# CLINICAL STUDY PROTOCOL

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|---|---|
| **Protocol Title:** | A Phase 1, Open-label, Single-dose, Randomized Crossover Study to Evaluate the Relative Bioavailability of Two Different Capsule Formulations of Sitravatinib in Healthy Subjects |
| **Protocol Number:** | BGB-Sitravatinib-101 |
| **Phase:** | Relative Bioavailability Study |
| **Investigational Product(s):** | Sitravatinib |
| **Sponsor:** | BeiGene, Ltd.<br>c/o BeiGene AUS Pty. Ltd.<br>1C/528 Compton Road,<br>Stretton, Queensland 4116,<br>Australia |
| **Sponsor Medical Monitor:** | [redacted]<br>Telephone: [redacted]<br>Email: [redacted] |
| **Original Protocol** | 03 June 2020 |
| **Amendment 1.0** | 12 July 2020 |





NCT04472650

# FINAL PROTOCOL APPROVAL SHEET

A Phase 1, Open-label, Single-dose, Randomized Crossover Study to Evaluate the Relative Bioavailability of Two Different Capsule Formulations of Sitravatinib in Healthy Subjects

**BeiGene Ltd., Approval:**

[redacted]

13 July 2020

Date

12 JULY 2020

Date

# INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 1, Open-label, Single-dose, Randomized Crossover Study to Evaluate the Relative Bioavailability of Two Different Capsule Formulations of Sitravatinib in Healthy Subjects

Protocol Identifier: BGB-Sitravatinib-101

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, that I understand it, and that I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

**Instructions for Investigator:** Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

## Protocol Amendment 1.0 (12 July 2020)

The main purpose of this amendment is to improve the feasibility of study execution.

| Applicable Section | Description of Revision |
|---|---|
| **Change:** | **Updated the title in approval sheet, signature page, and synopsis** |
| **Reason:** | **To keep consistent.** |
| Approval sheet, signature page and synopsis: title | Added "Randomized" in the title to keep consistent with title page. |
| **Change:** | **Clarified the rule for subject identification number** |
| **Reason:** | **To be more accurate.** |
| Section 4.3: Subject Number and identification | Revised the wording to be more accurate for the subject identification number at screening period and after randomization. |
| **Change:** | **Revised the assessment schedule of COVID-19 test** |
| **Reason:** | **To simplify the study procedures.** |
| Appendix 2<br><br>Appendix 6 | • Moved COVID-19 swab collection & analysis from category of "Serology" to "SARS-CoV-2 test"<br>• Added a line for "COVID-19 swab collection & analysis" |
| **Change:** | **Clarified the allowed time window for PK sampling** |
| **Reason:** | **To be more accurate.** |
| Appendix 6 | Revised the footnote "b" to clarify the allowed time window for 12hr post-dose timepoint to be ±2 minutes |

# TABLE OF CONTENTS

## LIST OF TABLES

# SYNOPSIS

**Name of Sponsor/Company:** BeiGene Ltd.

**Investigational Product:** Sitravatinib

**Title of Study:** A Phase 1, Open-label, Single-dose, Randomized Crossover Study to Evaluate the Relative Bioavailability of Two Different Capsule Formulations of Sitravatinib in Healthy Subjects

**Protocol Identifier:** BGB-Sitravatinib-101

**Phase of Development:** Relative Bioavailability Study

**Number of Subjects:** Up to 26 healthy subjects in total (include ≥16 Asian subjects)

**Study Centers:**
1 center in Australia

**Study Objectives:**

**Primary:**

- To investigate the relative bioavailability and pharmacokinetics (PK) of sitravatinib free base and malate salt capsule formulations following oral administration in healthy subjects.

**Secondary**:

- To assess the safety and tolerability of single-dose free base and malate salt capsule formulations of sitravatinib in healthy subjects.

**Study Endpoints:**

**Primary:**

- The primary PK parameters will include area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the last quantifiable concentration ($AUC_{0-t}$) and maximum observed plasma concentration ($C_{max}$). Other PK variables will be assessed for description purposes.

**Secondary:**

- Safety endpoints for this study include adverse events, clinical laboratory evaluations, 12-lead electrocardiograms, vital sign measurements, and physical examinations.

**Study design:**

This will be a Phase 1, open-label study using a 2-period crossover design to compare the bioavailability and PK of the free base formulation at 120 mg and the malate salt capsule formulation at 100 mg after a single oral administration to healthy male subjects. Subjects will be randomized into 2 dosing sequences and will participate in 2 dosing periods as shown below. The minimum washout period between dose administrations will be 14 days.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. In Periods 1 and 2, subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and will stay in the CRU until discharge on Day 4. In each period, subjects will attend a nonresidential visit on Day 8 for PK (168 hours postdose) sampling. A poststudy assessment will be performed on Day 8 of Period 2. Subjects will receive a Follow-up phone call on Days 13 to 15 of Period 2.

| Dosing sequence | Period 1 | Washout (minimum) | Period 2 |
|---|---|---|---|
| 1<br>N=13 | 120 mg sitravatinib free base capsule | 14 days | 100 mg sitravatinib malate salt capsule |
| 2<br>N=13 | 100 mg sitravatinib malate salt capsule | 14 days | 120 mg sitravatinib free base capsule |

N: number of subjects

**Diagnosis and main criteria for inclusion:**

Healthy male subjects aged between 18 and 55 years (inclusive) with a body mass index between 18.0 and 32.0 kg/$m^2$ (inclusive).

**Investigational products, dose, and mode of administration:**

120 mg sitravatinib free base formulation given orally as 3 × 40-mg capsules after an overnight fast period.

100 mg sitravatinib malate salt capsule formulation given orally as 2 × 50-mg capsules after an overnight fast period.

**Duration of subject participation in the study:**

Planned Screening duration: approximately 4 weeks.

Planned study duration (Screening to Follow-up phone call): up to approximately 8 weeks.

**Blood Sampling Timepoints**

Blood samples for PK analysis will be collected at the following time points: predose (within 30 minutes before administration of sitravatinib), 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 168 hours after dose in each period. A total of 12 samples will be collected from each subject in one period.

**Statistical methods:**

**Pharmacokinetics**

The primary PK parameters are $AUC_{0-\infty}$, $AUC_{0-t}$, and $C_{max}$ for sitravatinib. All other PK parameters will not be subject to inferential statistical analysis.

For the analysis of relative bioavailability between sitravatinib malate salt (test) and sitravatinib free base (reference), log-transformed primary PK parameters ($AUC_{0-\infty}$, $AUC_{0-t}$, and $C_{max}$) for sitravatinib will be analyzed by using a mixed effect model. This model will include formulation, period, and sequence as fixed effects, and subject as a random effect.

For each primary PK parameter, a point estimate and its associated 90% confidence interval (CI) will be constructed for the difference between test and reference capsules and this difference and its 90% CI will be exponentiated to obtain the estimate of the ratio of geometric least squares means and its 90% CI.

**Safety**

Safety parameters will be listed and summarized using descriptive statistics, as applicable. No formal statistical analysis of safety data is planned.

# LIST OF ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| ADL | activities of daily living |
| AE | adverse event |
| AUC | area under the plasma concentration-time curve |
| $AUC_{0-\infty}$ | area under the plasma concentration-time curve from time zero to infinity |
| $AUC_{0-t}$ | area under the plasma concentration-time curve from time zero to the last quantifiable concentration |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CIT | checkpoint inhibitor therapy |
| CL/F | apparent total plasma clearance |
| $C_{max}$ | maximum observed plasma concentration |
| COVID-19 | Corona Virus Disease-2019 |
| CRO | Contract Research Organization |
| CRU | Clinical Research Unit |
| CV% | coefficient of variation |
| CYP | cytochrome P450 |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for/Conference on Harmonisation |
| IMP | investigational medicinal product |
| IRB | Institutional Review Board |
| IV | intravenous |
| MTD | maximum tolerated dose |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NSCLC | non-small cell lung cancer |
| PK | pharmacokinetic(s) |

| | |
|---|---|
| QD | once daily |
| QTcF | QT interval corrected for heart rate using Fridericia's method |
| RP2D | recommended Phase 2 dose |
| SAE | serious adverse event |
| SUSAR | suspected unexpected serious adverse reaction |
| $t_{1/2}$ | apparent plasma terminal elimination half-life |
| $T_{max}$ | time of the maximum observed plasma concentration |
| Vz/F | apparent volume of distribution |

# 1. INTRODUCTION

Refer to the Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

## 1.1. Overview

Sitravatinib (MGCD516) is an orally available, potent small-molecule inhibitor of a closely related spectrum of tyrosine kinases. This subset of tyrosine kinases is involved in a number of processes implicated in human cancer, including regulation of tumor growth and cell survival pathways, tumor invasion and metastatic progression, as well as tumor angiogenesis. Antitumor activity of sitravatinib has been observed in several human tumor xenograft models exhibiting genetic alterations in receptor tyrosine kinase targets, providing the rationale for evaluating sitravatinib monotherapy in tumors driven by these pathways in the clinical setting.

Additionally, based on its tyrosine kinase target profile, sitravatinib may modulate effects on the tumor microenvironment to overcome resistance to checkpoint inhibitors by effects on relevant immune cell populations. These effects are predicted to complement and augment the activity observed with checkpoint inhibitor therapy (CIT).

## 1.2. Summary of Nonclinical Studies

Sitravatinib is metabolized to 8 putative metabolites (M1 to M8) in mouse, rat, dog, monkey, and human hepatocytes and to 13 putative metabolites (M1 to M7 and M9 to M14) in vivo in dog and rat plasma samples. Studies using human liver microsomes and recombinant human cytochrome P450 (CYP) enzymes suggest that multiple enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4) are involved in the metabolism of sitravatinib; therefore, there is a low risk of a single CYP enzyme demonstrating a disproportionate contribution to sitravatinib metabolism.

Toxicology studies with repeated dosing of sitravatinib for 7 days and 4 weeks demonstrated no target organ changes in the dog, despite overt decreases in body weight and food consumption. In rats, however, vascular endothelial growth factor-related target organ changes were identified in the adrenal gland, Brunner's glands in the duodenum, femur and sternum (bone and bone marrow), spleen, lymph nodes, thymus, ovary, kidney (glomerulopathy, tubule necrosis, increased basophilic tubules), pancreas, and tongue. All effects in rats, except those in the kidney and pancreas, either recovered or showed partial recovery.

## 1.3. Summary of Clinical Experience

In clinical studies, sitravatinib was administered as a single agent in the first-in-human Study 516-001 in patients with advanced solid tumors and in combination with the PD-1 inhibitor nivolumab in patients with advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who had experienced disease progression either on or after prior treatment with a CIT (CIT-experienced) or after treatment with a platinum-based doublet chemotherapy (CIT-naïve) in Study MRTX-500.

Study 516-001 is an ongoing multicenter, Phase 1/1b clinical study characterizing the safety, pharmacokinetics (PK), metabolism, the pharmacodynamic, and clinical activity of sitravatinib in

patients with advanced solid tumors. The primary objective of the Phase 1 study was the determination of the maximum tolerated dose (MTD), while Phase 1b objectives included assessment of safety and clinical activity in patients with certain tumor types (eg, renal cell carcinoma) or with tumors characterized by certain genetic alterations. Sitravatinib monotherapy was administered orally once daily (QD) and based on the Phase 1 results, the starting dose in Phase 1b was 150 mg daily, which was subsequently changed to 120 mg during the study. Study MRTX-500 is a parallel Phase 2 study of glesatinib, sitravatinib, or mocetinostat in combination with nivolumab administered at a dose of 240 mg intravenously (IV) every 2 weeks, with sitravatinib 120 mg administered QD after this dose was confirmed safe in the lead-in portion of the study.

Study 516-006 is an Mirati sponsored, open-label, 2 parts, Phase 1 study assessing relative bioavailability and PK of a single oral dose of sitravatinib administered as free base capsules (reference formulation) and malate salt capsules (test formulation, developed by Mirati) in healthy male subjects. The primary objective is to investigate the relative bioavailability and PK of sitravatinib free base and malate salt capsule formulations following oral administration in healthy subjects. The results showed that PK exposure of 100 mg sitravatinib malate salt capsule (roller compaction) was comparable with 120mg free base capsule.

### 1.3.1. Safety

As of 26 June 2019, a total of 422 patients received treatment with sitravatinib. Among the 422 patients with available safety data, 377 patients (89%) experienced at least one sitravatinib-related AE.

Sitravatinib-related Grade 3 AEs reported in ≥ 5% of patients were hypertension (19%), diarrhea (8%), and fatigue (6%). Sitravatinib-related Grade 4 AEs were reported in 7 patients (2%), and included lipase increased in 3 patients (1%), and febrile neutropenia, gastric ulcer perforation, hypertensive crisis, and lymphocyte count decreased in 1 patient each (<1%). Sitravatinib-related Grade 5 AEs were reported in 4 patients and included cardiac arrest in 3 patients (1%) and cardiac failure in 1 patient (<1%).

Among the 422 patients with available safety data, 176 patients (42%) experienced at least one treatment-emergent serious adverse event (SAE). Sitravatinib-related SAEs were reported in 61 patients (15%), and included diarrhea in 10 patients (2%), nausea and vomiting in 7 patients each (2%), hypertension in 6 patients (1%), fatigue in 5 patients (1%), pulmonary embolism in 4 patients each (1%), cardiac arrest, headache and pancreatitis in 3 patients each (1%), cardiac failure, deep vein thrombosis, ejection fraction decreased, embolism, non-cardiac chest pain, and palmar-plantar erythrodysesthesia syndrome in 2 patients each (1%), and anaphylactic reaction, anemia, cerebral vasoconstriction, clostridium difficile colitis, confusional state, dehydration, electrocardiogram QT prolonged, febrile neutropenia, gastric ulcer perforation, gastritis, hypertensive crisis, hyponatremia, hypotension, left ventricular dysfunction, lipase increased, myalgia, myocarditis, odynophagia, pericardial effusion, pneumonitis, posterior reversible encephalopathy syndrome, subarachnoid hemorrhage, syncope, tachycardia, transaminases increased, and Troponin T increased in 1 patient each (<1%).

As of the data cut-off date, safety data are available for a total of 16 subjects from study 516-006. Among the 16 subjects with available safety data, three subjects experienced one AE each of dyspepsia, ear discomfort, and toothache; all were Grade 1 and none were drug-related. The

toothache led to withdrawal from study prior to dosing in dosing period 2. There were no SAEs and no deaths reported.

### 1.3.2. Pharmacokinetics

Pharmacokinetic evaluation in Study 516-001 shows that after single-dose administration, sitravatinib reaches peak concentration in a median time of approximately 3 to 8 hours. Exposure parameters (maximum observed plasma concentration [$C_{max}$] and area under the plasma concentration-time curve [AUC]) are approximately dose-proportional with single doses up to 200 mg. Median apparent plasma terminal elimination half-life ($t_{1/2}$) varied between 42 and 58 hours after oral administration.

After multiple-dose administration, drug accumulation ranged from 1.8- to 3.5-fold for $C_{max}$ and 2.0- to 4.7-fold for AUC from time zero to 24 hours postdose ($AUC_{0-24}$). Steady-state $C_{max}$ to a minimum observed plasma concentration mean ratio was 1.10 to 1.78. The steady-state PK was reached in a mean time of 11 to 15 days.

## 1.4. Study Rationale

In order to introduce BeiGene malate salt capsule formulation (roller compaction) into the development of sitravatinib in China, this study is conducted to compare the systemic exposure of sitravatinib between the malate salt capsule (roller compaction, manufactured by BeiGene) and the free base formulation. The primary objective of the study is to evaluate the relative bioavailability and PK of the different formulations.

The sitravatinib doses in this study are based on the results from study 516-006. To ensure comparable exposures, the free base reference dose will be 120 mg and the malate salt capsule dose will be 100 mg. The exposure ratio information should be used to guide the dose for the selected malate salt capsule formulation needed to achieve exposure comparable to the recommended Phase 2 dose (RP2D) of the free base product.

## 1.5. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study products, although there may also be some discomfort from the collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with sitravatinib may be found in the IB[1].

# 2. OBJECTIVES AND ENDPOINTS

## 2.1. Objectives

The primary objective of the study is:

- To investigate the relative bioavailability and PK of sitravatinib free base and malate salt capsule formulations following oral administration in healthy subjects.

The secondary objective of the study is:

- To assess the safety and tolerability of single-dose free base and malate salt capsule formulations of sitravatinib in healthy subjects.

## 2.2. Endpoints

### 2.2.1. Primary Endpoints

The following PK parameters will be calculated separately for each of Parts 1 and 2 using noncompartmental methods, whenever possible, based on plasma sitravatinib concentrations:

- AUC from time zero to infinity ($AUC_{0-\infty}$)
- AUC from time zero to the last quantifiable concentration ($AUC_{0-t}$)
- $C_{max}$
- time of the maximum observed plasma concentration ($T_{max}$)
- $t_{1/2}$
- apparent total plasma clearance (CL/F)
- apparent volume of distribution (Vz/F).

Other PK parameters may also be reported, as appropriate. Dose-normalized PK parameters will also be derived.

### 2.2.2. Secondary Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- 12-lead electrocardiogram parameters
- vital sign measurements
- physical examinations.

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design and Plan

This will be a Phase 1, open-label study using a 2-period crossover design to compare the bioavailability and PK of the free base formulation at 120 mg and the malate salt capsule formulation at 100 mg after a single oral administration to healthy male subjects. Subjects will be randomized into 2 sequences and will participate in 2 dosing periods (Table 1). The minimum washout period between dose administrations will be 14 days. Up to 26 subjects (include ≥16 Asian subjects) will be enrolled to guarantee that at least 24 subjects complete the study.

**Table 1 Dosing Sequences**

| Dosing sequence | Period 1 | Washout (minimum) | Period 2 |
|---|---|---|---|
| 1<br>N=13 | 120 mg sitravatinib free base capsule | 14 days | 100 mg sitravatinib malate salt capsule |
| 2<br>N=13 | 100 mg sitravatinib malate salt capsule | 14 days | 120 mg sitravatinib free base capsule |

N: number of subjects

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. In Periods 1 and 2, subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and will stay in the CRU until discharge on Day 4. In each period, subjects will attend a nonresidential visit on Day 8 for PK (168 hours postdose) sampling. Subjects will receive a Follow-up phone call on Days 13 to 15 of Period 2. A Schedule of Assessments is presented in Appendix 6.

The total duration of study participation for each subject (from Screening through Follow-up phone call) is anticipated to be up to approximately 8 weeks.

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of randomization number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

## 3.2. Discussion of Study Design

This study has been designed according to the Food and Drug Administration (FDA) Guidance for bioavailability and bioequivalence studies[2]. A crossover design was selected in order to assess the PK of sitravatinib after administration of sitravatinib free base and malate salt capsule. The crossover design allows for the smallest number of subjects to be used in the comparison of formulations.

A minimum 14-day washout between periods is considered adequate to ensure elimination of study drug prior to dosing in the subsequent period. The sample size is typical for this type of study and is considered adequate to meet the study objectives.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

## 3.3. Selection of Doses in the Study

The PK profile of single-agent sitravatinib was evaluated in Study 516-001 after single and repeated dose administration in patients with advanced solid tumors. Study 516-001 evaluated sitravatinib dose levels between 10 and 200 mg administered QD. Exposure parameters ($C_{max}$ and AUC) were approximately dose proportional with single doses up to 200 mg. The MTD was identified as 150-mg QD, and based on long-term tolerability observed in patients enrolled into Study 516-001 treated with 120- or 150-mg QD, the Sponsor selected 120-mg QD as the current RP2D, using the sitravatinib free base capsule formulation.

The sitravatinib doses in this study are based on the results from study 516-006, in which the PK exposure of 100 mg sitravatinib malate salt capsule (roller compaction, manufactured by Mirati) is comparable with 120 mg sitravatinib free base capsule. In this study, the free base reference dose will be 120 mg and the malate salt capsule (roller compaction, manufactured by BeiGene) test dose will be 100 mg to compare their systemic exposure.

Doses of 100 or 120 mg sitravatinib proposed in this study are considered safe and appropriate for the evaluation of sitravatinib PK profiles in healthy subjects. Also, see additional dose rationale provided in Section 1.4.

# 4. SELECTION OF STUDY POPULATION

## 4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Males, between 18 and 55 years of age, inclusive.
2. Body mass index between 18.0 and 32.0 kg/m$^2$, inclusive.
3. Subjects of first-generation or second-generation Asian descent enrolled in this study will be defined as:

   A subject of first-generation Asian descent for this study is defined as an individual who was born to biological parents of Asian descent in any East/Southeast Asian countries and relocated, or whose biological parents were born in any East/Southeast Asian countries/territories (such as China, Korea, Taiwan, Hong Kong, Mongolia, Cambodia, Vietnam, Thailand, Indonesia, Malaysia, Philippines, Myanmar, Laos, Singapore, etc.).

   A subject of second-generation Asian descent for this study is defined as an individual whose 4 biological grandparents were born in any East/Southeast Asian countries and relocated, or whose biological parents were born in any East/Southeast Asian countries/territories (such as China, Korea, Taiwan, Hong Kong, Mongolia, Cambodia, Vietnam, Thailand, Indonesia, Malaysia, Philippines, Myanmar, Laos, Singapore, etc.).

   Subjects of non-Asian descent enrolled in this study will be defined as an individual whose biological parents and 4 biological grandparents were not born in any East/Southeast Asian countries and relocated, or whose biological parents were born in any East/Southeast Asian countries/territories (such as China, Korea, Taiwan, Hong Kong, Mongolia, Cambodia, Vietnam, Thailand, Indonesia, Malaysia, Philippines, Myanmar, Laos, Singapore, etc.).
4. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations at Screening and/or Check-in as assessed by the Investigator (or designee).
5. A non-vasectomized male subject when sexually active with female partners of childbearing potential must agree to use a male condom or abstain from sexual intercourse during the study until 6 months after the last dose of study drug (this also applies to male subjects with pregnant partners). A vasectomized male subject will be surgically sterile for at least 90 days prior to study start, with documented azoospermia. A male who has been vasectomized less than 90 days prior to study start must follow the same restrictions as a non-vasectomized male. Contraception is further detailed in Appendix 4.
6. Agree to not donate sperm for 6 months after last dose.
7. Are able to swallow multiple capsules.
8. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

## 4.2. Exclusion Criteria

Subjects will be excluded from the study if they fulfill any of the following criteria at the Screening visit, unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed).
4. History of alcoholism or drug/chemical abuse within 2 years prior to Period 1 Check-in.
5. Alcohol consumption of >21 units per week. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
6. Positive urine drug screen at Screening or positive alcohol test result or positive urine drug screen at Check-in.
7. Positive hepatitis panel and/or positive human immunodeficiency/SARS-CoV-2 test (Appendix 2).
8. Elevated thyroid-stimulating hormone at screening (may be confirmed by repeat).
9. History of Gilbert's syndrome or suspicion of Gilbert's syndrome based on elevated total and indirect bilirubin.
10. Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg (if either is elevated, repeat x2 and use average of 3 readings to determine eligibility).
11. Receiving an investigational drug (new chemical entity) in the past 30 days (or 5 half-lives, whichever is longer) prior to first study drug administration on Day 1.
12. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to first study drug administration on Day 1, unless deemed acceptable by the Investigator (or designee).
13. Use or intend to use any prescription medications/products within 14 days prior to dosing, unless deemed acceptable by the Investigator (or designee). Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication.
14. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).

15. Use or intend to use any nonprescription medications/products including vitamins, minerals, supplements and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
16. Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Period 1 Check-in until Period 2 Day 8.
17. Caffeine-containing foods and beverages will not be allowed from 48 hours before Check-in until discharge on Day 4 in each period.
18. Consumption of alcohol will not be permitted from 72 hours prior to Check-in until discharge on Day 4 in each period, and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not in the CRU, from Screening through the Follow-up phone call.
19. Use of tobacco- or nicotine-containing products, or e-cigarettes (with or without nicotine) within 6 months prior to Period 1 Check-in until the Follow-up phone call, or positive cotinine at Screening or Check-in.
20. Subjects are required to refrain from strenuous exercise from 48 hours before Period 1 Check-in until the Follow-up phone call and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).
21. Receipt of blood products within 2 months prior to Period 1 Check-in.
22. Donation of blood from 90 days prior to Screening, plasma/platelets from 2 weeks prior to Screening until 3 months after the Follow-up phone call.
23. Poor peripheral venous access.
24. Have previously completed or withdrawn from this study or any other study investigating sitravatinib, and have previously received the investigational product.
25. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

## 4.3. Subject Number and Identification

Subjects will have a unique identification number. Subjects will be assigned a screening number at screening. Assignment of screening numbers will be in ascending order. Subjects will be assigned a randomization number after randomization. Replacement subjects (Section 4.4) will be assigned a new randomization number corresponding to the number of the replaced subject. Subjects will be identified by screening and/or randomization number on all study documentation. A list identifying the subjects by screening and/or randomization number will be kept in the Site Master File.

## 4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form. If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is hospitalized, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

## 4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Medical Monitor if any of the following criteria are met:

- AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

# 5. STUDY PRODUCTS

## 5.1. Description, Storage, Packaging, and Labeling

The reference sitravatinib free base drug product consists of sitravatinib free base drug substance, [redacted] The new sitravatinib malate salt capsule formulation consists of sitravatinib malate salt drug substance, [redacted]

All sitravatinib capsules will be provided by the Sponsor as 40-mg (for free base products, manufactured at the manufacturing plant of Catalent San Diego in San Diego) and 50-mg (for malate salt capsule, manufactured at the manufacturing plant of BeiGene in Suzhou) unit dose strength capsules (expressed based on sitravatinib free base weight), packaged in 30-count, high-density polyethylene bottles. Refer to the Pharmacy Manual for further details. The IMPs will be stored according to the instructions on the label.

Study drugs will be stored at the study site in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The study drugs will be transferred from bulk supplies into the subject's dose container by qualified clinical staff.

## 5.2. Study Drug Administration

Following an overnight fast of at least 8 hours, subjects will receive a single oral dose of 100 mg sitravatinib malate salt capsule formulation (2 × 50-mg) or 120 mg free base (3 × 40-mg capsules) on Day 1 of Periods 1 and 2. All doses will be administered with room temperature water (approximately 240 mL [8 oz]). Subjects will be required to abstain from consuming water from 1 hour predose until 2 hours postdose, excluding the amount of water consumed at dosing. Subjects will remain fasted for at least 4 hours after dosing. The timing of standardized meals will be recorded.

Subjects will be dosed in numerical order while sitting and will not be permitted to lie supine for 2 hours after administration of sitravatinib, except as necessitated by the occurrence of an AE and/or study procedures.

## 5.3. Randomization

The randomization code will be produced by the statistics department using a computer-generated pseudo-random permutation procedure. Subjects will be randomized in a 1:1 ratio into 2 dosing sequences (see Table 1).

## 5.4. Blinding

This is an open-label study.

## 5.5. Dosing Compliance

The following measures will be employed to ensure dosing compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

## 5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of sitravatinib capsules received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures by qualified pharmacy staff. Any unused assembled unit doses will be retained until completion of the study.

If deemed appropriate by the Sponsor, sufficient samples will be randomly selected from the supply provided by the Sponsor or designee and retained by the study site or qualified third party to meet retention requirements as dictated by any local laws or regulations, or any applicable regulatory authority's requirements.

At the completion of the study, all unused sitravatinib capsules will be disposed by the study site, per the Sponsor's written instructions.

# 6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

## 6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the Follow-up phone call, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless their use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

## 6.2. Diet

While staying at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

Subjects will fast overnight (at least 8 hours) prior to dosing and refrain from consuming water (or other liquid) from 1 hour predose until 2 hours postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Period 1 Check-in until Period 2 Day 8.

Caffeine-containing foods and beverages will not be allowed from 48 hours before Check-in until discharge on Day 4 in each period.

Consumption of alcohol will not be permitted from 72 hours prior to Check-in until discharge on Day 4 in each period, and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not in the CRU, from Screening through the Follow-up phone call.

## 6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products, or e-cigarettes (with or without nicotine) within 6 months prior to Period 1 Check-in until the Follow-up phone call.

## 6.4. Exercise

Subjects are required to refrain from strenuous exercise from 48 hours before Period 1 Check-in until the Follow-up phone call and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

## 6.5. Blood Donation

Subjects are required to refrain from donation of blood from 90 days prior to Screening, plasma/platelets from 2 weeks prior to Screening until 3 months after the Follow-up phone call.

# 7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- blood PK samples
- any other procedures (ECGs will be scheduled before vital sign measurements).

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, blood draws (other than PK samples).

## 7.1. Pharmacokinetic Assessments

### 7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for sitravatinib will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Procedures for collection, processing, and shipping of PK blood samples will be detailed in the study lab manual.

### 7.1.2. Analytical Methodology

Plasma concentrations of sitravatinib will be determined using a validated analytical procedure. Specifics about the analytical method will be provided in the bioanalysis report.

## 7.2. Safety and Tolerability Assessments

### 7.2.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting serious AEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF until final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of study drug until study completion. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed until resolution, the condition stabilizes or is considered chronic or not clinically significant per the investigator (or

designee), the AE or SAE is otherwise explained, the subject is lost to follow-up, or the subject withdraws consent. This will be completed at the Investigator's (or designee's) discretion.

### 7.2.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test and will undergo an alcohol test at the times indicated in the Schedule of Assessments in Appendix 6

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

### 7.2.3. Vital Signs

Supine blood pressure, supine pulse rate, respirations, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

### 7.2.4. 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply:

- QT interval corrected for heart rate using Fridericia's method (QTcF) >500 msec
- QTcF change from the baseline (predose) is >60 msec. Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

### 7.2.5. Physical Examination

A full physical examination or symptom-directed physical examination including evaluations of 1) head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

# 8. SAMPLE SIZE AND DATA ANALYSIS

## 8.1. Determination of Sample Size

Up to 26 subjects (13 per dosing sequence) will be enrolled to guarantee that at least 24 subjects complete the study. The number of subjects is justified in powering the study to delineate comparability of the sitravatinib mean exposure between the 2 dose formulations. Assuming an intra-subject coefficient of variation (CV%) of 40% (which was the maximum CV% observed on $C_{max}$ in previous study), and a malate salt capsule to free base ratio of 100 ± 5%, 24 subjects in a 2-way crossover design will provide a probability of 92% for the ratio of geometric means (malate salt to free base) to be within the 80% to 125% limits if the true ratio is between 95% and 105%. The conclusions in the clinical study report will be drawn based on the estimated ratios of geometric means only and the 90% confidence intervals (CIs) will be presented for informational purposes.

## 8.2. Analysis Set

PK Concentration Analysis Set: all subjects who received at least 1 dose of sitravatinib and have at least 1 quantifiable concentration of sitravatinib.

PK Parameter Analysis Set: all subjects who received at least 1 dose of sitravatinib and have at least 1 PK parameter of sitravatinib. Subjects who experience events that may affect their PK profile (eg, has an AE of vomiting that occurs at or before 2 times median $T_{max}$) may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

Relative bioavailability Analysis Set: the subset of the PK Parameter analysis set and is defined as all subjects in PK Parameter analysis set who have at least one primary PK parameter ($AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ of sitravatinib) in both periods.

Safety analysis set: the safety analysis population is defined as all subjects who received at least 1 dose of sitravatinib.

## 8.3. Pharmacokinetic Analyses

The plasma PK parameters of sitravatinib will be calculated using standard noncompartmental methods, based on actual sample collection time rather than scheduled times.

For the analysis of relative bioavailability between sitravatinib malate salt (test) and sitravatinib free base (reference), log-transformed PK parameters ($AUC_{0-\infty}$, $AUC_{0-t}$, and $C_{max}$) for sitravatinib will be analyzed by a mixed effect model. This model will include formulation, period, and sequence as fixed effects and subject as a random effect.

For PK parameters ($AUC_{0-\infty}$, $AUC_{0-t}$, and $C_{max}$) for sitravatinib, a point estimate and its associated 90% CI will be constructed for the difference between test and reference capsules and this difference and its 90% CI will be exponentiated to obtain the estimate of the ratio of geometric least-squares means and its 90% CI. The ratio of test formulation to reference formulation will be calculated on both non-dose-normalized and dose-normalized PK parameters. Estimated geometric means will also be presented by each formulation.

All other PK parameters will not be subject to inferential statistical analysis and only descriptive statistics (n, arithmetic mean, standard deviation, arithmetic CV, geometric mean, geometric CV, median, min, max, as appropriate) will be presented for them.

## 8.4. Safety Analysis

All AEs will be listed and summarized using a descriptive methodology. The incidence of AEs for each dosing will be presented by severity and by association with the study drugs as determined by the Investigator (or designee). Each AE will be coded using the Medical Dictionary for Regulatory Activities. Vital sign data (supine blood pressure and pulse rate) will be summarized. Observed values for clinical laboratory test data, 12-lead ECGs, and vital signs, and physical examination findings will be listed. No formal statistical analysis of safety data is planned.

## 8.5. Interim Analysis

No interim analyses are planned for this study.

# 9. REFERENCES

1. Sitravatinib (MGCD516) – Investigator's Brochure. (Version 6.0). 01 November 2019.

2. Food and Drug Administration. Draft Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf. March 2014. Accessed 03 January 2019.

# APPENDIX 1. ADVERSE EVENT REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definitions of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

## 1. ADVERSE EVENTS

### 1.1. Definition and Reporting of an Adverse Event

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE).

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the electronic case report form (eCRF). However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

#### 1.1.1. Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. Adverse events and SAEs should be assessed and graded based upon the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE.

NOTE: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 6.3.

### 1.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when 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 makes assessment of causality for every SAE prior to transmission of the SAE report/eCRF to the sponsor since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report/eCRF accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study drug/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered "related" to study drug if any of the following are met:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the subject's clinical condition or other concomitant AEs).

An AE should be considered "unrelated" to study drug if any of the following are met:

- An unreasonable temporal relationship between administration of the study drug and the onset of the AE (eg, the AE occurred either before or too long after administration of the product for it to be considered product-related)
- A causal relationship between the study drug and the AE is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE)

### 1.1.3. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the sponsor on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic or not clinically significant per the investigator, the AE or SAE is otherwise explained, the subject is lost to follow-up, or the subject withdraws consent. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report, with all changes signed and dated by the investigator. The updated SAE report should be resent to the sponsor within the timeframes outlined in Section 6.1.

## 1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, electrocardiograms [ECGs] or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 1.1) or an SAE (as defined in Section 2). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during

the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

The investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

# 2. DEFINITION OF A SERIOUS ADVERSE EVENT

An SAE is any untoward medical occurrence that, at any dose:

- Results in death.
- Is life threatening.

  NOTE: The term "life threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization.

  NOTE: In general, hospitalization signifies that the subject was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the AE is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  The following are NOT considered SAEs:

  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
  - Hospitalization for social/convenience considerations is not considered an SAE.
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience.
  - Results in disability/incapacity.

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

  - Is a congenital anomaly/birth defect.
  - Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

# 3. SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (i.e., not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Investigator's Brochure.

# 4. TIMING, FREQUENCY, AND METHOD OF CAPTURING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

## 4.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last study dosing of study drug. After this period, the investigator should report any SAEs that are believed to be related to prior study drug.

## 4.2. Eliciting Responses About Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How do you feel?
- Any change in your health since your last visit?
- Have you taken any new medications since your last visit?

# 5. SPECIFIC INSTRUCTIONS FOR RECORDING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

## 5.1. Death

When recording a death as an SAE, the AE that caused or contributed to fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death."

# 6. PROMPT REPORTING OF SERIOUS ADVERSE EVENTS

## 6.1. Timeframes for Submitting Serious Adverse Events

Serious adverse events will be reported within 24 hours of first knowledge of the SAE to the sponsor or designee as described in Table 1 once the investigator determines that the AE meets the protocol definition of an SAE.

**Table 1: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee**

| | Timeframe for Making Initial Report | Documentation Method | Timeframe for Making Follow-up Report | Documentation Method | Reporting Method |
|---|---|---|---|---|---|
| All SAEs | Within 24 hours of first knowledge of the SAE | SAE Report | As expeditiously as possible | SAE Report | Email or fax SAE form |

AE = adverse event; SAE = serious adverse event

## 6.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a subject, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 6.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 1.1.2.

The sponsor will provide contact information for SAE receipt.

## 6.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 6.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC).

All SUSARs will be submitted to all applicable regulatory authorities and investigators for Sitravatinib studies.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

# 7. PREGNANCY REPORTING

If the partner of a male subject becomes pregnant within 6 months after the completion of the last dose of study drug, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be 1 year following the delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a subject exposed to the study drug should be recorded and reported as an SAE.

# 8. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, and IRBs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference documents:

- Sitravatinib Investigator's Brochure

# APPENDIX 2. CLINICAL LABORATORY EVALUATIONS

| **Clinical chemistry:** | **Hematology:** | **Urinalysis:** |
|---|---|---|
| Alanine aminotransferase<br>Albumin<br>Alkaline phosphatase<br>Aspartate aminotransferase<br>Bilirubin total (fractionate [direct and indirect bilirubin] only if total bilirubin is > upper limit of normal)<br>Blood urea nitrogen<br>Calcium<br>Chloride<br>$CO_2$/bicarbonate<br>Creatinine<br>Gamma-glutamyl transferase<br>Glucose<br>Phosphorus<br>Potassium<br>Sodium<br>Total protein | Hematocrit<br>Hemoglobin<br>Mean cell hemoglobin<br>Mean cell hemoglobin concentration<br>Mean cell volume<br>Platelet count<br>Red blood cell (RBC) count<br>White blood cell (WBC) count<br>WBC differential:<br>Basophils<br>Eosinophils<br>Lymphocytes<br>Monocytes<br>Neutrophils | Bilirubin<br>Blood<br>Glucose<br>Ketones<br>Leukocyte esterase<br>Nitrite<br>pH<br>Protein<br>Specific gravity<br>Urobilinogen<br>Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive) |
| **Serology[a]:** | **Drug screen:** | **Hormone panel:** |
| Hepatitis B surface antigen<br>Hepatitis C antibody<br>Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen | Including but not limited to:<br>Amphetamines/methamphetamines<br>Barbiturates<br>Benzodiazepines<br>Cocaine (metabolite)<br>Methadone<br>Phencyclidine<br>Opiates<br>Tetrahydrocannabinol/ cannabinoids<br>Cotinine test<br>Alcohol test[b] | Thyroid-stimulating hormone[a] |
| **SARS-CoV-2 test[a]:** | | |
| COVID-19 Swab Collection & Analysis | | |

[a] Only analyzed at Screening.
[b] Only analyzed at Check-in (both dosing periods). Alcohol testing not included at Screening.

# APPENDIX 3. TOTAL BLOOD VOLUME

The following blood volumes will be withdrawn for each subject.

| | Volume per blood sample (mL) | Maximum number of blood samples | Total amount of blood (mL) |
|---|---|---|---|
| Clinical laboratory evaluations (includes TSH, as applicable) | 9 | 6 | 54 |
| Serology | 5 | 1 | 5 |
| Sitravatinib pharmacokinetics | 4 | 24 | 96 |
| Total: | | | 155 |

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

# APPENDIX 4. CONTRACEPTION GUIDANCE

**Definitions**

**Fertile male**: a male that is considered fertile after puberty.

**Sterile male**: permanently sterile male via vasectomy with documented azoospermia.

**Contraception Guidance**

**Male Subjects**

Sexually active males who are non-vasectomized when sexually active with female partners of childbearing potential and males who have had a vasectomy within 90 days prior to study start must agree to use a male condom or abstain from sexual intercourse during the study from Period 1 Check-in until 6 months after the last dose of study drug. Sexually active males who have had a vasectomy and are surgically sterile for greater than 90 days prior to study start, with documented azoospermia, will not be required to use a male condom or abstain from sexual intercourse during the study from Period 1 Check-in until 6 months after the last dose of study drug. The use of a condom applies to sexual intercourse with female partners of childbearing potential and female partners who are pregnant and breastfeeding.

**Sexual Abstinence and Same-sex Relationships**

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the Informed Consent Form (ICF) until 6 months after the last dose.

For subjects in same-sex relationships at the time of signing the ICF, there must be an agreement to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 6 months after the last dose.

# APPENDIX 5. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

**Regulatory and Ethical Considerations**

This study will be conducted in accordance with the protocol and with the following:

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

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious adverse events or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

**Finances and Insurance**

Financing and insurance will be addressed in a separate agreement.

**Informed Consent**

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign a copy of the ICF in the presence of the Investigator (or designee) to indicate that they are freely giving their informed consent. The Investigator (or designee) will then also sign the document. The original

document will then be copied with a copy being given to the subject, and the original being maintained in the subject's records.

Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.

**Subject Data Protection**

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

**Information Disclosure and Inventions**

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

**Data Quality Assurance**

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and

verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

**Investigator Documentation Responsibilities**

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

**Study Report and Publications**

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Council for Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases.

If the results of this study will be published or presented at scientific meetings, it will be in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential.

Investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

**Study and Study Center Closure**

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return/provide all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of PK samples to the bioanalytic laboratory according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. Potential reasons for suspension or discontinuation include but are not limited to: safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform investigator and/or institution conducting the study if the study is suspended or terminated for safety reasons. The sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the clinical study agreement established between the investigator and/or institutions and the sponsor.

# APPENDIX 6. SCHEDULE OF ASSESSMENTS

| Study procedures | Screening (within 28 days prior to first dose) | Periods 1 and 2 | | | Follow-up telephone call (Period 2, Days 13 to 15) |
|---|---|---|---|---|---|
| | | Day -1 | Days 1 to 4 | Day 8 (168 hours postdose)/ Early termination | |
| **Assessment/Administrative procedures:** | | | | | |
| Informed consent | X | | | | |
| Inclusion/exclusion criteria | X | | | | |
| Medical history, demographic data | X | | | | |
| Urinary drug screen (including cotinine) | X | X | | | |
| Alcohol test | | X | | | |
| Serology | X | | | | |
| TSH testing | X | | | | |
| Height and body weight | X[a] | X | | | |
| COVID-19 swab collection & analysis | X | | | | |
| **Study residency:** | | | | | |
| Check-in | | X | | | |
| Check-out | | | Day 4 (72 hours postdose) | | |
| Nonresidential visit | X | | | X | |
| **Study drug administration:** | | | Day 1 (0 hour) | | |
| **Pharmacokinetics:** | | | | | |

| Study procedures | Screening (within 28 days prior to first dose) | Periods 1 and 2 | | | Follow-up telephone call (Period 2, Days 13 to 15) |
|---|---|---|---|---|---|
| | | Day -1 | Days 1 to 4 | Day 8 (168 hours postdose)/ Early termination | |
| Blood sampling[b] | | | Predose (-0.5), 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hours postdose | X | |
| **Safety and tolerability:** | | | | | |
| Adverse event recording | X | X | Ongoing | X | X |
| Prior/concomitant medication monitoring | X | X | Ongoing | X | X |
| Clinical laboratory evaluations[c] | X | X | Day 4 | X (Period 2 only or early termination, if applicable) | |
| Vital signs (supine)[d] | X | X | Predose, 4, 24, 48, and 72 hours postdose | X | |
| Single 12-lead ECG[e] | X | X | Predose, 4, and 72 hours postdose | X | |
| Physical examination | X | X[f] | Day 4[g] | X[g] | |

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic; QTcF = QT interval corrected for heart rate using Fridericia's method; TSH = thyroid-stimulating hormone.

Note: The minimum washout period between dose administrations will be 14 days.

a. Height measured at Screening only.

b. PK blood sampling: predose (within 30 minutes prior to dosing) and 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 168 hours post-dose, a total of 12 samples in each study period. The allowed time window will be ±2 minutes for the post-dose timepoints ≤ 12 hr, ±10 minutes for 24 to 72 hr post-dose, and ±2 hr for 168 hr post-dose.

c. Blood and urine samples will be collected (hematology, chemistry, and urinalysis) for clinical laboratory evaluations. Samples for serum chemistry will be obtained following a fast of at least 8 hours; however, in the case of dropouts or rechecks, subjects may be permitted not to have fasted for 8 hours before the serum chemistry sample is taken.

d. Blood pressure and pulse rate, respirations, and oral body temperature. Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements. The assessment will be performed after ECG, with the allowed time window of within 3 hr before dose administration for predose time point, ±20 minutes for the 4 hr post-dose, and ±30 minutes for 24 hr, 48 hr and 72 hr post-dose.

e. Electrocardiograms are to be performed as close to PK sampling time as possible and followed by vital assessment. The allowed time window will be within 3 hr before dose administration for Predose, and ±20 minutes for the 4 hr postdose, and ±30 minutes for the 72 hr postdose. Assessments will include an evaluation of heart rate, QT, and QTc intervals. RR interval should be recorded during each ECG assessment in order to calculate QTcF. ECGs are to be

performed prior to collection of vital signs and PK sample collection blood draws. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply: QTcF >500 msec OR QTcF change from the baseline (predose) is >60 msec.

f. Full physical examination at Check-in for Period 1; symptom-directed physical examination at Check-in for Period 2.

g. Symptom-directed physical examination.