Official Title of Study:

A Study to Assess the Absolute Oral Bioavailability of Milvexian Using a 14C-Microtracer and Oral Solution in Healthy Participants with Additional Food Effect Comparison of a Spray-Dried Dispersion Formulation of Milvexian in Capsules

NCT Number: NCT04965389

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CLINICAL PROTOCOL CV010-062

A Study to Assess the Absolute Oral Bioavailability of Milvexian Using a ^{14}C-Microtracer and Oral Solution in Healthy Participants with Additional Food Effect Comparison of a Spray-Dried Dispersion Formulation of Milvexian in Capsules

Brief Title:

Absolute Oral Bioavailability Study of Milvexian Using an IV Microtracer with Additional Formulation and Food Effect Comparison

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Original Protocol	14 April 2021	Not applicable

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Study to Assess the Absolute Oral Bioavailability of Milvexian Using a ^{14}C-Microtracer and Oral Solution in Healthy Participants with Additional Food Effect Comparison of a Spray-Dried Dispersion Formulation of Milvexian in Capsules

Brief Title: Absolute Oral Bioavailability Study of Milvexian Using an IV Microtracer with Additional Formulation and Food Effect Comparison

Rationale:

This study is being conducted to evaluate the absolute oral bioavailability of milvexian (known as BMS-986177 or JNJ-70033093) when administered as the spray-dried dispersion (SDD) in capsule formulation and an oral solution formulation. Additionally, fed and fasted state bioavailability comparisons of the capsule formulation will be conducted, at a clinically relevant dose range.

[redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary**
• To assess the absolute oral bioavailability of [redacted] doses of milvexian administered as: a [redacted] mg solution (fasted), [redacted] mg SDD capsule (fed and fasted) and [redacted] mg SDD capsule (fed and fasted), to healthy participants	• Absolute oral bioavailability (F) for each treatment

Objectives	Endpoints
Secondary • To characterize the IV and the oral PK of milvexian following [redacted] administration in the fed and fasted states to healthy participants	**Secondary** • Cmax, Tmax, AUC(0-T), AUC(INF), CLT or CLT/F, CLR, Vz or Vz/F, Ae, %UR, T-HALF, for each treatment • MRT and Vss of [^{14}C]milvexian following an IV dose • Frel for each SDD capsule treatment vs oral solution formulation • Food effect with [redacted] mg and [redacted] mg SDD capsules based on ratios of Cmax, AUC(0-T), and AUC(INF)
• To assess the safety and tolerability of milvexian following [redacted] oral and IV administration, to healthy participants	• Occurrence of AEs and SAEs, abnormalities in vital sign measurements exceeding pre-defined thresholds, findings on ECGs and physical examinations, and abnormalities in clinical laboratory tests

CLR: renal clearance; CLT: total clearance; CLT/F: apparent clearance of drug after extravascular administration; Cmax: maximum observed concentration; ECG: electrocardiogram; Frel: relative bioavailability; IV: intravenous; MRT: mean residence time; T-HALF: half-life; Tmax: time of maximum observed concentration; %UR: percent urinary recovery; Vss: volume of distribution at steady state; Vz: volume of distribution of terminal phase; Vz/F: apparent volume of distribution at terminal phase after extravascular administration.

Overall Design:

- This is a Phase 1, open-label, partially randomized, [redacted] period crossover study to evaluate the absolute bioavailability of milvexian following oral administration of a [redacted] dose of the oral solution in conjunction with a ^{14}C microdose given at the time of maximum observed concentration (Tmax) of the oral solution when fasted, and crossover [redacted] doses of SDD capsules at two dose levels in the fed and fasted state across [redacted] treatment periods in healthy volunteers.
- Participants will undergo screening evaluations to determine study eligibility within [redacted] days prior to initial administration of study treatment (Day [redacted], Treatment Period [redacted]). Participants will be admitted to the clinical facility on the morning of Day [redacted] of Treatment Period [redacted] and will remain in the facility for the entire duration of the dosing treatment periods, including washout.
- On Day [redacted] of Treatment Period [redacted] all participants will be randomized to a treatment sequence, with the treatment for Treatment Period [redacted] fixed owing to logistical consideration of the radiolabeled investigational product.
- Participants will be randomized to 1 of 4 treatment sequences immediately prior to administration of treatment in Treatment Period [redacted]. A 4-sequence Latin square will be used. Fasted study treatments will be administered following an overnight fast of at least 10 hours and fed study treatments will be administered 30 minutes after the start of a high-fat a meal.
- On the morning of Day [redacted] of Treatment Period [redacted] all participants will receive the milvexian [redacted] mg oral solution in the fasted state, followed 1 hour later by the intravenous (IV) [^{14}C]milvexian [redacted] µg containing not more than (NMT) [redacted] kBq microdose infused over 15 minutes.
- On the mornings of Day [redacted] for Treatment Periods [redacted], participants will receive milvexian SDD capsules, [redacted] mg in the fed and fasted states, and milvexian SDD capsules, [redacted] mg in the

fed and fasted states, in an order according to the randomization schedule, with a minimum 72 hour washout between dose administration in each treatment period.

- Participants will be discharged from the clinical unit 72 hours after the final dose of study treatment (ie following Treatment Period).
- There will be a follow up phone call 5 to 7 days post-final dose to ensure the ongoing wellbeing of the participants.

Number of Participants:

A total of 16 participants will be randomized to ensure at least 13 participants complete the study and are evaluable.

Study Population:

Healthy male volunteers or healthy female volunteers not of childbearing potential, aged 18 to 65 years, inclusive, at the time of the signing the informed consent.

Body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, at screening.

Intervention Groups and Duration:

- The duration of study participation is expected to be up to approximately 7 weeks (including screening).
- Participants will undergo screening evaluations to determine study eligibility within days prior to initial administration of study treatment (Day , Treatment Period).
- Participants will be admitted to the clinical facility on the morning of Day of Treatment Period and will remain in the facility for the entire duration of the dosing treatment periods, including washout.
- There will be a follow up phone call 5 to 7 days post-final dose (ie Treatment Period Day) to ensure the ongoing wellbeing of the participants.

Study intervention:

Study Intervention for CV010-062			
Medication	**Potency**	**IP/Non-IP**	**Duration of Dosing**
BMS-986177 oral solution mg	mg/mL	IP	mg dose on a occasion
[^{14}C]BMS-986177 Solution for Infusion µg/mL (NMT kBq/ mL)	µg/mL	IP	µg dose on a occasion
BMS-986177 SDD capsules, mg	mg	IP	dose on occasions; in the fasted state (at

Study Intervention for CV010-062			
Medication	**Potency**	**IP/Non-IP**	**Duration of Dosing**
			[redacted] mg and [redacted] mg), [redacted] in the fed state (at [redacted] mg and [redacted] mg)

IP: investigational product; NMT: not more than.

Statistical Methods

Sample size determination is based on consideration of the precision of the estimate of the geometric mean ratios (GMR) of the maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) of milvexian between test and reference treatments. With 13 evaluable participants, there will be an 80% probability that the 90% confidence interval (CI) of GMR will be within 80% and 125% of the point estimate. The precision estimate is based on the assumptions that Cmax and AUCs of milvexian are log-normally distributed with intra-subject coefficient of variation (CV) of no greater than 28.3%. [redacted]

The primary endpoint is to determine the absolute oral bioavailability for each treatment, which will be summarized with descriptive statistics and 90% CIs. The secondary endpoints include: plasma PK concentrations and PK parameters, which will be summarized by treatment for milvexian and [^{14}C]milvexian, as applicable; relative bioavailability assessment of the SDD capsule formulation versus the oral solution; fed versus fasted state bioavailability comparisons of the SDD capsule formulation; and additional safety information.

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

Data Monitoring Committee: No

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

Other Committee: No

Other review committee will not be used in the study.

Brief Summary:

Milvexian is being developed as an orally administered anticoagulant to prevent and treat atherothrombotic and thromboembolic disorders. The purpose of this study is to evaluate the absolute oral bioavailability of the SDD formulation of milvexian at a clinically relevant dose range, in the fed and fasted states and to bridge the exposures seen using the oral solution. The results from this study will provide insights into the understanding of milvexian PK at clinically relevant doses. Study details include:

Study Duration: Approximately 7 weeks (including screening)

Study Intervention Duration: [redacted] oral doses on [redacted] occasions, and a [redacted] oral dose with an IV ^{14}C-microdose on a [redacted] occasion (ie [redacted] dosing occasions in total)

Study Visit Frequency: A screening visit followed by a single admission to the clinical research unit.

2 SCHEDULE OF ACTIVITIES

Schedules of activities are presented in Table 2-1 for screening, pre-admission and admission, and Table 2-2 for the on-treatment procedural outline.

When the protocol requires more than one procedure to be completed at the same time point, the following will apply to post dose time points:

PK samples should take priority over other procedures scheduled at the same time point. The PK sample should be taken at the nominal time point.

As guidance, the preferred order of assessments is:

Vital signs → **ECGs** → **PK blood sampling (nominal time point)** → **Other assessments, eg, physical examinations**

Predose safety blood samples, electrocardiogram (ECG) and vital sign measurements should be taken within 2 hours of study treatment. To ensure PK samples can be collected on time, the ECG and vital signs measurements may be obtained ± 15 minutes from the nominal post dose time point. Discharge ECG and vital sign measurements will be taken ± 1 hour from the nominal time point. Post dose safety blood samples will be taken ± 1 hour from the nominal time point.

See Section 6.3.1 for details of meal timings.

Other assessments, eg, physical examinations, will be performed within the required time windows (ie, any time predose or on the specified day).

Admission and screening procedures can be repeated at the discretion of investigator or sub-investigator if there is a concern regarding a participant's safety or eligibility to participate in the clinical trial.

Table 2-1: Screening and Admission Procedural Outline (CV010-062)

Procedure	Screening [redacted]	Pre-Admission (If Required)	Admission –1	Notes
Eligibility Assessments				
Informed Consent	X			A participant is considered enrolled only when a protocol-specific informed consent is signed. Must be obtained prior to performing any screening procedures.
Inclusion/Exclusion Criteria	X		X	Admission, update only
Medical History	X		X	All medical history including any toxicities or allergies related to previous treatments. Include any COVID-19 history, including vaccinations. Refer to Section 6.2. Admission, update only
Demographics	X			
Vein Assessment	X			
Admission to Clinic			X	Admission will be in the morning of Day [redacted] of Treatment Period [redacted].
Safety Assessments				
Physical Examination	X			A full physical examination will be performed at screening. A targeted (symptom-driven) physical examination will be performed at admission at the discretion of the investigator or sub investigator (see Section 9.4.1).
Targeted Physical Examination			X	
Physical Measurements	X			Includes height, weight and BMI
Vital Signs	X		X	Includes body temperature, respiratory rate, and supine blood pressure and heart rate. All measurements should be taken after the participant has been supine for at least 5 minutes. See Section 9.4.2
Concomitant Medication Use	X		X	See Section 7.7
Electrocardiogram (ECG)	X		X	Single ECGs should be recorded after the participant has been supine for at least 5 minutes. See Section 9.4.3
Laboratory Tests				See Section 9.4.4.
Clinical Laboratory Assessments	X		X	Includes blood and urine samples. Participants are required to fast for at least 10 hours prior to the collection of blood specimens for clinical laboratory tests. Results from the laboratory tests performed on

Table 2-1: Screening and Admission Procedural Outline (CV010-062)

Procedure	Screening [redacted]	Pre-Admission (If Required)	Admission –1	Notes
				Day [redacted] of Treatment Period [redacted] must be available and reviewed prior to dosing on Day [redacted]
Follicle-stimulating Hormone	X			Women only, to confirm post-menopausal status. Refer to APPENDIX 4.
Urine Pregnancy Test	X		X	Women only.
Serology	X			Includes hepatitis C antibody, hepatitis B surface antigen, and human immunodeficiency virus-1 and -2 antibody.
Tests for drugs of abuse (urine) and alcohol (breath)	X		X	Urine drug screen (including cotinine) and alcohol breath test. See Table 9.4.4-1 in Section 9.4.4. These results must also be reviewed before dosing on Day [redacted]
SARS-CoV-2 Antibody	X			Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening (IgG), and an antigen PCR test or other antigen test performed at screening, the day before admission and discharge from the clinical unit or the day before discharge from the clinical unit. The decision on COVID-19 testing and the definition of the testing time points will be agreed and documented in the ISF.
SARS-CoV-2 Antigen	X	X		
Adverse Event Reporting				
Monitor for Serious Adverse Events	X		X	All SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time

COVID-19: coronavirus disease 2019; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Table 2-2: On-Treatment Procedural Outline (CV010-062)

Procedure	Treatment Periods [redacted]				Treatment Period [redacted] only		Notes
	[redacted]						
Clinical Residency	X	X	X	X	X		Participants will be admitted to the clinical unit in the morning of Day [redacted] of Treatment Period [redacted], and will remain resident in the clinic until Day [redacted] of Treatment Period [redacted].
Discharge from Clinic					X		Participants will be discharged from the clinic on Day [redacted] of Treatment Period [redacted].
Discharge from Study						X	Participants will be considered to have been discharged from the study after the follow-up phone call (or after the last contact if following up on an AE).
Follow-up Phone Call						X	To ensure the ongoing wellbeing of the participants.
Safety Assessments							
Targeted Physical Examination					X[c]		A targeted (symptom driven) physical examination may be performed at the discretion of the investigator or sub-investigator.
Vital Signs	X	X		X	X[c]		See notes in screening procedures. Vital signs will be examined at pre-dose and at 3, 24 and 72 hours post dose. For Treatment Period [redacted] only, vital signs will also be assessed at 1 hour 15 minutes post dose (ie at the end of infusion).
Electrocardiogram	X	X		X	X[c]		See note in screening procedures. ECGs will be examined at pre-dose and at 3, 24 and 72 hours post dose. For Treatment Period [redacted] only, ECGs will also be assessed at 1 hour 15 minutes post dose (ie at the end of infusion).
Concomitant Medication Use	X	X	X	X	X[c]	X	
Adverse Event Reporting							
Monitor for Serious Adverse Events	X	X	X	X	X[c]	X	All SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

Table 2-2: On-Treatment Procedural Outline (CV010-062)

Procedure	Treatment Periods [redacted]				Treatment Period [redacted] only		Notes
	[redacted]						
Monitor for Nonserious Adverse Events	X	X	X	X	X[c]	X	Nonserious AEs will be recorded from first dose of study treatment until the follow-up call.
Laboratory Tests							See Section 9.4.4.
Clinical Laboratory Assessments	X	X			X[c]		Participants are required to fast for at least 10 hours prior to the collection of specimens. Safety laboratory blood samples will be drawn at predose, 24 hour post dose, and safety laboratory blood and urine samples will be collected at discharge from the clinical unit.
SARS-CoV-2 Antigen					X[c]		Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, testing will comprise an antigen PCR test or other antigen test performed at discharge from the clinical unit or the day before discharge from the clinical unit. The decision on COVID-19 testing and the definition of the testing time points will be agreed and documented in the ISF.
PK Assessments							
Serial Blood PK Collections	X	X	X	X	X		Refer to PK collection tables in Section 9.5 for timing of collections
Urine PK Collection	X	X	X	X	X		
[redacted]							
Study intervention							
Randomize	X						Participants will be randomized prior to study treatment administration on Day [redacted], Treatment Period [redacted] only

Table 2-2: On-Treatment Procedural Outline (CV010-062)

Procedure	Treatment Periods [redacted]	Treatment Period [redacted] only	Notes
Administer Study intervention	[redacted]		

COVID-19: coronavirus disease 2019; IV: intravenous; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

[a] If Day [redacted] of a treatment period coincides with the Day [redacted] of the previous treatment period, assessments will be documented as 72 hour post dose/predose.

[b] Not Treatment Period [redacted].

[c] If early withdrawal occurs, the assessments will be the same as for discharge from the clinical unit.

3 INTRODUCTION

Thrombosis is a maladaptive process of vascular occlusion and remains a primary cause of cardiovascular morbidity and mortality. The clinical benefits of anticoagulant therapy are well established for prevention of thrombosis in patients with existing cardiovascular disease (eg, atrial fibrillation, deep vein thrombosis and pulmonary embolism). The growing role of anticoagulant therapy in the treatment and prevention of thrombosis is continually balanced by the potential complications and risks associated with excess bleeding. Although improvements in the therapeutic index of anticoagulant therapy have been made with the advent of small molecule inhibitors of factor Xa (FXa) or thrombin relative to vitamin K antagonists, dose-dependent bleeding continues to be observed.[1] Therefore, improving the risk-to-benefit ratio remains a viable goal for antithrombotic drug discovery. This requires selecting a molecular target that defines a difference between hemostasis and thrombosis.

Factor XI (FXI) is a component of the intrinsic pathway of the coagulation cascade and has been postulated to play an important role in maintaining and propagating a formed thrombus. Epidemiologic data collected over the past 15 years indicate that, in humans, factor XIa (FXIa) could play a greater part in thrombosis than in hemostasis. In the Leiden Thrombophilia Study, participants with plasma FXI levels in the top 10% of the normal distribution were nearly twice as likely to develop venous thromboembolism as the rest of the study population.[2] Similarly, human participants with severe FXI genetic deficiency have a reduced incidence of deep vein thrombosis.[3] Severe FXI deficiency appears to confer protection from ischemic stroke.[4] Conversely, higher FXI levels were associated with increased risk for ischemic stroke in a study by Yang et al.[5] and in the Atherosclerosis Risk in Communities (ARIC) study.[6] In young women enrolled in the Risk of Arterial Thrombosis In relation to Oral (RATIO) contraceptives study, levels of FXIa and FXI antigen correlated with arterial thrombosis and stroke risk.[7]

The attractiveness of FXI as a therapeutic target for anticoagulation is further supported by the lack of clinically meaningful bleeding associated with FXI deficiency. Spontaneous bleeding in humans with a deficiency in FXI (hemophilia C) is generally rare, and when observed it is usually limited to tissues with high fibrinolytic activity (eg, oral cavity, nose, and urinary tract) after direct injury or trauma.[8] In fact, increased tendency for bleeding has only been documented after surgery in patients with very severe FXI deficiency (≤ 15 to 20 IU/dL).[9] In a 2015 study in patients undergoing total knee arthroplasty, a 60% to 80% reduction in circulating FXI induced by an antisense oligonucleotide proved more effective than enoxaparin in reducing the risk of postoperative venous thromboembolism without an increased risk of bleeding. This study provides a proof-of-concept in humans for FXI inhibition.[10] Current evidence supports the hypothesis that inhibition of FXI is a novel mechanism for systemic anticoagulation with a low risk of clinically significant bleeding.

3.1 Background

Milvexian (also known as BMS-986177 or JNJ-70033093) is a small molecule therapeutic agent that binds and inhibits FXIa with high affinity and selectivity. Milvexian is being developed as an orally administered anticoagulant to prevent and treat atherothrombotic and thromboembolic disorders. Depending on the specific situation, milvexian is expected to provide benefit to patients as add-on therapy to the current standard of care therapy or, potentially, as a replacement of current standard of care.

The Investigator Brochure (IB) for milvexian provides detailed information on the preclinical pharmacology, toxicology, metabolism, PK, absorption, distribution, metabolism, elimination, and potential for drug-drug interactions of milvexian. The clinical experience to date is summarized below, and in addition can be found in the IB.[11]

3.1.1 Clinical Pharmacology and Safety

As of 07 December 2020, 2211 participants (ie, 513 healthy participants [includes 17 mild and moderate hepatic-impaired participants and 16 moderate and severe renal-impaired participants], 984 participants who underwent elective total knee replacement (TKR) surgery, 39 participants with end-stage renal disease undergoing regularly scheduled chronic stable hemodialysis (HD) treatment, and 675 participants with acute ischemic stroke or transient ischemic attack within 48 hours of symptom onset) have been included and exposed to study drug (milvexian, placebo, or comparator) in the milvexian clinical program.

Of the 2211 participants randomized and exposed, 1763 participants received milvexian, of which 458 participants were exposed to milvexian in the Phase 1 studies and 1305 participants were exposed to milvexian in the Phase 2 and 2a studies. One participant [redacted] was discontinued early due [redacted]. This participant was replaced and was not included in the total counts of participants treated (2211).

[redacted]

Nonclinical toxicity and clinical studies to date have demonstrated an acceptable safety profile to allow continued testing of milvexian in humans.

3.2 Study Rationale

This study is being conducted to evaluate the absolute oral bioavailability of milvexian when administered as the spray-dried dispersion (SDD) in capsule formulation and an oral solution formulation. Additionally, fed and fasted state bioavailability comparisons of the capsule formulation will be conducted, at a clinically relevant dose range.

Milvexian is targeted as a safe and effective oral agent for the treatment and prevention of atherothrombotic and thromboembolic disorders associated with a variety of diseases. Information on the renal elimination and clarification of the PK at clinically relevant doses are required to take into future clinical studies. The study is not testing statistically any formal hypotheses.

3.2.1 Pharmacokinetics

In the FIH study, after single doses of milvexian ranging from 4 mg to 500 mg in the fasted state, milvexian plasma concentrations reached the maximum observed concentration (Cmax) at 3 hours post dose in all panels, indicating a similar rate of absorption. Over the 4 mg to 500 mg dose range, the geometric mean milvexian Cmax and AUC(0-T) values increased in a greater than dose proportional manner, at 139- and 168-fold, respectively, for a 125-fold dose increase; while the AUC(INF) increased 102-fold, which was lower than dose proportional.

At the 200 mg and 500 mg doses, the rate of absorption was delayed by 1 hour by food intake, indicated by a 1-hour shift in median time of maximum observed concentration (Tmax). In addition, the mean T1/2 was 1.5 hours shorter following administration with food (9.04 hours vs 10.5 hours for 200 mg, and 10.7 hours vs 12.2 hours for 500 mg in study CV010001).

The mean total amount of milvexian excreted in the urine over the 0- to 24-hour period in the 200 mg once daily (QD) panel (fasted and fed) and 300 mg QD panel was low to moderate, with

values ranging from 6.94% to 17.8% of the dose; it was also low in the 500 mg fasted treatment, with a value of 7.09% of the dose excreted in the urine over the 0- to 24-hour period and moderate in the 500-mg fed treatment, with a value of 16.3% of the dose excreted in the urine over the 0- to 24-hour period.

[redacted]

3.2.2 Pharmacodynamics

In the FIH study, administration of a single oral dose or multiple oral doses of milvexian resulted in a dose- and concentration-related prolongation of activated partial thromboplastin time (aPTT) and decreased FXI clotting activity. The magnitude of aPTT prolongation reduced following the decline in milvexian plasma concentration. The changes in aPTT are consistent with the proposed mechanism of action of milvexian, reflecting a highly selective, direct, and reversible inhibition of FXIa by milvexian. Prothrombin time and international normalized ratio (INR) were not impacted by the administration of a single dose or multiple doses of milvexian, with a maximal mean percent change from baseline of approximately 5%.

3.2.3 Safety and Tolerability

Milvexian was safe and well tolerated in healthy participants at doses up to 500 mg daily for 14 days and in participants with end-stage renal disease or renal impairment at a single dose up to 300 mg, and in participants with hepatic impairment at a single dose of 60 mg.

[redacted]

[redacted]

3.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of milvexian may be found in the IB.[11]

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 Interventions		
Exposure to milvexian	[redacted] oral dose of [redacted] mg milvexian (as SDD capsules in the fed and fasted state, and as the oral solution) and a [redacted] dose of [redacted] mg (as SDD capsule in the fed state), will be dosed across [redacted] treatment periods in this study	Milvexian has been shown to be safe and well tolerated in healthy participants at doses up to 500 mg daily for 14 days. Only healthy participants will be enrolled in this study (see Sections 6.1 and 6.2). The overall safety profile of milvexian in healthy participants supports clinical evaluation of the PK profile and safety/tolerability of [redacted] oral doses of [redacted] mg and [redacted] mg milvexian in healthy participants. Based on available data, a low risk of bleeding is expected with administration of [redacted] doses.
Exposure to radiolabeled intravenous microdose	Participants in this study are exposed to ionizing radiation. It is believed that any increase in the amount of radiation that is received above background radiation carries a risk of later developing serious and possibly fatal conditions	Based on National Radiological Protection Board (NRPB) publication NRPB-R245, the radioactive administrations will result in an effective dose of <0.1 mSv. In comparison, the UK average radiation exposure for an individual is about 2.7 mSv (data obtained from Public Health England [PHE] Ionising Radiation Exposure of the UK Population: 2010 Review) per year and as such the radiation risk to participants in this study is considered negligible.
Study Procedures		
ECG stickers	Stickers on the participants' chests and limbs may cause some local irritation and may be uncomfortable to remove	Participants will be closely monitored to ensure any local irritation does not persist

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Collecting blood samples	Collecting a blood sample from a vein may cause pain, swelling, bruising, 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
Cannulation	During cannulation, more than one attempt may be needed to insert the cannula in a vein of a participant and it is possible that bruising and/or inflammation may be experienced at the site of cannulation	Participants will be closely monitored to ensure any local irritation/inflammation does not persist

3.3.2 COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to the time in which the study is conducted during the coronavirus disease 2019 (COVID-19) pandemic.

3.3.2.1 IMP Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a participant developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of the IMP – as a reversible FXIa inhibitor – has been considered alongside available pre-clinical and clinical data (including class effects) and it is considered that a participant would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, the IMP has no known immunomodulatory effect that would confer an increased risk to healthy participants enrolled in the study.

3.3.2.2 General COVID-19 Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with [redacted] monitoring and prevention control measures.

COVID-19 testing may be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening, and an antigen polymerase chain reaction (PCR) test or other antigen test performed at screening, the day before admission and discharge from the clinical unit or the day before discharge from the clinical unit. Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points will be agreed and documented in the Investigator Site File (ISF).

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

3.3.2.3 COVID-19 Vaccine-Related Risk

Approved (including health authority conditional marketing authorization) COVID-19 vaccines eg killed, inactivated, peptide DNA and RNA vaccines may be permitted before enrollment according to the investigator's discretion and as per local guidance.

Based on the mechanism of action of the IMP, as a reversible FXIa inhibitor, there is no perceived impact on the safety of the study participants or on the study objectives for participants who may receive these vaccines (either first or second doses). It is also very unlikely that administration of the IP would interfere with COVID-19 vaccination response; however, no specific preclinical or clinical investigations have been conducted at this point with milvexian.

3.3.3 Benefit Assessment

The current study is a Phase 1 study of milvexian in healthy participants. Participants will receive no known health benefit from participating in the study beyond that of an assessment of their overall status.

3.3.4 Overall Benefit/Risk Conclusion

There is no benefit to the participants from taking part in this study. The development of a product for the prevention and treatment of atherothrombotic and thromboembolic disorders could benefit patients with diseases associated with atherothrombotic and thromboembolic disorders.

The overall risk benefit balance is therefore considered to be acceptable.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
• To assess the absolute oral bioavailability of [redacted] doses of milvexian administered as: a [redacted] mg solution (fasted), [redacted] mg SDD capsule (fed and fasted) and [redacted] mg SDD capsule (fed and fasted), to healthy participants	• Absolute oral bioavailability (F) for each treatment
Secondary	**Secondary**
• To characterize the IV and the oral PK of milvexian following [redacted] administration in the fed and fasted states to healthy participants	• Cmax, Tmax, AUC(0-T), AUC(INF), CLT or CLT/F, CLR, Vz or Vz/F, Ae, %UR, T-HALF, for each treatment • MRT and Vss of [^{14}C]milvexian following an IV dose • Frel for each SDD capsule treatment vs oral solution formulation • Food effect with [redacted] mg and [redacted] mg SDD capsules based on ratios of Cmax, AUC(0-T), and AUC(INF)
• To assess the safety and tolerability of milvexian following [redacted] oral and IV administration, to healthy participants	• Occurrence of AEs and SAEs, abnormalities in vital sign measurements exceeding pre-defined thresholds, findings on ECGs and physical examinations, and abnormalities in clinical laboratory tests

Table 4-1: Objectives and Endpoints

Objectives	Endpoints

CLR: renal clearance; CLT: total clearance; CLT/F: apparent clearance of drug after extravascular administration; Frel: relative bioavailability ; IV: intravenous; MRT: mean residence time; T-HALF: half-life; %UR: percent urinary recovery; Vss: volume of distribution at steady state; Vz: volume of distribution of terminal phase; Vz/F: apparent volume of distribution at terminal phase after extravascular administration.

5 STUDY DESIGN

5.1 Overall Design

- This is a Phase 1, open-label, partially randomized, [redacted]period crossover study to evaluate the absolute bioavailability of milvexian following oral administration of a [redacted] dose of the oral solution in conjunction with a ^{14}C microdose given at the Tmax of the oral solution when fasted, and crossover [redacted] doses of SDD capsules at two dose levels in the fed and fasted state across [redacted] treatment periods in healthy volunteers. The duration of study participation is expected to be up to approximately 7 weeks (including screening).
- Participants will undergo screening evaluations to determine study eligibility within [redacted] days prior to initial administration of study treatment (Day [redacted], Treatment Period [redacted]). Participants will be admitted to the clinical facility on the morning of Day [redacted] of Treatment Period [redacted] and will remain in the facility for the entire duration of the dosing treatment periods, including washout.
- On Day [redacted] of Treatment Period [redacted] all participants will be randomized to a treatment sequence, with the treatment for Treatment Period [redacted] fixed owing to logistical consideration of the radiolabeled investigational product.
- Participants will be randomized to 1 of 4 treatment sequences immediately prior to administration of treatment in Treatment Period [redacted]. A 4-sequence Latin square, will be used; the treatment sequences are presented in Table 5.1-1 [redacted]. Fasted study treatments will be administered following an overnight fast of at least 10 hours and fed study treatments will be administered 30 minutes after the start of a high-fat a meal.
- On the morning of Day [redacted] of Treatment Period [redacted] all participants will receive the milvexian [redacted] mg oral solution, in the fasted state followed 1 hour later by the IV [^{14}C]milvexian [redacted] µg microdose, containing NMT [redacted] kBq, infused over 15 minutes.
- On the morning of Day [redacted] for Treatment Periods [redacted], participants will receive milvexian SDD capsules, at doses of [redacted] mg and [redacted] mg in the fed and fasted states, in an order according to the randomization schedule, with a minimum 72 hour washout between dose administration in each treatment period.
- Participants will be discharged from the clinical unit 72 hours after the final dose of study treatment (ie following Treatment Period [redacted]).
- There will be a follow up phone call 5 to 7 days post final dose (ie Treatment Period [redacted], Day [redacted]) to ensure the ongoing wellbeing of the participants.

Table 5.1-1: Treatment Sequences

Sequence number	[redacted]				
1	A	B	C	E	D

Table 5.1-1: Treatment Sequences

Sequence number	[redacted]				
2	A	C	D	B	E
3	A	D	E	C	B
4	A	E	B	D	C

A: [redacted] mg milvexian oral solution with [redacted] µg IV microdose; B: [redacted] mg milvexian SDD fasted; C: [redacted] mg milvexian SDD fed; D: [redacted] mg milvexian SDD fasted; E: [redacted] mg milvexian SDD fed. TP: treatment period.

[redacted]

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for AEs throughout the study. Blood and urine samples will be collected for up to 72 hours after study intervention administration for pharmacokinetic (PK) analysis. Less than 550 mL of blood will be drawn from each participant during the study.

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

A total of 16 participants will be randomized to ensure at least 13 participants complete the study and are evaluable.

5.3 End of Study Definition

The start of the trial is defined as the first participant first visit.

End of trial is defined as the last participant last visit (ie follow-up phone call or last contact if following up on an AE).

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

A participant is considered to have completed the study if he/she has completed the last procedure shown in the schedule of activities.

The EC and MHRA should be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

ARSAC and the ARSAC Practitioner will also be notified of the end of trial or early termination of the trial in writing within an appropriate timeframe.

5.4 Scientific Rationale for Study Design

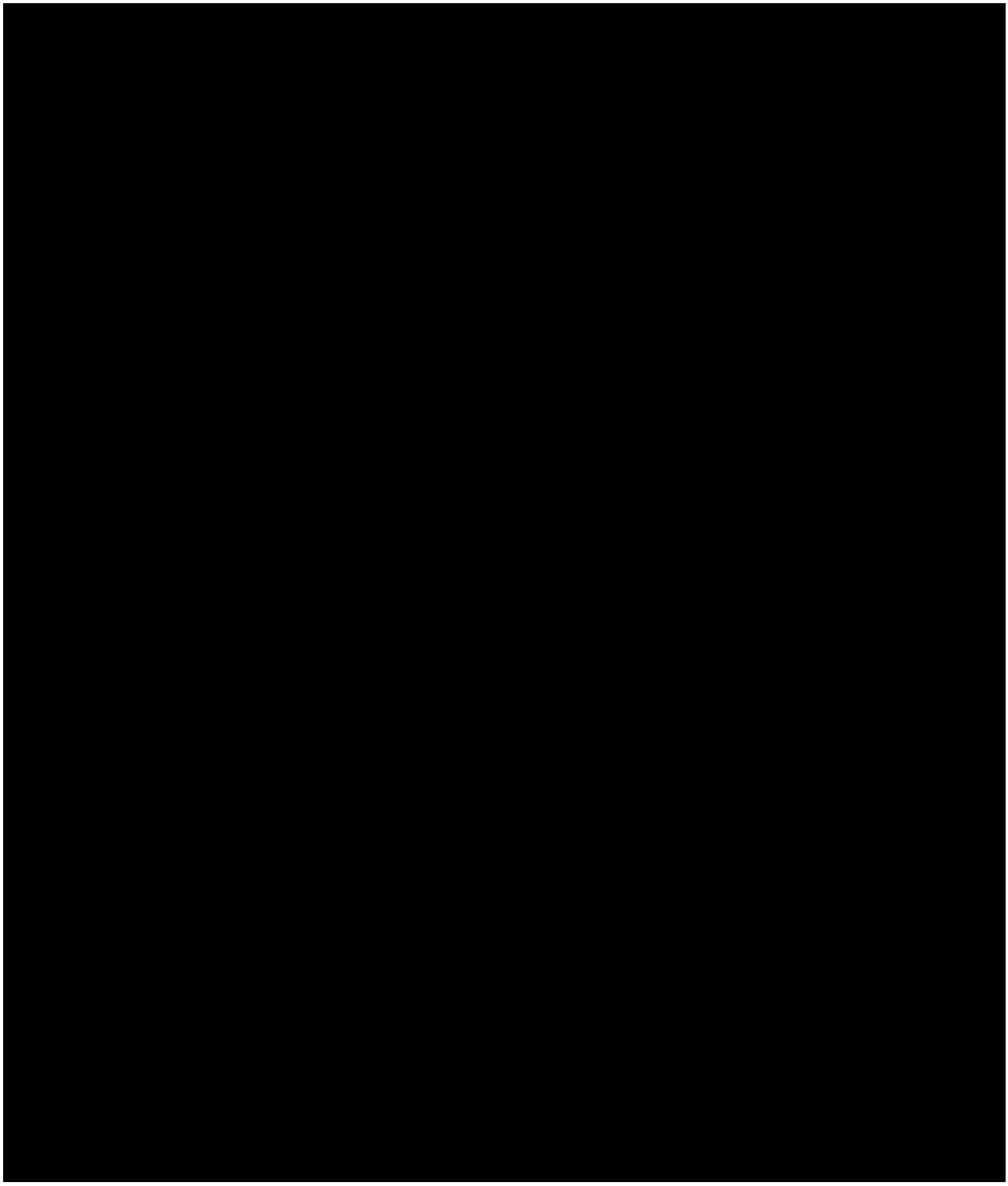
The purpose of this study is to assess the absolute oral bioavailability of an SDD formulation of milvexian at a clinically relevant dose range, in the fed and fasted states, and to bridge the exposures seen using the oral solution.

Randomization will be used for 4 of the 5 regimens to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of comparisons across dose groups. The regimen containing the radiolabeled intravenous (IV) microdose will not be randomized owing to logistical considerations.

[redacted]

The IV microtracer technique is an established methodology for measuring the IV and oral kinetics of a drug in the same individuals in a single dosing period. The technique involves concurrent administration of a microdose of the drug containing microtracer amounts of ^{14}C with a single oral therapeutic dose, which avoids the concerns of dose-dependent kinetics when extrapolating IV PK from a microdose, as the systemic exposure is at therapeutic concentrations. Moreover, for this reason the IV administration is timed to coincide with the expected Tmax of the oral dose. This design enables measurement of ^{14}C-labelled drug in plasma following IV dosing via sensitive accelerator mass spectrometry (AMS) techniques, and measurement of the unlabeled parent in the plasma by standard high performance liquid chromatography mass spectrometry/mass spectrometry (HPLC MS/MS) techniques. Thus, it is possible to obtain the IV PK parameters with

the associated variability and calculate the absolute bioavailability. In addition, because the IV dose administration involves giving a low volume of a low concentration of parent drug, an advantage of this approach is that it is much easier to develop an IV formulation for micro dosing, than it would be for a higher clinical dose.



[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

a) Participants must have signed and dated an Independent Ethics Committee (IEC)-approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures.

b) Participants must be willing and able to communicate and complete all study-specific procedures and visits.

2) Type of Participant and Target Disease Characteristics

a) Healthy male or female volunteer, as determined by no clinically significant deviation from normal in medical history, physical examination, ECGs, and clinical laboratory determinations.

b) Body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, at screening. BMI = weight (kg)/(height [m])^2.

3) Age of Participant

Participant must be 18 to 65 years of age, inclusive, at the time of signing the informed consent.

4) Reproductive Status

- Investigators shall counsel male participants who are sexually active with women of childbearing potential (WOCBP) on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

a) Female Participants:

- A female participant is eligible to participate if:

She is a woman not of childbearing potential (WNOCBP), as defined in APPENDIX 4: WOCBP Definitions and Methods of Contraception.

She has a negative urine pregnancy test at screening and admission.

b) Male Participants:

- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception as defined in APPENDIX 4 and as described below.
  - i) Azoospermic males are exempt from contraceptive requirements.
  - ii) Male participants are required to use a condom during the intervention period and for at least 92 days after the last dose of study intervention.
  - iii) Female partners of males participating in the study should also be advised to use highly effective methods of contraception during the study intervention period and for at least 92 days after the last dose of the male participant's study intervention.
  - iv) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the intervention period and for at least 92 days after the last dose of study intervention.
  - v) Male participants must refrain from donating sperm during the intervention period and for at least 92 days after the last dose of study intervention.
  - vi) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

The following criterion will be reassessed at admission: 2)a).

6.2 Exclusion Criteria

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

5) Medical Conditions

a) History of gastrointestinal (GI) disease: gastroesophageal reflux, dyspepsia, protracted nausea, chronic diarrhea, upper GI ulcer disease within 6 months, ulcerative colitis, regional enteritis, diverticulosis, diverticulitis, or surgery that could affect the absorption of study drug

b) History of upper or lower GI bleeding within 6 months, including hemorrhoids with rectal bleeding

c) Any gastrointestinal surgery that could affect the absorption of study intervention

d) Clinically relevant head injury within the last 2 years, as judged by the investigator

e) Any intracranial bleeding or history of intracranial bleeding

f) Intracranial tumor or aneurysm or abdominal aneurysm

g) Major surgical procedures within 4 weeks prior to dosing) or planned within 2 weeks after completion of the study

h) History or evidence of abnormal bleeding or coagulation disorder and/or evidence of coagulopathy, prolonged or unexplained clinically significant bleeding, or frequent unexplained bruising or thrombus formation, or a history of spontaneous bleeding, such as epistaxis, or family history of coagulopathies

i) History of menorrhagia

j) Inability or not willing to be venipunctured/cannulated and/or tolerate venous access

k) Any history of drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders (5th Edition) (DSM 5), Diagnostic Criteria for Drug and Alcohol Abuse

a) Regular alcohol consumption in males > 21 units per week and females > 14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type)

b) Current smokers and those who have smoked (or used other nicotine-containing products or devices) within the last 12 months. A positive urine cotinine result at screening or admission

l) Any acute or chronic medical illness considered clinically significant by the investigator

m) Donation of blood to a blood bank or in a clinical study (except a screening visit) within 4 weeks of study enrollment (within 2 weeks for plasma only)

n) Blood transfusion within 4 weeks of study enrollment

o) Evidence of current SARS-CoV-2 infection

p) Suspected or confirmed history of SARS-CoV-2 infection within 12 weeks prior to signing consent or people with a history of the infection who have not fully recovered weeks or even months after first experiencing symptoms, so called “long COVID”.

q) History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory, neurological or psychiatric disorder, as judged by the investigator

r) History of cholecystectomy or gall stones

6) Reproductive Status

a) Women who are of childbearing potential. All women must have a negative urine pregnancy test at screening and admission

7) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7: Concomitant Therapy

b) Prior exposure to or allergy to milvexian and/or allergy to its excipients (Study CV010020 [QCL118141])

c) Use within 2 weeks prior to dosing of study drug: non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants and any other drug or agent known to increase the risk for bleeding

d) Exposure to any investigational drug within 90 days prior to first milvexian administration

e) Participants who are taking, or have taken, any prescribed or over-the-counter drug (other than ≤4 g of paracetamol per day on an as-needed basis or hormone replacement therapy [HRT]) or herbal remedies in the 14 days before study treatment administration (See

Section 7.7). Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as agreed by the investigator and cleared by the BMS Medical Monitor.

8) 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

b) Any of 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) QTcF ≥ 450 msec

c) Positive urine screen for drugs of abuse

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

e) A confirmed positive alcohol breath test at screening or admission

f) Any other 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). Participants with Gilbert's Syndrome are allowed

9) Allergies and Adverse Drug Reaction

a) History of allergy to FXIa inhibitors or related compounds

b) History of any drug allergy considered clinically significant by the investigator. Hay fever is allowed unless it is active

10) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and Bristol Myers Squibb (BMS) approval is required.)

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

c) Participants who are sponsor or study site employees, or immediate family members of a study site or sponsor employee

d) Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017,[12] shall participate in the study

e) Participants who have been administered investigational product (IP) in an ADME study in the last 12 months

f) Failure to satisfy the investigator of fitness to participate for any other reason

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

The following criteria will be re-assessed at admission: 5)g), b), 5)l), 5)o), 6)a), 7)c), 7)e), 8)b), 8)c), 8)e), 8)f), 9)b), 6)b) and 6)f).

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 below are not exclusion criteria; if noncompliance occurs, following discussion between the investigator and medical monitor, a protocol deviation will be completed and the participant will be allowed to participate in the study.

6.3.1 Meals and Dietary Restrictions

11) Eligible participants will be admitted to the clinical facility on the morning of Day [redacted] of Treatment Period [redacted] and will fast overnight for a minimum of 10 hours. Participants will be confined at the study site through 72 hours (to morning of Day [redacted]) post final IP dose in Treatment Period [redacted]. Standardized meals will be served throughout the confinement portion of the study and should be the same for every treatment period (except for the high-fat meal which is only served in 2 of the treatment periods).

1) Participants should fast (nothing to eat or drink except water) for at least 10 hours prior to collection of specimens for scheduled clinical laboratory tests.

12) Fasting Requirements:

   a) On the evening prior to dosing the fasted regimens, participants will be provided with a light snack and will then be required to fast (nothing to eat or drink except water) from 10 hours prior to administration of study treatment. Participants must not drink water from 1 hour before until 1 hour after administration of study treatment except water provided to take study treatment. Water may be consumed ad libitum at other times. Decaffeinated fluids will be allowed ad libitum from lunch time (approximately 4 hours after study treatment administration).

   b) On Day [redacted] (dosing day), a standard lunch will be served approximately 4 hours post dose. A standard evening meal will be served approximately 10 hours post dose, and an evening snack at approximately 14 hours post dose. The percentage of food consumed and timing of meals will be recorded for all Day [redacted] meals. Meals will be provided to participants at standardized times on non-dosing days.

13) Fed Dosing: Two regimens will be dosed in the fed state, following a high-fat breakfast.

   a) On the evening prior to dosing the fed regimen, participants will be provided with a light snack and will fast from all food and drink (except water) for a minimum of 10 hours prior to administration of study treatment until the following morning, when they will be provided with a high-fat breakfast.

   b) Participants must not drink water from 1 hour before until 1 hour after administration of study treatment except water provided to take study treatment and fluids given with the high-fat meal. Water may be consumed ad libitum from 1 hour after administration of study

treatment. Decaffeinated fluids will be allowed ad libitum from lunch time (approximately 4 hours after administration of study treatment).

c) The meal (high fat) should be consumed over a maximum period of 25 minutes, with dosing occurring 30 minutes after the start of the meal. Participants should be encouraged to eat their meal evenly over the 25-minute period. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 minutes after the start of the meal. Participants must consume 100% of the predose meal in order to be eligible for dosing.

14) The acceptable deviation for the predose meal from the nominal dosing time point is:

15) The meal will be administered ± 5 minutes of the nominal time point

a) A standardized lunch will be provided at approximately 4 hours post dose, a standardized evening meal at approximately 10 hours post dose and a standardized evening snack at approximately 14 hours post dose. The percentage of food consumed and timing of meals will be recorded for all Day [redacted] meals. Meals will be provided to participants at standardized times on non-dosing days.

6.3.2 Other Dietary Restrictions

- Participants are not permitted to consume any nutrients known to modulate cytochrome p-450 (CYP) enzyme activity (eg, grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) from 48 hours prior to admission until after discharge from the clinical unit.
- Participants are not permitted to consume food containing poppy seeds for 48 hours prior to screening and for 48 hours prior to admission until after discharge from the clinical unit.

6.3.3 Caffeine, Alcohol and Tobacco

- During the study, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours prior to admission until discharge from the study.
- During the study, participants will abstain from alcohol for 24 hours prior to screening and the 24 hours prior to admission until discharge from the study.
- Participants are not permitted to smoke or use electronic cigarettes or any nicotine-containing products within 12 months prior to screening until discharge from the study.

6.3.4 Activity

- Participants are to refrain from strenuous exercise and contact sports from at least 72 hours before the screening visit and then from 72 hours prior to admission until discharge from the study.
- Must not donate blood or plasma (outside of this study), within 4 weeks of study enrollment throughout the study duration, and for at least 90 days following last dose of study medication

6.4 Screen Failures

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

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

6.4.1 Retesting During Screening or Lead-in Period

Participant Re-enrollment: This study does not permit the re-enrollment of a participant who has discontinued the study as a pretreatment failure.

Retesting of laboratory parameters and/or other assessments within any single Screening will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to randomization 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 included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

6.4.2 Activity

- Participants are to refrain from strenuous exercise and contact sports from at least 72 hours before the screening visit and then from 72 hours prior to admission until discharge from the study.
- Must not donate blood or plasma (outside of this study), from screening throughout the study duration, and for at least 90 days following last dose of study medication

7 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

Study intervention includes IP as indicated in Table 7.1-1.

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

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

7.1 Study Interventions Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Study Interventions

Intervention Name	BMS-986177 oral solution [redacted] mg	BMS-986177 SDD capsules, [redacted] mg	[^{14}C]BMS-986177 Solution for Infusion [redacted] µg/mL (NMT [redacted] kBq/[redacted] mL)
Dose Formulation	Solution	SDD Capsules	Solution for IV infusion
Unit Dose Strength(s)	[redacted] mg/mL	[redacted] mg	[redacted] µg/mL
Dosage Level(s)	[redacted] mg [redacted] dose	[redacted] mg [redacted] dose AND [redacted] mg [redacted] dose (as [redacted] × [redacted] mg capsules)	[redacted] µg [redacted] dose
Route of Administration	Oral, fasted	Oral, fasted AND fed	IV infusion, fasted
Sourcing	Prepared by the trial site	Provided centrally by the Sponsor	Prepared by the trial site
Packaging and Labeling	The oral solution will be provided in bulk container. Each bulk container will be labeled as required per country requirement.	Study intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement	Study intervention will be provided in a bulk container. Each bulk container will be labeled as required per country requirement

In the morning of Treatment Period [redacted], Day [redacted], after fasting for at least 10 hours, each participant will receive a [redacted] oral dose of milvexian oral solution, which will be followed by appropriate rinses and additional water, for a total volume of 240 mL. The time of dose administration will be called "0" hour. At 1 hour post dose (approximately Tmax), participants will receive an IV microdose of [^{14}C]milvexian solution for infusion over 15 minutes.

For IV dosing only: the IV dose will be infused over approximately 15 minutes. This infusion will be in the opposite arm being used for PK sampling.

To assess tolerability of the IV administration, the first participant will be dosed at least 30 minutes prior to dosing the second participant. All subsequent dosing of the IV formulation will be staggered by at least 15 minutes. To allow for potential interruptions and pump variations, up to a 20% difference in duration of the infusion will not be considered a protocol deviation provided the full planned dosed is administered as these minor discrepancies should not have a significant impact on the overall study objectives.

The planned infusion time will be 15 minutes; the actual infusion start and stop time will be recorded in the source.

- The infusion will finish within ± 3 minutes of the nominal time point

For Treatment Periods [redacted], in the morning on Day [redacted], after fasting for at least 10 hours or following a standardized high-fat meal, each participant will receive a [redacted] oral dose of milvexian as SDD capsule(s).

At the time of dosing, 240 mL of water will be administered to the participant along with his/her oral 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.

7.2 Method of Study Intervention Assignment

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001 (eg, 00001, 00002, 00003...). Those enrolled participants meeting inclusion and not meeting exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing in Treatment Period [redacted]. The allocation for Treatment Period [redacted] will be fixed with all participants to receive the [redacted] mg oral solution and the [redacted] µg microdose in Treatment Period [redacted].

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 treatment. If a participant is replaced after dosing, then the replacement participant will be assigned the original participant's number plus 100. The replacement participant will be assigned to the same treatment sequence and will receive all the same treatments as the participant being replaced, but a new randomization number will be assigned to him/her. For example, Participant 00004 would be replaced by Participant 00104.

Up to 4 replacement participants may be enrolled into the study. The maximum number of participants that may be dosed is 20, including any replacements.

7.3 Blinding

This is a randomized open-label study. It has been determined that blinding is not required to meet study objectives. Blinding procedures are not applicable and access to treatment assignment information is unrestricted.

7.4 Dosage Modification

Not applicable for this Phase 1 study.

7.5 Preparation/Handling/Storage/Accountability

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

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If

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

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

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

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the APPENDIX 2.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

7.6 Treatment Compliance

The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Study intervention will be administered in the clinical facility. After administration of milvexian, an examination of the oral cavity is required to verify that a participant has swallowed the capsule/solution. When multiple capsules are administered as part of a [redacted] dose, the mouth check should be performed after the final capsule has been taken. The participant should drink the entire aliquot of water given to swallow the capsules.

The IV microdose will be administered by trained staff to ensure dosing compliance.

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 prior to study intervention administration must be recorded on the CRF. Any past vaccinations for SARS-CoV-2 should also be recorded on the CRF.

- Prior exposure to milvexian.
- Exposure to any investigational drug or placebo within 90 days of study intervention administration.

- Exposure to IP in an ADME study in the previous 12 months
- Use of any prescription drugs or over-the-counter medications within 14 days prior to study intervention administration, except those medications cleared by the investigator and the BMS Medical Monitor.
- Use of any other drugs, including over-the-counter medications drug (other than 4 g of paracetamol per day on an as needed basis or HRT) and herbal remedies, within 14 days prior to study intervention administration, except those medications cleared by the investigator and the BMS Medical Monitor.

No concomitant medications (prescription, over-the-counter, or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

Approved (including health authority conditional marketing authorization) COVID-19 vaccines, eg killed, inactivated, peptide, DNA and RNA vaccines, may be permitted before enrollment according to the investigator's discretion and as per local guidance

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

At the end of the study, BMS will not continue to provide BMS-supplied study intervention to participants as this is a healthy volunteer study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention

Participants MUST discontinue IP for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Significant noncompliance with protocol (eg, procedures, assessments, medications). The investigator should discuss such issues with the Medical Monitor.
- Pregnancy
- Any current evidence of SARS-CoV-2 infection
- Overt bleeding producing a hemoglobin decrease ≥ 2 g/dL in 24 hours

- Any overt bleeding deemed by the investigator to necessitate discontinuation of study medication
- aPTT values 5× Admission value, confirmed by repeat evaluation and if any bleeding is detected
- alanine aminotransferase (ALT) > 3 × ULN (confirmed following a repeat ALT blood test)
- QTc interval of > 500 msec or increase in QTc interval of > 60 msec from baseline (confirmed by repeat ECG)
- Bleeding that persists despite application of pressure for at least 15 minutes or cold compresses
- Need for treatment with a strong CYP3A4/P-gp inhibitor or any CYP3A4/P-gp inducer
- At the discretion of the investigator for any other reason

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

All participants who discontinue study intervention should comply with protocol-specified discharge and follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures, including post treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the 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 Stopping Criteria

The study will be halted, and the risk to other participants evaluated if any of the following criteria are met:

- A serious adverse reaction (ie, a SAE considered at least possibly related to the IP administration) in 1 participant.
- Severe nonserious adverse reactions (ie, severe nonserious AEs considered as, at least possibly related to the IP administration) in 2 participants in the same cohort, independent of within or not within the same system organ class.

Relatedness to IP will be determined by the investigator.

If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

The ARSAC Practitioner will also be informed of the temporary halt.

8.1.2 Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the sponsor and investigator without consultation with the MHRA, EC, ARSAC practitioner or ARSAC. Notification of early termination must be provided to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of any follow-up measures taken for safety reasons if applicable, will also be provided. The ARSAC Practitioner and ARSAC will also be notified within an appropriate timeframe.

If the study is abandoned prior to commencement of any protocol activities, the investigator or sponsor must notify the EC, MHRA, ARSAC practitioner and ARSAC (if ARSAC research application has been submitted or approved) in writing outlining the reasons for abandonment of the trial.

Once exposure to dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study:

- The occurrence of serious or severe AEs, as defined in APPENDIX 3, if considered to be related to the IP, as defined in APPENDIX 3.
- New information regarding the safety of the IP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

If any of the above occurs, the study will be terminated if careful review of the overall risk/benefit analysis described in Section 3.3 demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances, termination can only take place with the agreement of the investigator and sponsor. The MHRA, EC, ARSAC practitioner and ARSAC will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator, sponsor and ARSAC practitioner (where discussion is related to administration of radiation). Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

8.1.3 Post-study Intervention Study Follow-up

Participants who discontinue study intervention may continue to be followed (also see Section 8.1).

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is

when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

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

8.2.1 Individual Discontinuation Criteria

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

8.3 Lost to Follow-up

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

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

- If the investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- 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 randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 550 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Efficacy Assessments

Not applicable to this Phase 1 study.

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 Time Period and Frequency for Collecting AE and SAE Information

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 30 days following discontinuation of dosing. Nonserious AEs will be recorded until the follow up call.

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 judgement 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 abnormalities that are reported/identified during the course of 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 and [redacted] 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities, ethics committees and ARSAC, as appropriate, according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of AEs that is believed to be related to an IMP and is both unexpected (ie the nature or severity is not expected from the information provided in the IB) and serious; and must be reported to the appropriate regulatory authorities, EC and investigators following local and global guidelines and requirements.

The ARSAC Practitioner will be notified of any SUSAR that is considered related to the exposure to radioactivity.

9.2.5 Reporting of COVID-19 Vaccine-Related Adverse Events

AEs considered by the investigator to be related to COVID-19 vaccines will be reported to the MHRA via the Yellow Card system.

9.2.6 Pregnancy

Not applicable for WNOCBP - Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Any pregnancy that occurs in a female participant or a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from a female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE eCRF, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

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

9.2.8 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory 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).

Potential DILI is defined as:

- Aminotransferase (ALT or aspartate aminotransferase [AST]) elevation > 3 times upper limit of normal (ULN)

  AND

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

  AND

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

9.2.9 Other Safety Considerations

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

9.3 Overdose

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 SAE will be reported as an SAE (see APPENDIX 3).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities. A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines[13], each participant will receive a card stating the telephone number of the investigator and the 24/7 contact details of the [redacted] on-call physician.

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

Physical examinations may be performed by a physician.

Physical examinations will include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular system, lungs, abdominal, extremities, skin, and musculoskeletal system.

If the screening physical examination is performed within 48 hours prior to Treatment Period [redacted] Day [redacted], then a single examination may count as both the screening and admission evaluation.

A targeted (symptom-driven) physical examination may be performed the discretion of the investigator or sub-investigator, see Section 2.

All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

Documentation of who performed the examination is to be recorded in source notes.

9.4.2 Vital signs

Refer to Schedule of Activities (Section 2).

Vital signs will include oral body temperature, respiratory rate, systolic and diastolic blood pressure, and heart rate (HR); all measurements should be taken after the participant has been supine for at least 5 minutes.

9.4.3 Electrocardiograms

Refer to Schedule of Activities (Section 2).

Single ECG readings should be recorded after the participant has been supine for at least 5 minutes. ECG parameters QTcF, QRS, QT interval, PR interval, HR and QRS axis will be collected on the CRF.

In the event that multiple procedures are required at a single time point, ECG assessments will be collected prior to PK sample collection. In addition, vital signs should be taken prior to ECGs when both measurements are scheduled at the same time point, with a 5 minute rest period between vital signs assessment and ECG assessment.

9.4.4 Clinical Safety Laboratory Assessments

A central laboratory will perform the analyses and will provide reference ranges for these tests. Details on clinical safety laboratory sample collection, labeling, processing, storage, and shipment will be provided in the laboratory/procedure manual.

Results of clinical laboratory tests performed on Day [redacted] of Treatment Period [redacted] must be available prior to dosing.

The schedule for collection of samples for each assessment is provided in Section 2. Laboratory assessments to be conducted during the study are listed in Table 9.4.4-1.

- Investigators must document their review of each laboratory safety report.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
• Hemoglobin • Hematocrit (PCV) • Platelet count • MCH • MCHC • MCV • Red blood cell count	• Basophils • Eosinophils • Monocytes • Neutrophils • WBC Count • Lymphocytes
Coagulation	
• PT • aPTT • INR	
Chemistry	
• Aspartate aminotransferase • Alanine aminotransferase • Total bilirubin • Direct bilirubin (only required if total is >ULN) • Alkaline phosphatase (as reflex test if ALT > ULN)	• Total protein • Albumin • Sodium • Potassium • Chloride • Calcium

Table 9.4.4-1: Clinical Laboratory Assessments

• Gamma-glutamyl transferase (as reflex test if ALT > ULN) • Lactate dehydrogenase (as reflex test if ALT > ULN) • Creatinine • Blood urea nitrogen • Uric acid • Fasting glucose	• Magnesium (as reflex test if calcium < lower limit of normal or > ULN) • Phosphorus (as reflex test if calcium < lower limit of normal or > ULN) • Creatine kinase
Urinalysis	
• Protein • Glucose • Blood • Leukocytes • Specific gravity • Microscopic or microbiological examination at the discretion of the investigator based on urinalysis results	• Bilirubin • Ketones • Nitrites • Urobilinogen • pH
Serology (at screening only)	
• hepatitis C antibody • hepatitis B surface antigen • HIV-1 and -2 antibody	• if required: SARS-CoV-2 Antibody • if required: SARS-CoV-2 Antigen
Other Analyses	
Test for drugs of abuse (urine) • Amphetamines • Barbiturates • Benzodiazepines • Cocaine • Marijuana/Cannabis • Methadone • Methamphetamine/Ecstasy • Morphine/Opiates • Phencyclidine • Tricyclic Antidepressants • • Cotinine	• Alcohol breath test (screening and admission on Day [redacted] of Treatment Period [redacted]) • Follicle stimulating hormone (screening only for women only to confirm postmenopausal status) • Urine pregnancy test (women only: screening and admission)

Abbreviations: MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; PCV, packed cell volume; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell.

9.4.5 Physical Measurements

Physical measurements including height, weight and BMI will be performed at screening (Section 2).

Measurement of height should be performed with the participant's shoes removed, pockets emptied and no overcoat. The participant's knees should be straightened, head held erect, and eyes forward. Weight must be recorded using a calibrated scale.

BMI is a method of defining normal body weight and excess body fat. Method of BMI calculation is as follows:

- Use actual height and weight
  - To calculate BMI:
    - BMI = weight (kg)/(height [m])^2
    - Round to 1 decimal place (if 0.05 or greater, round up)

The BMI calculation is used for assessment for inclusion. All analysis calculations for BMI will be derived internally using the weight and height at the specified time point or the most recent height measurement (if not applicable).

9.5 Pharmacokinetics

Pharmacokinetics of milvexian and [^{14}C] milvexian, as applicable, will be derived from plasma concentration vs time and urinary excretion data. The pharmacokinetic parameters to be assessed include:

F	Absolute oral bioavailability (oral versus IV)
Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma 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 concentration-time curve from time zero extrapolated to infinity
Ae	Amount of unchanged drug excreted into the urine
%UR	Percent urinary recovery
T-HALF	Terminal plasma half-life
CLT	Total clearance
CLT/F	Apparent clearance of drug after extravascular administration
CLR	Renal clearance

Frel	Relative bioavailability based on Cmax, AUC(0-T) and AUC(INF)
MRT	Mean residence time
Vss	Volume of distribution at steady state
Vz	Volume of distribution of terminal phase
Vz/F	Apparent volume of distribution at terminal phase after extravascular administration

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.

Table 9.5-1Table 9.5-2ist the sampling schedules to be followed for the assessment of pharmacokinetics in the plasma and urine, respectively.

Table 9.5-1: Pharmacokinetic Plasma Sampling Schedule for Milvexian Treatment Periods [redacted])

Study Day of Sample Collection	Event	Time (Relative To Milvexian Dose/Oral Dose) Hour:Min	Milvexian Blood Sample (for LC-MS/MS analysis)	[^{14}C]Milvexian Blood Sample (for AMS analysis)[a]
[redacted]	Predose	00:00	X	X
	Post dose	00:30	X	
	Post dose/SOI	01:00[b]	X	
	Post dose	01:05[a]		X
	Post dose	01:10[a]		X
	Post dose/EOI	01:15	X	X[c]
	Post dose	01:20[a]		X
	Post dose	01:30	X	X
	Post dose	01:45[a]		X
	Post dose	02:00	X	X
	Post dose	03:00	X	X
	Post dose	04:00	X	X
	Post dose	05:00	X	X
	Post dose	06:00	X	X
	Post dose	08:00	X	X
	Post dose	10:00	X	X
	Post dose	12:00	X	X
	Post dose	14:00	X	X
	Post dose	18:00	X	X

Table 9.5-1: Pharmacokinetic Plasma Sampling Schedule for Milvexian Treatment Periods [redacted])

Study Day of Sample Collection	Event	Time (Relative To Milvexian Dose/Oral Dose) Hour:Min	Milvexian Blood Sample (for LC-MS/MS analysis)	[^{14}C]Milvexian Blood Sample (for AMS analysis)[a]
[redacted]	Post dose	24:00	X	X
	Post dose	36:00	X	X
	Post dose	48:00	X	X
	Post dose	72:00[d]	X	X

AMS: accelerator mass spectrometry; EOI: End of infusion; LC-MS/MS: liquid chromatography mass spectrometry/mass spectrometry; SOI: Start of infusion

[a] Treatment Period [redacted] (IV microdose regimen) only.

[b] The SOI blood sample for LC-MS/MS analysis will be taken prior to administration of the microdose.

[c] This sample should be taken immediately after stopping the IV infusion. If the end of infusion is delayed, the collection of this sample should also be delayed.

[d] Where Day [redacted] of a treatment period coincides with the 72 hour time point of the previous treatment period, only a single predose/72 hour post dose sample is required.

Table 9.5-2: Pharmacokinetic Urine Sampling Schedule for Milvexian (Treatment Periods [redacted])

Study Day of Sample Collection	Event	Time (Relative To Milvexian Dose/Oral Dose) Hour:Min	Milvexian Urine Sample (for LC-MS/MS analysis)
[redacted]	Predose[a]	00:00	X
	0 to 6 h	06:00	X
	6 to 12 h	12:00	X
	12 to 24 h	24:00	X
	24 to 36 h	36:00	X
	36 to 48 h	48:00	X
	48 to 72 h	72:00[b]	X

[a] A single urine sample will be taken at predose (or the first void of the day).

[b] Where Day [redacted] of a treatment period coincides with the 72 hour time point of the previous period, only a single 72 hour post dose collection is required.

All on-treatment timepoints are intended to align with days on which study intervention is administered. If it is known that a dose is going to be delayed, then the predose sample for milvexian, if appropriate, should be collected just prior to the delayed dose. However, if a predose milvexian sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. Blood samples should be drawn from a site other than the infusion site (ie,

contralateral arm) on days of infusion. If the infusion was interrupted, the interruption details will also be documented on the CRF. Further details of the PK blood and urine sample collection, labeling, processing, storage, and shipment will be provided in the laboratory/procedure manual.

The plasma samples will be analyzed for milvexian by a validated liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) assay or by a qualified accelerator mass spectrometry (AMS) assay (analyzed according to the PK sampling schedule described in Table 9.5-1). Milvexian in urine will be analyzed by a validated LC-MS/MS assay.

Bioanalytical samples designated for assessments from the same collection time point may be used interchangeably for analyses, if needed.

9.6 Immunogenicity Assessments

Not applicable.

9.7 Genetics

Not applicable.

[redacted]

9.9 Additional Research

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

9.10 Other Assessments

Not applicable.

9.11 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

Sample size determination is based on consideration of the precision of the estimate of the geometric mean ratios (GMR) of Cmax and AUCs of milvexian between test and reference treatments. With 13 evaluable participants, there will be an 80% probability that the 90% confidence interval (CI) of GMR will be within 80% and 125% of the point estimate. The precision estimate is based on the assumptions that Cmax and AUCs of milvexian are log-normally distributed with intra-subject coefficient of variation (CV) of no greater than 28.3%. [redacted]

[redacted]

A sample size of 16 participants to achieve 13 evaluable participants is considered appropriate to meet the objectives of the study.

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
Treated	All participants who received at least 1 dose of study intervention. This population will be used for the safety analyses
PK	All randomized participants who receive at least 1 dose of study drug and have any available concentration-time data
Evaluable PK	The Evaluable PK Population includes all participants in the PK Population with adequate PK profiles for accurate estimation of PK parameters

10.4 Statistical Analyses

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

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

10.4.1 Primary Endpoint

Pharmacokinetic results will be listed for the PK Population; descriptive summary statistics will use the Evaluable PK Population

Table 10.4.1-1: Primary Endpoint

Primary Endpoint	Description	Timeframe
Pharmacokinetics – F	Absolute oral bioavailability (F) for each treatment will be summarized, and descriptive statistics and 90% CI for F will be presented	Following [redacted] oral dose on [redacted] separate occasions and a [redacted] oral dose followed by an IV injection on a [redacted] occasion (i.e., Day [redacted] of Period [redacted])

10.4.2 Secondary Endpoints

Table 10.4.2-1: Secondary Endpoints

Secondary Endpoint	Description	Timeframe
Pharmacokinetics – Cmax, Tmax, AUC(0-T), AUC(INF), CLT or CLT/F, CLR, Vz or Vz/F, Ae, %UR, T-HALF, for each treatment	Summary statistics by treatment will be tabulated for plasma concentrations and PK parameters of milvexian and [^{14}C]milvexian, as applicable. Geometric means and coefficients of variation (CV%) will be presented for Cmax, AUC(0-T), AUC(INF), CLT or CLT/F, CLR, Vz or Vz/F, Ae, %UR. Medians and ranges will be presented for Tmax. Means and standard deviations (SDs) will be presented for T-HALF.	Following [redacted] oral dose on [redacted] separate occasions and a [redacted] oral dose followed by an IV injection on a single occasion (i.e., Day [redacted] of Period [redacted])
Pharmacokinetics – MRT and Vss of [^{14}C]milvexian following an IV dose	Summary statistics by treatment will be tabulated for plasma concentrations and PK parameters of ^{14}C]milvexian. Geometric means and coefficients of variation (CV%) will be presented for MRT and Vss.	Following [redacted] oral dose on [redacted] separate occasions and a [redacted] oral dose followed by an IV injection on a [redacted] occasion (i.e., Day [redacted] of Period [redacted])
Pharmacokinetics – Frel for each SDD capsule treatment vs oral solution formulation	Point estimates and 90% CI for the ratio of geometric means for Cmax, AUC(0-T) and AUC(INF) will be constructed for the comparison of: • each milvexian capsule treatment separately versus [redacted] mg oral solution A linear mixed-effect model will be used on log transformed data with treatment and period as fixed effects, and measurements within each participant as repeated measures.	Following [redacted] oral dose on [redacted] separate occasions and a [redacted] oral dose followed by an IV injection on a [redacted] occasion (i.e., Day [redacted] of Period [redacted])
Pharmacokinetics – Food effect with [redacted] mg and [redacted] mg SDD capsules based on ratios of Cmax, AUC(0-T), and AUC(INF)	Point estimates and 90% CI for the ratio of geometric means for Cmax, AUC(0-T) and AUC(INF) will be constructed for the comparison of: • [redacted] mg SDD fed versus [redacted] mg SDD fasted • [redacted] mg SDD fed versus [redacted] mg SDD fasted A linear mixed-effect model will be used on log transformed data with treatment and period as fixed effects, and measurements within each subject as repeated measures.	Following [redacted] oral dose on [redacted] separate occasions and a [redacted] oral dose followed by an IV injection on a [redacted] occasion (i.e., Day [redacted] of Period [redacted])

Table 10.4.2-1: Secondary Endpoints

Secondary Endpoint	Description	Timeframe
Safety – Occurrence of AEs and SAEs, abnormalities in vital sign measurements exceeding pre-defined thresholds, findings on ECGs and physical examinations, and abnormalities in clinical laboratory tests	All recorded SAEs and AEs will be listed and tabulated by system organ class, preferred term and treatment. Adverse events leading to discontinuation will be listed. All nonserious AEs reported up to the follow up call will be included in - the AE summary tables. Any abnormal physical examination findings will be listed. Vital signs and clinical laboratory test results will be listed. The frequency of marked abnormalities in clinical laboratory test results will also be tabulated by treatment. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed.	Following [redacted] oral dose on [redacted] separate occasions and a [redacted] oral dose followed by an IV injection on a [redacted] occasion (i.e., Day [redacted] of Period [redacted])

10.4.3 Exploratory Endpoint(s)

Not applicable.

10.4.4 Other Safety Analysis

Not applicable.

10.4.5 Other Analyses

Not applicable.

10.5 Interim Analyses

Not applicable.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
Ae	Amount of unchanged drug excreted into the urine
ALT	alanine aminotransferase
AMS	accelerator mass spectrometry
aPTT	activated partial thromboplastin time
ARSAC	Administration of Radioactive Substances Advisory Committee
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinity
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
[redacted]	[redacted]
BMI	body mass index
BMS	Bristol Myers Squibb
CI	confidence interval
CLR	renal clearance
CLT	total clearance
CLT/F	apparent clearance of drug after extravascular administration
Cmax	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
[redacted]	[redacted]
CV	coefficient of variation
CYP	cytochrome P450
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic Case Report Form
F	absolute oral bioavailability (oral versus IV)
FIH	first-in-human
FSH	follicle-stimulating hormone
Frel	Relative bioavailability
FXa	factor Xa

Term	Definition
FXI	factor XI
FX1a	factor XIa
GI	gastrointestinal
GMR	geometric mean ratios
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IP	Investigational Product
INR	international normalized ratio
IV	intravenous
MRT	Mean residence time
N/A	not applicable
NMT	not more than
PK	pharmacokinetic
QD	quaque die, once daily
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDD	spray-dried dispersion
T-HALF	Terminal plasma half-life
Tmax	time of maximum observed plasma concentration
%UR	percent urinary recovery
Vss	Volume of distribution at steady state
Vz	volume of distribution of terminal phase
Vz/F	Apparent volume of distribution at terminal phase after extravascular administration
WNOCBP	women **not** of childbearing potential
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one 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 Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

ADMINISTRATION OF RADIATION

[redacted] will be the Principal Investigator and the ARSAC practitioner for this study, which includes the administration of radiation at [redacted]. Administration will be conducted in accordance with [redacted] current ARSAC practitioner license and [redacted] current ARSAC Employer license. Additionally a research application will be submitted to ARSAC to obtain approval for the conduct of the study before dosing.

Dosimetry will be calculated in accordance with the current approved ARSAC Employer License Application for [redacted] and the current Practitioner License for [redacted].

The protocol will be reviewed and the final version will be approved by the ARSAC practitioner [redacted].

Any amendments relating to the administration of radioactive substances will be reviewed by the ARSAC practitioner prior to submission to ARSAC as required by the current ARSAC Notes for Guidance.[14] The ARSAC practitioner will also be notified of any substantial amendments to the PIS and ICF and/or protocol.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant 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.

SOURCE DOCUMENTS

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

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

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in the Source Document ID List.

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

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

STUDY INTERVENTION RECORDS

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

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

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

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the 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 abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be

reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

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

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

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

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

MONITORING

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.

RETURN OF STUDY TREATMENT

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

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

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

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

- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE START AND CLOSURE

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

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

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

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

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

DISSEMINATION OF CLINICAL STUDY DATA

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year [6 months for studies including pediatric population] of the end of trial in EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

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

For 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 Clinical Trial Agreement (CTAg) governing [study site or investigator]

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

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious 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 NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.8 for the definition of potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.6 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 one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

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

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

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

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

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: [redacted]

SAE Fax Number: [redacted]

SAE Telephone Contact (required for SAE and pregnancy reporting): [redacted].

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

- Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c]
- Bilateral tubal occlusion.

- Vasectomized partner

Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.

- Sexual abstinence.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. 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.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

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

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED 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 WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.6 and Appendix 3.