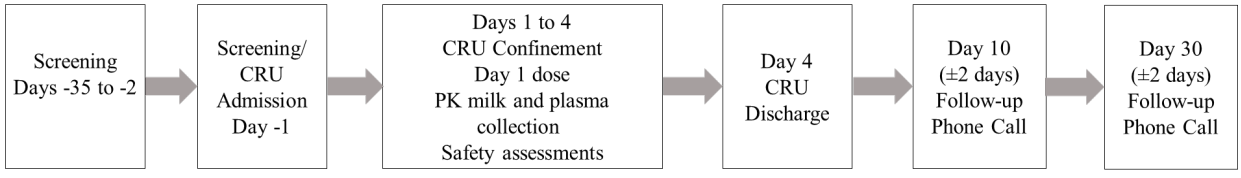
Abbreviations: AR, total amount recovered in milk; AR(24), amount recovered in milk within 24 hours of dosing; AUC(0-24), area under the plasma or milk concentration-time curve from time zero to 24 hours; AUC(0-T), area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; AUC(INF), area under the plasma or milk concentration-time curve from time zero extrapolated to infinite time; Cavg, average plasma or milk concentration; Cmax, maximum observed plasma or milk concentration; M/P, milk-plasma ratio; PK, pharmacokinetics; Tmax, time of maximum observed plasma or milk concentration.

Overall Design:

This is an open-label, single-group, nonrandomized, single-dose, postmarketing study that will enroll healthy lactating adult female participants.

- Participants will undergo screening evaluations to determine eligibility within 35 days prior to administration of study intervention. Participants will be offered consultations with a certified lactation consultant from screening until approximately 30 days post dose.
- On Day -1, participants will be admitted to the clinical research unit (CRU) to ensure sufficient time to complete baseline assessments and to confirm eligibility as needed.
- On Day 1, all participants will receive a single 9-mg oral dose of study intervention. Study assessments and procedures will be performed during the on-treatment period (Days 1 to 4). Milk and plasma samples will be collected up to 72 hours post dose for PK analysis.
- On Day 4, participants will be discharged from the CRU following completion of the required study procedures. Participants can resume breastfeeding (or pumping milk for infant consumption) after CRU discharge (beginning 72 hours post dose).
- On Day 10 (± 2 days) and Day 30 (± 2 days), the site staff will contact each participant via phone follow-up to inquire about concomitant medications and procedures, nonserious adverse events, and serious adverse events.

Study Design Schema:



Abbreviations: CRU, clinical research unit; PK, pharmacokinetic.

Number of Participants:

Approximately 8 healthy lactating female adult participants are planned to receive study intervention.

Study Population:

Eligible participants must be 18 to 45 years of age, inclusive, have well-established lactation, and can produce stable breast milk product. Participants must be willing to exclusively pump breast milk for the 72-hour post-dose period of milk collection during CRU confinement, and not to breastfeed or provide milk to their infant until after CRU discharge (beginning 72 hours post dose).

Study Duration and Study Intervention Duration:

The approximate study duration will be up to 67 days (including a 35-day screening period, a 4-day treatment period, and safety follow-up phone calls on Day 10 [± 2 days] and Day 30 [± 2 days]). In addition, participants will be offered consultations with a certified lactation consultant from screening until approximately 30 days post dose.

Study intervention will be administered as a single oral dose to all participants on Day 1.

Study Intervention:

Study Intervention		
Intervention Name	**Unit Dose Strength(s)**	**IMP/ Non-IMP/AxMP**
Deucravacitinib tablet	[redacted]	IMP

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product.

Statistical Methods:

No prospective hypotheses are being formally evaluated.

[redacted]

Data Monitoring Committee: No

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

Other Committee: No

Other review committees will not be used in the study.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures for screening and on treatment are presented in Table 2-1 and Table 2-2.

Table 2-1: Screening Procedural Outline (IM0111123)

Procedure	Screening		Notes
	Days -35 to -2	Day -1	
CRU Visit	X	X	
Admission to CRU		X	
Eligibility Assessments and Procedures			
Informed Consent	X		A participant is considered enrolled only when a protocol-specific informed consent is signed; informed consent must be obtained prior to performing any screening procedures.
[redacted]			
Inclusion/Exclusion Criteria	X	X	
Demography	X		
Medical History	X	X	Include any toxicities or allergies related to previous treatments. Include clinically significant findings from the PE.
Gestational and Postpartum History	X		Includes maternal age at delivery, length of time postpartum, and stage of lactation.
Breastfeeding Questionnaire	X		See Section 9.4.5 and Appendix 5. Includes previous experience with breastfeeding, frequency of breastfeeding, duration of breastfeeding, estimated volume of milk production, and use of formula supplementation.
Smoking History	X		Record history for the past 6 months prior to screening.
Provide Electric Milk Pump	X	X	Site staff will provide instructions for use of milk pump and offer certified lactation consultation for additional guidance if needed.
Offer Certified Lactation Consultation	X	X	
Verification of Breast Milk Expression	X	X	To be done anytime during screening to determine if the participant can produce stable milk product (defined per Inclusion Criterion 2c [Section 6.1]).
Provide Instructions for Storage of Breast Milk	X		See Section 9.4.6. Participants will be provided instructions on how to store their breast milk in order to ensure a sufficient supply of food for the infant (during the

Table 2-1: Screening Procedural Outline (IM0111123)

Procedure	Screening		Notes
	Days -35 to -2	Day -1	
			time the participant must temporarily discontinue breastfeeding due to their study participation).
Safety Assessments and Procedures			
Complete PE	X		Any clinically significant findings from the screening PE(s) will be recorded as medical history in the participant's medical records and on the appropriate CRF. Refer to Section 9.4.1.
Physical Measurements	X	X	Includes height, weight, and BMI. Height and BMI will be measured at the first screening visit (Days -35 to -2) only.
Vital Signs	X	X	Includes oral or tympanic body temperature, respiratory rate, blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly in the supine position for at least 5 min.
Single 12-lead ECG	X		ECG should be recorded after the participant has been supine for at least 5 min.
Prior and Concomitant Medications and Procedures	X	X	Includes prescription, over-the-counter medications, vitamins, and herbal supplements. See Section 7.7 for prohibited and/or restricted treatments and permitted treatments.
Laboratory Tests			See Section 9.4.4 and Table 9.4.4-1 for a detailed list of clinical laboratory assessments.
Clinical Laboratory Assessments: Hematology, Chemistry, and Urinalysis	X	X	Participants are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests.
Serum Pregnancy Test (All Participants)	X	X	
Serology	X		Includes hepatitis C antibody, hepatitis B surface antigen, and HIV-1 and HIV-2 antibody.
Drugs of Abuse Test (Urine)	X	X	Screen for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, and cannabinoids.
Cotinine Test (Urine)	X	X	Screen for smoking.

Table 2-1: Screening Procedural Outline (IM0111123)

Procedure	Screening		Notes
	Days -35 to -2	Day -1	
Alcohol Test (Urine or Breath)	X	X	
QuantiFERON® TB Gold Plus Test or equivalent	X		A documented negative result within 1 month prior to Day -1 from a healthcare provider/facility is acceptable.
AE Reporting			
Monitor for Nonserious and Serious AEs	X	X	All AEs and SAEs must be collected from the date of the participant's written consent during screening. See Section 9.2.1 for further details.

Abbreviations: AE, adverse event; BMI, body mass index; CRF, Case Report Form; CRU, clinical research unit; ECG, electrocardiogram; HIV, human immunodeficiency virus; min, minute(s); PE, physical examination; SAE, serious adverse event; TB, tuberculosis.

Table 2-2: On-treatment Procedural Outline (IM0111123)

Procedure	Day 1 (Predose)	Day 1	Day 2	Day 3	Day 4/ Early Termination	Day 10 ±2 days Follow-up	Day 30 ±2 days Follow-up	Notes
Confinement in CRU	X	X	X	X	X			
Discharge from CRU					X			
Phone Call						X	X	
Safety Assessments and Procedures								
Complete PE					X			Refer to Section 9.4.1.
Targeted PE	X							Refer to Section 9.4.1.
Vital Signs	X	X			X			Refer to VS in Table 2-1 for details. On Day 1, VS will be conducted at predose (up to 90 min prior to dosing), approximately 2 hours post dose, and prior to discharge on Day 4/ET.
Single 12-lead ECG	X				X			ECG should be recorded after the participant has been supine for at least 5 min. On Day 1, ECG will be conducted at predose (up to 90 min prior to dosing) and prior to discharge on Day 4/ET.
Concomitant Medications and Procedures	X	X	X	X	X	X	X	Refer to Section 7.7 for prohibited and/or restricted treatments.
Offer Certified Lactation Consultation	X	X	X	X	X	X	X	Lactation consultation will be available for approximately 30 days post dose (Section 9.4.6).
Breastfeeding Questionnaire						X		See Section 9.4.5 and Appendix 5. Includes participant-reported effects on milk production before (ie, screening) and after discontinuation (ie, CRU discharge) of study intervention.

Table 2-2: On-treatment Procedural Outline (IM0111123)

Procedure	Day 1 (Predose)	Day 1	Day 2	Day 3	Day 4/ Early Termination	Day 10 ±2 days Follow-up	Day 30 ±2 days Follow-up	Notes
AE Reporting								
Monitor for Nonserious and Serious AEs	X	X	X	X	X	X	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days post dose (or until ET, if the participant was not dosed).
Laboratory Tests								See Section 9.4.4 and Table 9.4.4-1 for a detailed list of clinical laboratory assessments.
Clinical Laboratory Assessments: Hematology, Chemistry, and Urinalysis			X		X			Participants are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests.
Serum Pregnancy Test (All Participants)					X			
PK Assessments								
PK Milk and Plasma Collections	[redacted].							Refer to Section 9.5.1 for details.
Study Intervention								
Administer Deucravacitinib		X						

Abbreviations: AE, adverse event; CRU, clinical research unit; ECG, electrocardiogram; ET, early termination; min, minute(s); PE, physical examination; PK, pharmacokinetic; SAE, serious adverse event; VS, vital signs.

In the event that multiple procedures are required at a single post-dose time point, the following is the order in which the procedures should be performed to ensure that the pharmacokinetic (PK) samples are collected as close as possible to the nominal time point:

- Safety (vital signs measurements)
- Safety (single 12-lead electrocardiogram [ECG])
- PK sampling
- Safety (clinical laboratory tests)

Note: Safety assessments in response to adverse events (AEs) are not impacted by this priority list.

[redacted] For more information, refer to Section 9.5: Pharmacokinetics. Further details of milk and plasma sample collection, processing, and shipping will be provided to the site in the laboratory/procedure manual.

[redacted]

3 INTRODUCTION

Deucravacitinib (BMS-986165) is an inhibitor of tyrosine kinase 2 (TYK2). TYK2 is a member of the Janus kinase (JAK) family. Deucravacitinib binds to the regulatory domain of TYK2, stabilizing an inhibitory interaction between the regulatory and the catalytic domains of the enzyme. This results in allosteric inhibition of receptor-mediated activation of TYK2 and its downstream activation of signal transducers and activators of transcription (STATs). JAK kinases, including TYK2, function as pairs of homo- or heterodimers in the JAK-STAT pathways. TYK2-dependent receptors (eg, receptors for Type I interferons [IFNs], interleukin [IL]-10, IL-12, IL-23) are distinct from those highly dependent on JAK1/JAK3 (eg, receptors for IL-2, IL-15, IL-6) or JAK2 (eg, erythropoietin, thrombopoietin, granulocyte macrophage colony-stimulating factor); a TYK2 inhibitor would be expected to have a highly differentiated profile from inhibitors of other JAK family kinases. The TYK2-dependent pathways and the cytokine networks they modulate (eg, IL-17, IL-22, IFNγ) have been implicated in the pathophysiology of multiple immune-mediated diseases including psoriasis, lupus, spondyloarthritides, dermatomyositis, and Type I interferonopathies.

Deucravacitinib is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Deucravacitinib is also being developed as an oral treatment for other inflammatory diseases such as psoriatic arthritis and systemic lupus erythematosus.[1]

3.1 Study Rationale

Psoriasis is a chronic inflammatory skin disorder, characterized primarily by erythematous scaly plaques, that affects up to 3% of the general population. In the US adult population, it is estimated that more than 7.5 million adults 20 years or older have psoriasis. This suggest that psoriasis remains one of the most common immune-mediated diseases affecting US adults.[2] Men and women are equally affected, and it can present at any age.[3,4] 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.[5,6,7]

Roughly 50% of patients with psoriasis are women, and in more than 75% of cases, onset of psoriasis occurs at 40 years or younger, indicating many patients will be affected during their reproductive years.[8,9] It is anticipated that deucravacitinib will be administered to lactating females of reproductive age in clinical practice.

A milk-only clinical study for deucravacitinib in lactating females [redacted] to assess the concentrations of deucravacitinib in breast milk.

To date, no data are available on the presence of deucravacitinib in human milk.

The purpose of this study is to determine the PK of deucravacitinib and its major active metabolite, BMT-153261, in the breast milk of healthy lactating female participants following a single oral administration of deucravacitinib. Breastfeeding (or providing milk for infant consumption) will

be discontinued from dosing through 72 hours post dose (CRU discharge) so that the participants' infants are not exposed to deucravacitinib.

Knowledge of the PK of deucravacitinib and its major active metabolite BMT-153261 in breast milk is relevant for potential exposure to breast fed infants and the appropriate labeling of the product for the treatment of plaque psoriasis and future approved indications.

3.2 Background

[redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of deucravacitinib from nonclinical and clinical studies is provided in the Investigator's Brochure (IB)[10] and package insert.[1]

3.2.1 Reproductive and Developmental Toxicity and Lactation

Deucravacitinib was administered orally during the period of organogenesis at doses of 5, 15, or 75 mg/kg/day in rats and 1, 3, or 10 mg/kg/day in rabbits. Deucravacitinib was neither embryolethal nor teratogenic at the highest doses tested in either species. These doses resulted in maternal exposures (area under the concentration-time curve [AUC]) that were approximately 266 times (rat) or 91 times (rabbit) the exposure at the recommended human dose.

In a pre- and post-natal development study in rats, deucravacitinib was administered from Gestation Day 6 through Lactation Day 20, at doses of 5, 15, or 50 mg/kg/day. At 50 mg/kg/day, pup body weights were reduced, relative to control values, during the preweaning period; during postweaning, their weights caught up and were comparable to those in control offspring by Postnatal Days 73 or 35 in males and females, respectively. There were no additional adverse findings in the F1 offspring, nor in F2 intrauterine survival. Maternal exposures at 50 mg/kg/day were approximately 110 times the recommended human dose.

A single oral dose of 5 mg/kg radiolabeled deucravacitinib was administered to lactating (Postpartum Days 8 to 12) rats. Deucravacitinib and/or its metabolites were present in the milk of lactating rats, with milk-to-plasma concentration ratios of 2.7 (at 0.5 hours post dose) to 30.9 (at 12 hours post dose), then declining to 16.6 (at 24 hours post dose). Concentrations of radioactivity in milk were below the limit of quantitation after 48 hours post dose.[11]

3.2.2 Clinical Studies

The clinical development program for deucravacitinib as of 22-May-2023 consists of studies in healthy participants, participants with renal or hepatic insufficiency, and participants with

psoriasis, psoriatic arthritis, discoid lupus erythematosus/subacute cutaneous lupus erythematosus, systemic lupus erythematosus, lupus nephritis, and alopecia areata.

In healthy participants, there are 27 completed Phase 1 studies of deucravacitinib. Details for these studies are provided in the IB.[10]

3.3 Benefit/Risk Assessment

Because this study will enroll healthy participants and not patients, there is no direct benefit to participants except for a baseline assessment of their health. Deucravacitinib had an overall acceptable safety profile when investigated in Study IM011002 with healthy participants at single doses up to 40 mg and multiple doses up to 24 mg/day (12 mg twice daily) for 14 days.

The most common drug-related AE in healthy participants was acneiform skin reactions, which were observed at higher doses across Phase 1 studies with deucravacitinib. They appeared to be dose related with the highest incidence at the 12 mg twice daily dose (24 mg/day). These reactions were mild or moderate, nonserious, reversible, and managed with topical treatment when required. All events requiring treatment responded appropriately and rarely resulted in discontinuation of study intervention. There were no signs or symptoms of circulatory or respiratory impairment and no suggestion of systemic hypersensitivity associated with skin reactions.

To mitigate and monitor for potential risk of immunomodulatory effects of TYK2 inhibition during the study, the exclusion criteria have been designed to prevent potential participants at risk for infection from participating, and participants will be monitored in clinic for a 4-day washout period prior to discharge from the clinical research unit (CRU).

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of deucravacitinib may be found in the IB[10] and package insert[4].

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: deucravacitinib		
Exposure of infants to deucravacitinib due to excretion of deucravacitinib into breast milk	IB Sections 7.3.3 SOTYKTU® USPI Section 8.2	Breastfeeding (or providing milk for infant consumption) will be discontinued from dosing through 72 hours post dose until CRU discharge (72 hours post dose) so that infants are exposed to a minimal amount of deucravacitinib.
Hypersensitivity	IB Section 7.1.2.3, SOTYKTU® USPI Section 5.1	Participants with a history of allergy to deucravacitinib (or related compounds) or of any significant drug allergy will be excluded.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Skin events	IB Sections 7.1 and 7.1.2.3 The totality of the clinical data shows that treatment with deucravacitinib is associated with folliculitis and acne. These skin events were not severe or serious, resolved spontaneously or with topical or oral antimicrobial treatments, and rarely led to treatment discontinuation. The events appeared to be dose related, with the highest incidence at the 12-mg dose twice daily.	Participants will be administered a single dose of 9 mg deucravacitinib only and will be monitored for any skin-related AEs that develop.
Malignancy	IB Section 7.1.2.2, SOTYKTU® USPI Section 5.4 Based on the available clinical data and the relevant epidemiology for malignancy and specifically lymphoma, there does not appear to be a clear association with deucravacitinib exposure. However, the potential role of deucravacitinib in the development of malignancies is unknown and will continue to be monitored in studies with deucravacitinib.	Participants will be administered a single dose of 9 mg deucravacitinib only and will be monitored for any malignancy-related AEs that develop. Participants with a known malignancy will be excluded.
Infection	IB Section 7.1.2.1, SOTYKTU® USPI Sections 2.1, 5.2, and 5.3 Based on its mechanism of action, deucravacitinib may increase the risk of infections, yet broad immunosuppressive effects are not expected.	The study has been designed with exclusion criteria aimed at minimizing the risk for serious and acute infections. Excluding participants with the following: • Active herpes infection • Clinically significant history or known presence of acute, recurrent, or chronic bacterial, fungal, or viral infection • History or risk for tuberculosis • Positive screen for hepatitis C antibody, hepatitis B surface antigen, or HIV-1 and HIV-2 antibody Participants will be domiciled up to 72 hours post dose to allow for close monitoring of participants' safety throughout the duration of the study. Participants will be evaluated for tuberculosis prior to study drug intervention.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiovascular risk	IB Section 7.1.2.4 SOTYKTU® USPI Section 5.8	Excluding participants with the following: • Presence or history of any clinically relevant abnormality, condition, or disease (such as cardiovascular or pulmonary diseases) which places the participant at an unacceptable risk if participating in the study • Any of the following on 12-lead ECG prior to study intervention administration, confirmed by repeat: PR ≥ 210 msec, QRS ≥ 120 msec, QT ≥ 500 msec, QTcF ≥ 470 msec. • Persistent or intermittent complete bundle branch block, incomplete bundle branch block, or intraventricular conduction delay with QRS > 120 msec • Clinically significant vital signs examination results outside the normal reference range prior to study intervention administration, confirmed by repeat.
Rhabdomyolysis and elevated creatine phosphokinase	IB Section 7.1.3, SOTYKTU® USPI Section 5.5	Participants are instructed to refrain from strenuous exercise and contact sports from at least 2 days prior to Day -1 until CRU discharge.
Liver injury	SOTYKTU® USPI Section 5.6	Excluding participants with the following: • Presence or history of any clinically relevant abnormality, condition, or disease (such as liver disease or abnormal liver function tests) which places the participant at an unacceptable risk if participating in the study • History of biliary disorders, including Gilbert's syndrome or Dubin-Johnson disease.
Renal injury	SOTYKTU® USPI Section 6.1	Requiring that participants have normal renal function at screening.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Fetal risk	IB Section 7.3.2, SOTYKTU® USPI Section 8.1	Excluding individuals who are pregnant, are planning to become pregnant during the course of the study, or are of childbearing potential and not using an effective contraceptive method. Pregnancy testing throughout the study.
Drug-drug interaction with broader transporter/enzyme inducers/inhibitors	IB Section 7.3.1, SOTYKTU® USPI Section 12.1 Dedicated drug interaction studies confirmed that deucravacitinib does not have clinically meaningful impact on the exposure of coadministered drugs. No drug interactions are anticipated with substrates of major CYPs, UGTs, or transporters. Coadministered drugs do not have a clinically meaningful effect on deucravacitinib exposure.	Restricting consumption of any nutrients or food products known to modulate CYP450 enzyme activity (eg, grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products). Excluding current smokers, as well as those who have stopped smoking less than 6 months prior to administration of study intervention.
Other		
Immunizations	SOTYKTU® USPI Section 5.7	Receipt of any live vaccinations is prohibited within 60 days before screening, while on study, and for 30 days after last study intervention administration.
Coronavirus disease 2019 (COVID-19)-associated risks	The ongoing COVID-19 pandemic is a risk that needs to be considered by the site investigator. Based on its mechanism of action, deucravacitinib may increase the risk of infections, including COVID-19.	Participants with recent acute infection with SARS-CoV-2 are excluded in this clinical trial. Local measures at the CRU to limit the risk of infection with SARS-CoV-2, as applicable.
Early Cessation of Breastfeeding	The interruption of breastfeeding for the study may inadvertently contribute to early cessation of breastfeeding.	A certified lactation consultant will be available for consultations from screening throughout the participant's study participation (up until approximately 30 days post dose) in order to support the participant's breastfeeding routine and return to breastfeeding after study completion. Informed consent form will detail the risks and benefits of breastfeeding. Participants will be provided instructions at screening on how to store their breast milk in order to ensure a sufficient supply of food for the infant during the time the participant must temporarily discontinue breastfeeding.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
ECG: Application of electrodes	Adhesive electrodes placed on participants' chests and limbs during ECG procedures may cause some local irritation and may be uncomfortable to remove.	Participants will be closely monitored by site personnel and action may be taken to ensure any local irritation does not persist.
Blood sample collection	Collecting a blood sample from a vein may cause pain, bruising, swelling, light headedness, fainting, and very rarely clot formation, nerve damage, and/or infection at the site of the needle stick.	Participants will be closely monitored by site personnel during and after blood draws.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; CRU, clinical research unit; CYP, cytochrome P450; ECG, electrocardiogram; HIV, human immunodeficiency virus; IB, Investigator's Brochure; QTcF, QT interval corrected for heart rate using Fridericia's formula; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; UGT, uridine diphosphate glucuronosyltransferase; USPI, United States prescribing information.

3.3.2 Benefit Assessment

This study will provide data for future lactating females treated with deucravacitinib who decide to provide breast milk to their infants.

3.3.3 Overall General COVID-19-related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with the site's monitoring and prevention control procedures, and relevant governmental and Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-associated requirements. Such measures aim to minimize the prevalence and transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) amongst site staff and participants, and may include distancing, sanitization, testing, and the use of personal protective equipment. The risk mitigation measures are part of the site's generic informed consent and, when and where applicable, will be amended based on emerging guidance. The informed consent form (ICF) and any other documentation regarding these general measures are independent of this protocol and will be entered into this study's trial master file if used for participants in this study.

3.3.4 Overall Benefit/Risk Conclusion

Given the safety and tolerability profile of deucravacitinib, a single dose of the study intervention is deemed to be safe and well tolerated in healthy populations. The overall risk to the participants in this study is deemed to be low and acceptable. Therefore, the Sponsor considers that it is medically acceptable to conduct a study of the PK of deucravacitinib in the breast milk of healthy lactating females to determine whether deucravacitinib can be safely taken by lactating females.

The Sponsor will evaluate the benefit/risk profile of the study on an ongoing basis. This evaluation will be based on all available data, with particular attention to (i) AEs or other safety trends in this or any other clinical study of deucravacitinib whose character, severity, and/or frequency suggest

that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new nonclinical data suggesting unreasonable and significant risk of illness or injury.

If such evaluation suggests that the benefit/risk profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the PK of deucravacitinib and its major active metabolite (BMT-153261) in breast milk of healthy lactating females	• Milk Cmax • Milk Tmax • Milk AUC(0-24) • Milk AUC(INF) • Milk Cavg • Milk AR(24) • Milk AR • M/P
To estimate dose in infants	• Estimated daily infant dose • Relative infant dose
Secondary	
To assess the PK of deucravacitinib and its major active metabolite (BMT-153261) in plasma of healthy lactating females	• Plasma Cmax • Plasma AUC(INF) • Plasma AUC(0-24) • Plasma AUC(0-T) • Plasma Tmax • Plasma Cavg
To evaluate the safety and tolerability of deucravacitinib and its major active metabolite (BMT-153261) in healthy lactating females	• Incidence, severity, and relationship of TEAEs; and clinically significant changes in clinical laboratory tests (hematology and chemistry), vital signs, physical examinations, and ECGs
[redacted]	

Abbreviations: AR, total amount recovered in milk; AR(24), amount recovered in milk within 24 hours of dosing; AUC(0-24), area under the plasma or milk concentration-time curve from time zero to 24 hours; AUC(0-T), area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; AUC(INF), area under the plasma or milk concentration-time curve from time zero extrapolated to infinite time; Cavg, average plasma

or milk concentration; Cmax, maximum observed plasma or milk concentration; ECG, electrocardiogram; [redacted]; M/P, milk-plasma ratio; PK, pharmacokinetics; TEAE, treatment-emergent adverse event; Tmax, time of maximum observed plasma or milk concentration.

5 STUDY DESIGN

5.1 Overall Design

This is an open-label, single-group, nonrandomized, single-dose, postmarketing study that will enroll healthy lactating adult female participants.

Participants will undergo screening evaluations to determine eligibility within 35 days prior to administration of study intervention. Screening assessments to determine eligibility are shown in Table 2-1. Participants may be rescreened once (refer to Section 6.4.1). Participants will be offered consultations with a certified lactation consultant from screening until approximately 30 days post dose.

On Day -1, participants will be admitted to the CRU to ensure sufficient time to complete baseline assessments and to confirm eligibility as needed.

On Day 1, all participants will receive a single 9-mg oral dose of study intervention. Study assessments and procedures that will be performed during the on-treatment period (Days 1 to 4) are shown in Table 2-2. Milk and plasma samples will be collected up to 72 hours post dose for PK analysis. Less than 500 mL of blood will be drawn from each participant during the study.

During the domiciling period at the CRU, mother-infant visits will be provided as needed on a case-by-case basis. The visits will be supervised by the site staff to ensure that no breastfeeding takes place during the visits.

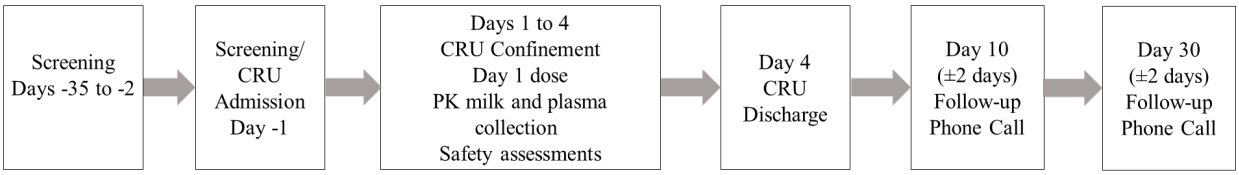
On Day 4, participants will be discharged from the CRU following completion of the required study procedures. Participants can resume breastfeeding (or pumping milk for infant consumption) after CRU discharge (beginning 72 hours post dose).

On Day 10 (± 2 days) and Day 30 (± 2 days), the site staff will contact each participant via phone follow-up to inquire about concomitant medications and procedures, nonserious AEs, and serious AEs (SAEs).

The total study duration will be up to approximately 67 days (including a 35-day screening period, a 4-day treatment period, and safety follow-up phone calls on Day 10 [± 2 days] and Day 30 [± 2 days]). In addition, participants will be offered a certified lactation consultant from screening until approximately 30 days post dose.

The study design schema is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schema



Abbreviations: CRU, clinical research unit; PK, pharmacokinetic.

5.1.1 Data Monitoring Committee and Other Committees

A Data Monitoring Committee or other review committee will not be used in the study.

5.2 Number of Participants

Approximately 8 healthy lactating female adult participants are planned to receive study intervention. [redacted]

5.3 End of Study Definition

The start of the study is defined as the first participant's first visit.

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

End of study is defined as the last participant's last visit.

A participant is considered to have completed the study if she has completed the last procedure shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

This study aims to determine the PK of deucravacitinib and its major active metabolite, BMT-153261, in breast milk in healthy lactating female participants following a single oral administration of deucravacitinib.

An open-label study design is appropriate since the primary endpoint (PK of deucravacitinib and BMT-153261 in milk) is objective.

[redacted]

Deucravacitinib was studied in multiple animal studies and clinical studies. Deucravacitinib was safe in multiple studies in healthy participants at single doses up to 40 mg and multiple doses up to 24 mg/day for up to 14 days. Further, the PK of deucravacitinib and its active metabolite, BMT-153261, were comparable between healthy participants and participants with psoriasis. Population PK indicated comparable clearance (11.3 L/h vs 10.0 L/h) and volume of central compartment in multi-compartment model (90.2 L vs 108 L) in healthy participants and

participants with psoriasis, respectively. Therefore, it is appropriate to enroll healthy lactating female participants in this study.

PK samples of milk and plasma will be collected predose and post dose up to 72 hours. Although the half-life (T-HALF) of deucravacitinib is approximately [redacted] and it is expected that all deucravacitinib would be cleared within 5× T-HALF (approximately [redacted], or sooner due to the milk expression), this study will collect samples up to 72 hours post dose. This extra caution will ensure that a minimum amount of deucravacitinib is left in the body at the time of discharge.

[redacted]

6 STUDY POPULATION

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 IRB/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) Healthy female participants without, in the opinion of the investigator, clinically significant deviation from normal in medical history, physical examination, ECGs, vital signs, and clinical laboratory determinations.

b) Body mass index (BMI) of 18.0 kg/m^2 to 35.0 kg/m^2, inclusive, and body weight ≥ 50 kg (110 lb), at screening. Given participants are postpartum, BMI accommodation up to 35.0 kg/m^2 may be expected.

c) Has well-established lactation (ie, at least 4 weeks postpartum) and can produce stable milk product (ie, approximately 3 oz per 3 hours at screening) using the methods required for the study.

Note: Lactating participants who are planning to wean their infants independent of study participation will be allowed to participate in the study, provided that these participants have not yet started the process of weaning and will maintain an adequate supply of breast milk by breastfeeding and/or pumping prior to study intervention administration.

d) Is willing to exclusively pump breast milk for the 72-hour post dose period of milk collection during CRU confinement, and not to breastfeed or provide milk to infant until after CRU discharge (72 hours post dose).

3) Age of Participant

Participant must be 18 to 45 years of age, inclusive, at the time of signing the ICF.

4) Reproductive Status

- The investigator or designee shall counsel individuals of childbearing potential (IOCBPs) participants (as defined in Appendix 4) (as assigned at birth) on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
- The investigator or designee 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 (as assigned at birth) participants:

i) IOCBP must have a negative highly sensitive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to administration of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are in the Schedule of Activities in Section 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to potentially decrease the risk for inclusion of a woman with an undetected pregnancy.

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

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

iii) A female participant (as assigned at birth) is eligible to participate if she is not pregnant, and at least 1 of the following conditions applies:

(1) Is not a IOCBP

OR

(2) Is a IOCBP and using a contraceptive method as described in Appendix 4 during the intervention period (at a minimum until 3 days after the last dose of study intervention).

6.2 Exclusion Criteria

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

1) Medical Conditions

a) Presence or history of any clinically relevant abnormality, condition, or disease (such as liver disease or abnormal liver function tests, or cardiovascular or pulmonary diseases) that, in the opinion of the investigator, may affect absorption, distribution, metabolism, or elimination of the study intervention, that would prevent the participant from participating in the study, or which places the participant at unacceptable risk if she were to participate in the study.

b) Current or recent (within 3 months of study intervention administration) clinically significant gastrointestinal disease that, in the opinion of the investigator, could impact upon the absorption of study intervention.

c) Presence or history of mastitis, breast surgery or trauma, or other breast conditions, which are considered clinically significant by the investigator and/or, in the investigator's opinion, may significantly impact breastfeeding or collection of milk from one or both breasts.

d) History of biliary disorders, including Gilbert's syndrome or Dubin-Johnson disease, except for isolated gallbladder issues, which are not by themselves exclusionary.

e) Active herpes infection, including herpes simplex 1 and 2, or herpes zoster.

f) Clinically significant history or known presence of acute, recurrent, or chronic bacterial, fungal, or viral infection (eg, pneumonia, septicemia) within 3 months prior to screening. For nonsevere upper respiratory viral infection associated with cold season (ie, the common cold), participants will only be excluded if it has occurred within 1 month prior to screening or is present at screening (a history of recurrent urinary tract infections is not exclusionary; however, infection must not be present at screening).

g) Any history or risk for tuberculosis (TB), specifically participants with:

i) current clinical, radiographic, or laboratory evidence of active TB.

ii) history of active TB unless there is documentation that the prior anti-TB treatment was appropriate in duration and type.

iii) latent TB that has not been successfully treated; a QuantiFERON Gold Plus test or equivalent at screening or within 1 month prior to Day -1 from a healthcare provider/facility is acceptable as long as there is documentation of a negative result.

h) Known malignancy.

i) Any clinically significant symptoms of coronavirus disease 2019 (COVID-19) in the last 4 weeks, including, but not limited to, fever, new and persistent cough, breathlessness, or loss of taste or smell, as per the judgement of the investigator.

2) Reproductive Status

a) Individuals who are pregnant, are planning to become pregnant during the course of the study, or are of childbearing potential and not using an effective contraceptive method.

3) Prior/Concomitant Therapy

a) Prior exposure to deucravacitinib, JAK inhibitors, or related compounds.

b) Exposure to any investigational drug or placebo within 4 weeks or 5 half-lives (if known), whichever is longer, prior to study intervention administration.

c) Use of any prescription drugs or over-the-counter acid controllers within 4 weeks or 5 half-lives (if known), whichever is longer, prior to study intervention administration, except those medications cleared by the Sponsor Medical Monitor.

d) Use of any other drugs, including over-the-counter medications and herbal preparations, within 1 week prior to study intervention administration, except those medications cleared by the Sponsor Medical Monitor.

e) Receipt of any vaccination or plans for vaccination with any live vaccine within 60 days before screening, during the course of the study, or 30 days after last study intervention administration. The use of inactivated seasonal influenza vaccines (eg, Fluzone®) and non-live COVID-19 vaccines will be permitted on the study without restriction.

f) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7.

4) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population (ie, healthy adult females).

b) Any significant deviation from the following on 12-lead ECG prior to study intervention administration, confirmed by repeat:

i) PR ≥ 210 msec

ii) QRS ≥ 120 msec

iii) QT ≥ 500 msec

iv) QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 msec

c) Persistent or intermittent complete bundle branch block, incomplete bundle branch block, or intraventricular conduction delay with QRS > 120 msec.

d) Clinically significant vital signs examination results outside the normal reference range prior to study intervention administration, confirmed by repeat; normal ranges are:

i) Heart rate 40 to 100 bpm,

ii) Systolic blood pressure 90 to 140 mmHg,

iii) Diastolic blood pressure 50 to 90 mmHg.

e) Positive urine screen for drugs of abuse, urine cotinine, or alcohol breath or urine test.

f) Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or human immunodeficiency virus (HIV)-1 and HIV-2 antibody.

g) Any other significant laboratory or procedure abnormalities that, in the opinion of the investigator, might place the participant at unacceptable risk for participation in this study (see Table 9.4.4-1 for laboratory parameters).

5) Allergies and Adverse Drug Reactions

a) History of allergy or hypersensitivity to deucravacitinib, JAK inhibitors, or related compounds.

b) History of any significant drug allergy or adverse reaction (such as anaphylaxis or hepatotoxicity).

c) Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Seasonal pollen allergies are allowed unless they are active.

6) Other Exclusion Criteria

a) Currently breastfeeding a pre-term infant, a sick infant, or any other infant for whom it is medically advised for the mother to continue breastfeeding.

b) Prisoners or participants who are involuntarily incarcerated.

c) Inability to comply with restrictions as listed in Section 6.3: Lifestyle Restrictions.

d) Currently smoke, as well as those who have stopped smoking less than 6 months prior to administration of study intervention. This includes participants using electronic cigarettes, vaporizers, or nicotine-containing products, such as tobacco for chewing, nicotine patches, nicotine lozenges, or nicotine gum.

e) Participation in an interventional clinical trial of an investigational agent concurrent with this study.

f) Inability to tolerate oral medication.

g) Any major surgery within 4 weeks of study intervention administration.

h) Any gastrointestinal surgery, including cholecystectomy, that could impact the absorption of study intervention.

i) Donation of blood to a blood bank or in a clinical study (except at a screening visit) greater than 400 mL within 4 weeks of study intervention administration (within 2 weeks for plasma only) until end of study.

j) Blood transfusion within 4 weeks of study intervention administration until end of study.

k) Inability to be venipunctured and/or tolerate venous access.

l) Recent (within 6 months of study intervention administration) drug or alcohol abuse as defined in the current version of the Diagnostic and Statistical Manual of Mental Disorders Diagnostic Criteria for Drug and Alcohol Abuse.

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

n) Participants who are Sponsor or study site employees, or immediate family members of a study site or Sponsor employee.

6.3 Lifestyle Restrictions

In addition to the eligibility criteria at screening (Sections 6.1 and 6.2), participants are required to adhere to the following restrictions during the study.

The lifestyle restrictions listed in Sections 6.3.1, 6.3.2, and 6.3.3 are not exclusion criteria; if noncompliance occurs, following discussion between the investigator and medical monitor, a protocol deviation may be completed and the participant may be allowed to participate in the study.

6.3.1 Meals and Dietary Restrictions

- To avoid false positive drug screen results, participants should refrain from consuming any foods containing poppy seeds within 48 hours (2 days) prior to screening and CRU admission on Day -1.
- From at least 7 days prior to study intervention administration on Day 1 until CRU discharge on Day 4, participants should not consume any nutrients or food products known to modulate CYP450 enzyme activity (eg, grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products).
- Participants are required to fast (nothing to eat or drink except water) for 10 hours prior to the collection of specimens for clinical laboratory tests.

6.3.2 Caffeine, Alcohol, and Tobacco

- Participants are not permitted to consume caffeine-containing beverages for 3 days prior to Day -1 until CRU discharge on Day 4.
- Participants are not permitted to consume alcohol-containing beverages from 3 days prior to Day -1 until CRU discharge on Day 4.
- Participants are not permitted to smoke or use electronic cigarettes, vaporizers, or any tobacco/nicotine-containing products for 6 months prior to study intervention administration on Day 1 until CRU discharge on Day 4.

6.3.3 Activity

- Participants are to refrain from strenuous exercise and contact sports from at least 2 days prior to Day -1 until CRU discharge on Day 4.
- Participants are required to remain in the CRU from admission on Day -1 until discharge on Day 4.

6.4 Screen Failures

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

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

6.4.1 Re-testing During Screening

Participant re-enrollment: This study permits the 1-time re-enrollment of a participant who has discontinued the study as a screen failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented.

Re-testing of laboratory parameters and/or other assessments once within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to administration of study intervention is the value by which study inclusion will be assessed because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are required during Screening may be repeated to identify all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of a parameter is clinically relevant.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are defined as all pre-specified, investigational interventions, marketed products, placebos, procedures, or medical devices intended to be administered to study participants according to the study protocol.

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

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

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered Non-IMPs/Auxiliary Medicinal Products (AxMPs). Not applicable for this study.

7.1 Study Interventions Administered

In the morning on Day 1, each participant will receive a single oral 9-mg dose of deucravacitinib [redacted].

At the time of dosing, 240 mL of water will be administered to the participant along with her dose of study intervention. The time of dose administration will be called "0" hour.

Restrictions related to food and fluid intake are described in Section 6.3.

Table 7.1-1: Study Intervention

Type/ Intervention Name/ Dose Formulation	Unit Dose Strength(s)	IMP/Non-IMP/ AxMP Blinded or Open-label Use	[redacted]	Current/ Former Name(s) or Alias(es)
Deucravacitinib tablet	[redacted]	IMP		BMS-986165
Deucravacitinib tablet	[redacted]	IMP		BMS-986165 SOTYKTU®

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product.

7.2 Assignment to Study Intervention

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted]. Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed.

Participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to study intervention. The Sponsor may replace participants for other reasons.

7.3 Blinding

This is a nonrandomized, open-label study. Blinding procedures are not applicable.

7.4 Dosage Modification

Not applicable.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of records).
- Further guidance and information for the final disposition of unused study interventions are provided in Appendix 2.

7.6 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff. Study intervention will be administered in the CRU. After administration of deucravacitinib, an examination of the oral cavity is required to verify that a participant has swallowed a tablet. Since multiple tablets are administered as part of a single dose, the mouth check should be performed after the final tablet has been taken. The participant should drink the entire amount of water given to swallow the tablets.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study intervention administration in the study are described below. Medications taken within 4 weeks or 5 half-lives (if known), whichever is longer, prior to study intervention administration must be recorded on the Case Report Form (CRF).

- Prior exposure to deucravacitinib, JAK inhibitors, or related compounds.
- Exposure to any investigational drug or placebo within 4 weeks or 5 half-lives (if known), whichever is longer, prior to study intervention administration.
- Use of any prescription drugs or over-the-counter acid controllers within 4 weeks or 5 half-lives (if known), whichever is longer, prior to study intervention administration, except those medications cleared by the Sponsor Medical Monitor.
- Use of any other drugs, including over-the-counter medications and herbal preparations, within 1 week prior to study intervention administration, except those medications cleared by the Sponsor Medical Monitor.
- Receipt of any vaccination or plans for vaccination with any live vaccine within 60 days before screening, during the course of the study, or 30 days after last study intervention administration. The use of inactivated seasonal influenza vaccines (eg, Fluzone®) and non-live COVID-19 vaccines will be permitted on the study without restriction.

Other than hormonal contraception and those mentioned in Section 7.7.2, no concomitant medications (prescription, over-the-counter, or herbal) are to be administered during the study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

The investigator should contact and confirm agreement with the Sponsor Medical Monitor (and acknowledgement from the contract research organization Medical Monitor) prior to the administration of any concomitant medications.

7.7.2 Permitted Treatments

Permitted treatments, if needed, may be given 4 hours post dose.

- Acetaminophen (paracetamol), when given according to the package insert, may be used as a mild analgesic at the discretion of the investigator.
- Prune juice may be given to help alleviate constipation or to facilitate a bowel movement during the CRU domiciling period.
- Use of a standard dose of vitamins (including pre/post-natal vitamins) during the study will be allowed.

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

This is a healthy volunteer PK study. The purpose is not to treat any condition. Therefore, study intervention will not be provided to participants after the end of the study.

The Sponsor reserves the right to terminate access to Sponsor-supplied study intervention if any of the following occur: 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. In all cases, the Sponsor will follow local regulations.

8 DISCONTINUATION CRITERIA

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

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP/IMP (and Non-IMP/AxMP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study intervention.
- Any clinical AE, laboratory test result abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue the study. Strict conditions apply, and Sponsor approval is required.)
- Pregnancy (refer to Section 9.2.5).
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The investigator should discuss such issues with the Medical Monitor.
- At the discretion of the investigator for any other reason.

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

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

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

8.1.1 Study Stopping Criteria

Dosing of new participants will pause if either of the following criteria are met:

- Two participants experience an SAE or severe AE that is assessed as related to deucravacitinib by the investigator.
- The investigator or Sponsor assesses for any reason that further dosing may pose an unacceptable risk to study participants.

If either of the above criteria are met, the investigator and Sponsor will perform a review of available data, and the overall risk of continuing the study will be assessed. Upon conclusion of the review, one of the following decisions will be taken: (1) to continue with the study as planned; (2) to continue the study with adjustments to the study plan, which may include modified selection criteria, additional safety monitoring measures, etc; or (3) to terminate the study.

8.1.2 Post-study Intervention Study Follow-up

Participants who discontinue study intervention may continue to be followed.

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 her or persons previously authorized by the participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.

- If 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

- Participants may withdraw completely from the study at any time at her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. 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 Section 2: Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up, if applicable, and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from both the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

To ensure a sufficient number of completers, the participant may be replaced if they discontinue during the study (see Section 5.2 and Section 7.2).

8.3 Lost to Follow-up

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

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

- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Section 2: Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue the study.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, 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 CRU admission and/or administration of study intervention. 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. Participants may be rescreened once.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Efficacy Assessments

Not applicable.

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).

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

Refer to Appendix 3 for SAE reporting.

9.2.1 Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and until 30 days post dose or early termination (if the participant was not dosed).

The investigator must report any SAE that occurs after these periods and that is believed to be related to a study intervention or protocol-specified procedure (eg, a follow-up skin biopsy).

- All SAEs will be recorded and reported to the Sponsor or designee promptly and not to exceed 24 hours of awareness of the event, as indicated in Appendix 3.

- The investigator will submit any updated SAE data to the Sponsor or designee promptly and not to exceed 24 hours of updated information being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for 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 CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported/identified during the study.

All SAEs 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.

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study intervention, it is discovered that a participant is pregnant or may have been pregnant at the time of study intervention exposure, including 5 half-lives of study intervention after study intervention administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor designee within 24 hours of awareness of the event. Pregnancy reporting must follow the same transmission timing and processes to BMS as those used for SAEs, in accordance with reporting procedures described in Appendix 3.

In all cases, the study intervention will be discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

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.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug-induced Liver Injury

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

A potential DILI is defined as follows:

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

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

  AND

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of an SAE will be reported as SAEs (see Appendix 3).

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs and laboratory test result abnormalities until study intervention can no longer be detected systemically (at least 4 days).
- Obtain a plasma sample for PK analysis within 4 days from the date of the dose of study intervention if requested by the Sponsor Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities in Section 2.

9.4.1 Physical Examinations

A complete PE will include an evaluation of the heart, lungs, head and neck, abdomen, skin, breasts (screening only), and extremities, as well as a check for visual or neurologic symptoms.

At a minimum, a targeted PE will include an evaluation of the skin and mucus membranes, a symptom-oriented evaluation, and a check for any previously noted abnormalities.

The PE may be performed by a Doctor of Medicine or someone who is authorized to perform the examinations by training and has been delegated this task by the investigator.

Refer to Schedule of Activities in Section 2.

9.4.2 Vital Signs

Refer to Schedule of Activities in Section 2.

9.4.3 Electrocardiograms

Refer to Schedule of Activities in Section 2.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Central and local laboratories may perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests (including serum pregnancy test, serology, and QuantiFERON® TB Gold Test [or equivalent]) performed at screening must be available and reviewed prior to dosing.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Red blood cell count	
Basophils	
Eosinophils	
Monocytes	
Neutrophils	
Lymphocytes	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen or serum urea Uric acid Glucose	Total protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase eGFR using CKD-EPI (screening only)
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick	
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and HIV-2 antibody	

Table 9.4.4-1: Clinical Laboratory Assessments

TB testing (QuantiFERON-TB Gold Plus or equivalent)
Other Analyses
Drugs of abuse test (urine)
Cotinine tests (urine)
Alcohol test (urine or breath)
Pregnancy test (serum) (all participants)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; TB, tuberculosis.

9.4.5 Breastfeeding Questionnaire

At screening and Day 10, designated site staff will ask participants questions about their breastfeeding history, current breastfeeding practices (eg, frequency of breastfeeding [including pumping], duration of breast feeds, estimated volume of milk production [if information is available], use of formula supplementation), and intentions for continuing breastfeeding after the study.

The questionnaire will include previous and current experience with breastfeeding as well as participant-reported effects on milk production before (ie, screening) and after discontinuation (ie, CRU discharge) of study intervention (Appendix 5).

9.4.6 Instructions for Storage of Breast Milk

Participants will be provided instructions on how to store their breast milk in order to ensure a sufficient supply of food for the infant during the time the participant must temporarily discontinue breastfeeding. If sufficient pumped breastmilk is not available, alternative infant nutrition (previously stored breastmilk or infant formula) can be suggested for feeding the infant until after CRU discharge (beginning 72 hours post dose).

A certified lactation consultant will be available for consultations from screening throughout the participant's study participation (up until approximately 30 days post dose) in order to support the participant's breastfeeding routine and return to breastfeeding.

9.5 Pharmacokinetics

Pharmacokinetics of deucravacitinib (BMS-986165) and its major active metabolite, BMT-153261, will be derived from plasma and breast milk concentration-time data.

The PK parameters to be assessed for breast milk and plasma include the following:

Cmax	Maximum observed plasma or milk concentration
Tmax	Time of maximum observed plasma or milk concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	Area under the plasma or milk concentration-time curve from time zero extrapolated to infinite time
AUC(0-24)	Area under the plasma or milk concentration-time curve from time zero to 24 hours
Cavg	Average plasma or milk concentration
AR(24)	Amount recovered in milk within 24 hours of dosing
AR	Total amount recovered in milk
M/P	Milk-plasma ratio, calculated as milk AUC(0-24)/plasma AUC(0-24)
Daily Infant Dose	Total deucravacitinib consumed by the infant per day (estimated)
Relative Infant Dose	The percent of the weight-adjusted maternal deucravacitinib dosage consumed in breast milk over 24 hours (estimated)

[redacted]

Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

9.5.1 Milk and Plasma Collection and Processing

[redacted]

Both breasts should be pumped such that they are completely emptied with each milk expression and within -25 minutes of the end of the scheduled collection time.

Multiple milk expressions within each collection interval are allowed if needed. All milk collected within each collection interval will be pooled. The total volume of the breast milk expressed during each collection interval will be recorded.

It is expected that every effort be made to collect the PK plasma samples at the times indicated in the PK sampling schedule[redacted].

The following time windows serve as a guideline for PK plasma sample collections:

- All predose samples should be taken within [redacted] prior to dosing
- [redacted] for samples collected [redacted] post dose
- [redacted] for all samples drawn [redacted].

Concentration analyses for deucravacitinib and BMT-153261 will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment to follow-up on suspected immunogenicity-related AEs, etc).

Additionally, residual bioanalytical samples will be archived for up to [redacted] after the end of the study or the maximum period allowed by applicable law and [redacted].

Detailed instructions for PK milk and plasma collection, labeling, processing, storage, and shipping will be provided to the site in the laboratory/procedure manual.

9.6 Immunogenicity Assessments

Not applicable.

9.7 Biomarkers

Not applicable.

[redacted]

9.9 Other Assessments

Not applicable.

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

10.1 Statistical Hypotheses

No prospective hypotheses are being formally evaluated.

10.2 Sample Size Determination

Approximately 8 healthy lactating female adult participants are planned to receive study intervention. [redacted]

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have agreed to participate in a clinical study following completion of the informed consent process, unless otherwise specified by the protocol.
Pharmacokinetic (PK)	All participants who received the single dose of study intervention and have any available concentration-time datum.
Evaluable PK	All participants in the PK population who have adequate PK profiles or have at least 1 evaluable PK parameter. Participants with any missing milk sample collection within 24 hours post dose will be excluded from the milk PK evaluable analysis population.
Safety	All participants who received the single dose of study intervention.

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.4.1 General Considerations

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US).

In general, summary statistics (n [number of available measurements], arithmetic mean, standard deviation, median, minimum, and maximum) for quantitative variables and frequency tables for qualitative data will be presented. Any deviations from this general approach will be outlined in the SAP.

The PK population will be used for all PK-related listings. The Evaluable PK population will be used for all PK parameter summaries and statistical analyses. All safety analyses will be performed using the Safety population.

10.4.2 Primary Endpoint(s)

The primary endpoints are defined in Table 10.4.2-1.

Table 10.4.2-1: Primary Endpoints

Primary Endpoint	Description	Time Frame
Milk PK – Cmax	Maximum observed milk concentration for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Milk PK – Tmax	Time of milk Cmax for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Milk PK – AUC(0-24)	Area under the milk concentration-time curve from time zero to 24 hours for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Milk PK – AUC(INF)	Area under the milk concentration-time curve from time zero extrapolated to infinite time for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Milk PK – Cavg	Average milk concentration. The milk Cavg for deucravacitinib and its major active metabolite BMT-153261 to be calculated as AUC(INF) divided by 24, assuming AUC(INF) after a single dose represents steady-state AUC(TAU) (TAU = 24 hours)	Up to 72 hours
Milk PK – AR(24)	Amount recovered in milk within 24 hours of dosing for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Milk PK – AR	Total amount recovered in milk for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
M/P	Milk-plasma ratio for both deucravacitinib and its major active metabolite BMT-153261, calculated as milk AUC(0-24)/plasma AUC(0-24)	Up to 72 hours
Daily Infant Dose	Total deucravacitinib consumed by the infant per day, as estimated below: Estimated Daily Infant Dosage (mg/kg/day) = Mean M/P multiplied by the average maternal plasma concentration (Cavg) multiplied by 200 mL/kg/day	Up to 72 hours
Relative Infant Dose	The percent of the weight-adjusted maternal deucravacitinib dosage consumed in breast milk over 24 hours. As calculated below: Relative Infant Dose = Infant Dosage (mg/kg/day)/Maternal Dosage (mg/kg/day) multiplied by 100	Up to 72 hours

Abbreviations: AR, total amount recovered in milk; AR(24), amount recovered in milk within 24 hours of dosing; AUC(0-24), area under the milk concentration-time curve from time zero to 24 hours; AUC(INF), area under the milk concentration-time curve from time zero extrapolated to infinite time; AUC(TAU), area under the milk concentration-time curve within a dosing interval; Cavg, average plasma or milk concentration; Cmax, maximum observed milk concentration; M/P, milk-plasma ratio; PK, pharmacokinetics; Tmax, time of maximum observed milk concentration.

10.4.3 Secondary Endpoint(s)

The secondary endpoints are defined in Table 10.4.3-1.

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Description	Time Frame
Plasma PK – Cmax	Maximum observed plasma concentration for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Plasma PK – AUC(0-24)	Area under the plasma concentration-time curve from time 0 to 24 hours for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Plasma PK – AUC(INF)	Area under the plasma concentration-time curve from time zero extrapolated to infinite time for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Plasma PK – AUC(0-T)	Area under the plasma concentration-time curve from time 0 to last quantifiable concentration for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Plasma PK – Tmax	Time of plasma Cmax for deucravacitinib and its major active metabolite BMT-153261	Up to 72 hours
Plasma PK – Cavg	Average maternal plasma concentration. The plasma Cavg for deucravacitinib and its major active metabolite BMT-153261 to be calculated as AUC(INF) divided by 24, assuming AUC(INF) after a single dose represents steady-state AUC(TAU) (TAU = 24 hours)	Up to 72 hours
Safety	Incidence, severity, and relationship of TEAEs; and clinically significant changes in clinical laboratory tests (hematology and chemistry), vital signs, physical examinations, and ECGs	Up to 30 days

Abbreviations: AUC(0-24), area under the plasma concentration-time curve from time zero to 24 hours; AUC(0-T), area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; AUC(INF), area under the plasma concentration-time curve from time zero extrapolated to infinite time; AUC(TAU), area under the milk concentration-time curve within a dosing interval; Cavg, average plasma concentration; Cmax, maximum observed plasma concentration; ECG, electrocardiogram; PK, pharmacokinetics; TEAE, treatment-emergent adverse event; Tmax, time of maximum observed plasma concentration.

[redacted]

10.4.5 Pharmacokinetic Analyses

Individual milk and plasma PK concentrations will be listed and summarized by study day and nominal collection time for deucravacitinib and its major active metabolite BMT-153261, where appropriate. Plots of individual and mean milk and plasma concentrations versus time will be provided.

All individual milk and plasma PK parameters will be listed for deucravacitinib and its major active metabolite BMT-153261, where appropriate. Summary statistics will be tabulated for each PK parameter as appropriate. Geometric means and geometric coefficients of variation will be presented for milk and plasma Cmax, AUCs, and Cavg, milk AR, and M/P. Medians and ranges will be presented for milk and plasma Tmax. Daily and relative infant dose will be reported.

Further details will be provided in the SAP.

[redacted]

10.5 Interim Analyses

Not applicable.

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[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS

Term	Definition
[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
AR(24)	amount recovered in milk within 24 hours of dosing
AR	total amount recovered in milk
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-T)	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	area under the plasma or milk concentration-time curve from time zero extrapolated to infinite time
AUC(0-24)	area under the plasma or milk concentration-time curve from time zero to 24 hours
AUC(TAU)	area under the milk concentration-time curve within a dosing interval
AxMP	Auxiliary Medicinal Product
BMI	body mass index
BMS	Bristol-Myers Squibb Company
Cavg	average plasma or milk concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	maximum observed plasma or milk concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	Case Report Form, paper or electronic
CRU	clinical research unit
CSR	Clinical Study Report
CTAg	Clinical Trial Agreement
CYP	cytochrome P450
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture

Term	Definition
ET	early termination
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IMP	Investigational Medicinal Product
IOCBP	individual of childbearing potential
IP	Investigational Product
IRB	Institutional Review Board
JAK	Janus kinase
min	minute(s)
M/P	milk-plasma ratio, calculated as milk AUC(0-24)/plasma AUC(0-24)
PE	physical examination
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event

Term	Definition
T-HALF	half-life
Tmax	time of maximum observed plasma or milk concentration
TYK2	tyrosine kinase 2
UGT	uridine glucuronyl transferase
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
VS	vital signs

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

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

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

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

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

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

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

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

To honor this commitment and to evaluate population-specific signals, data on race and ethnicity data will be collected for this trial. A participant's race/ethnicity should be self-reported to the local study team and not assumed. These data will be documented by the study team in the electronic Case Report Form (eCRF), where permissible by local guidance, and will not be used as determinants of participant eligibility and/or continuation in the clinical trial. These data will be protected consistent with all other data collected during this trial.

RECRUITMENT STRATEGY

A participant engagement and recruitment program using continuous multi-channel marketing campaigns will be developed in cooperation with the site and will focus on assessing drop-out risks and the feasibility of the study schedule with the participants.

Throughout this process, the length of time the participant must temporarily discontinue breastfeeding after dosing is detailed, along with encouraging participants to pump and store sufficient breastmilk prior to study check-in. In order to support the participant's breastfeeding routine and return to breastfeeding upon study completion, a certified lactation consultant will be available from screening throughout the participant's study participation (up until approximately 30 days post dose); utilization of this study resource also promotes study participation and retention. Participants will be encouraged by site staff to utilize this resource throughout the study as needed.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

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

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

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

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

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

SOURCE DOCUMENTS

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

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

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

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures.

Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

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

STUDY INTERVENTION RECORDS

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

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

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

CASE REPORT FORMS

The terms “participant” and “subject” refer to a person who has consented to participate in the clinical research study. Typically, the term “participant” is used in the protocol and the term “subject” is used in the CRF.

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

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

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

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

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

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

MONITORING

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them

with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

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

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

RECORDS RETENTION

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

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

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

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

RETURN OF STUDY INTERVENTION

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

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/clinical research associate prior to destruction.

If	Then
	If study interventions will be returned, the return will be arranged by the responsible study monitor.

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE CLOSURE

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

DISSEMINATION OF CLINICAL STUDY DATA

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

CLINICAL STUDY REPORT

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

For this single-site protocol, the Principal Investigator for the site will sign the CSR.

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 CTAg governing study site or investigator participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the period set forth in the CTAg.

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

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

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion)
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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

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

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

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

ADVERSE EVENTS

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTES: The following hospitalizations are not considered SAEs in BMS clinical studies: A visit to the emergency department or other hospital department that does not result in admission. These visits should be evaluated for an occurrence of 1 of the other serious outcomes that would qualify as an SAE. • Elective surgery that was planned prior to signing consent. • Admissions per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to enrollment in the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life threatening or results in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent 1 of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency department or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7: Potential Drug-induced Liver Injury of the protocol for the definition of a potential DILI.)

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

EVALUATING AES AND SAES

Assessment of Causality

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

Assessment of Intensity

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

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

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

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (NOTE: Follow-up SAE reports must include the same investigator term[s] initially reported.) If an ongoing SAE changes in its intensity or relationship to study intervention or if new information becomes available, the SAE report must be updated and submitted promptly and not to exceed 24 hours to BMS (or the designee) using the same procedure used for transmitting the initial SAE report. All AEs/SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 24 hours of awareness of the event.
- SAEs must be recorded on the paper SAE Report Form.
  - The paper form is transmitted via email or confirmed fax transmission.
  - The original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed fax transmission.

SAE reporting contact information will be provided locally.

APPENDIX 4 INDIVIDUALS OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Individuals of Childbearing Potential (IOCBP)

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

Individuals in the following categories are not considered IOCBP:

- Premenarchal
- Pre-menopausal individual with 1 of the following:
  - Hysterectomy
  - Bilateral salpingectomy
  - Bilateral oophorectomy
- Postmenopausal individual

A postmenopausal state is defined as 12 months of amenorrhea in an individual over the age of 45 years in the absence of other biological or physiological causes. In addition, individuals under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point at which the study intervention (Investigational Medicinal Product [IMP] and other study interventions ie, Non-IMP/Auxiliary Medicinal Product required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require the 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 participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Contraceptive 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 participants in studies in which hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device. • Intrauterine system. (This method of contraception can only be used by participants in studies in which hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion.

- Vasectomized partner.

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

- Sexual abstinence.

Sexual abstinence is considered a highly effective contraceptive 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.
- IOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 of the protocol.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the IOCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method are not acceptable methods of contraception for this study.

NOTES:

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

[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol.

[c] Intrauterine systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments 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 participants in studies in which hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • Lactational amenorrhea method.

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 BREASTFEEDING QUESTIONNAIRE

Screening Visit (Days -35 to -2)

1. Does the participant breastfeed and/or pump?

__ Breastfeed __ Pump __ Breastfeed and pump

2. Frequency (how many times does the participant pump/feed per day): _____

2a. Average duration of feeds (pumping):

Left breast _____ min Right breast _____ min

2b. Average volume of breast milk per feeding/pumping session (if known): _____

2c. Average duration of feeds (breastfeeding):

Left breast _____ min Right breast _____ min

3. Does the participant give their infant any formula for supplementation? ___ yes ___ no

3a. If yes, how often? (Choose one)

__ Less than 25% of the time __ 25% of the time __ 50% of the time __ 75% of the time

4. Does the participant intend to continue breastfeeding after the study period? ___ yes ___ no

5. Does the participant plan on weaning their infant from breastfeeding following participation in the study? ___ yes ___ no

6. Was the participant encouraged to have stored breastmilk available for feeding their infant for the duration of the required study period? ___ yes ___ no

7. How does the participant feel like their breast milk production is going? (Choose one)

___ 1-Very Poor ___ 2-Poor ___ 3-Acceptable ___ 4-Good ___ 5-Very Good

8. Confirm the participant was offered a lactation consultant to be available from screening until approximately 30 days post dose. ___ yes ___ no

9. Does the participant wish to speak with a lactation consultant? ___ yes ___ no (if yes, notify lactation consultant for scheduling)

Safety Follow-up Phone Call (Day 10)

1. How does the participant feel like their breast milk production is going? (Choose one)

___ 1-Very Poor ___ 2-Poor ___ 3-Acceptable ___ 4-Good ___ 5-Very Good

2. After the participant took the study drug, how was their milk production?

___ Same as before ___ Less than before ___ More than before

3. Does the participant give their infant any formula for supplementation? ___ yes ___ no

3a. If yes, how often? (Choose one)

__ Less than 25% of the time __ 25% of the time __ 50% of the time __75% of the time

4. Were there any problems with re-initiating breastfeeding? ___ yes ___ no

4a. If yes, please specify_____

5. Confirm the participant was offered a lactation consultant to be available from screening until approximately 30 days post dose. ___ yes ___ no

6. Does the participant wish to speak with a lactation consultant? ___ yes ___ no (if yes, notify lactation consultant for scheduling)