Protocol

A Phase 1, Open-label, Nonrandomized Study to Investigate the Mass Balance Recovery and Metabolic Profile of ^{14}C-bemcentinib Following Single Oral Administration in Healthy Male Subjects

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Investigational Medicinal Product: Bemcentinib, formerly known as BGB324

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SPONSOR APPROVAL

I have read the protocol and approve it.

Electronically signed below

13 May 2022

[redacted]

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

Electronically signed below on behalf of [redacted]

13 May 2022

[redacted]

Date

[redacted]

STUDY IDENTIFICATION

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Protocol Amendment Summary of Changes

The following key changes have been made in Protocol Version 2.0:

Section	Revision Description
General	The Principal Investigator was updated. The radiolabeled dose was corrected to 32.8 µCi (1.21 MBq) throughout the protocol. The discharge criteria were updated to remove plasma radioactivity levels below the limit of quantitation for 2 consecutive collections. Editorial, formatting, and consistency updates throughout. Amendments to abbreviations list to align with text. Version 16 of the Investigator's Brochure was added to reference section.
Section 1.2 Summary of Nonclinical Pharmacokinetics	Updated in line with Version 16 of the Investigator's Brochure.
Section 1.3 Summary of Clinical Experience	Updated in line with Version 16 of the Investigator's Brochure.
Section 3.3 Selection of Doses in the Study	Updated to correct committed effective radiation dose of 0.997 mSv.
Appendix 4: Contraception Guidance	Updated to allow for the reduction in duration of contraception from 120 days to 90 days based on new available data within Version 16 of the Investigator's Brochure. Clarification was included to highlight vasectomy applied to male subjects.

SYNOPSIS

Study Title

A Phase 1, open-label, nonrandomized study to investigate the mass balance recovery and metabolic profile of ^{14}C-bemcentinib following single oral administration in healthy male subjects.

Objectives and Endpoints

Objectives	Endpoints
Primary: • to determine the mass balance recovery (urine and feces) and route and rate of elimination of ^{14}C-bemcentinib • to determine the PK of total radioactivity in plasma and whole blood and of bemcentinib in plasma after a single oral dose of ^{14}C-bemcentinib in healthy male subjects.	• total radioactivity recovery (fe_{t1-t2}) in urine and feces • PK parameters including, but not limited to, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, t_{max}, and $t_{1/2}$ for bemcentinib in plasma and total radioactivity in plasma and whole blood and urinary recovery of bemcentinib (fe_{t1-t2}).
Secondary: • to determine the metabolite profile of ^{14}C-bemcentinib in plasma, urine, and feces • to identify the chemical structure of the major* metabolites of bemcentinib *based on the MIST guidelines: >10% of bemcentinib parent exposure in plasma after oral administration • to assess safety and tolerability of ^{14}C-bemcentinib when administered to healthy subjects.	• quantitative metabolic profiles of bemcentinib in plasma and excreta • identification of bemcentinib major metabolites in plasma (>10% relative total drug related exposure) and excreta (>10% of excreted dose) • incidence and severity of AEs • incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results • 12-lead ECG parameters • vital signs measurements • physical examinations.

Abbreviations: AE = adverse event; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; ECG = electrocardiogram; fe_{t1-t2} = percentage of the dose administered recovered over the time interval t1 to t2; MIST = Metabolites in Safety Testing; PK = pharmacokinetics; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of the maximum observed concentration.

Study Design

This will be a Phase 1, open-label, nonrandomized, single oral dose study in healthy male subjects.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to dose administration. Subjects will be admitted into the study site on Day -1 and be confined to the study site until at least Day 8. On Day 1, subjects will receive a single oral dose of ^{14}C-bemcentinib. Subjects will be discharged if the following discharge criteria are

met: ≥90% mass balance recovery and <1% of the total radioactive dose is recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods.

If these discharge criteria are not met by Day 8, subjects will be required to remain resident until discharge criteria are met, up to Day 15. If criteria are not met by Day 15, subjects may be asked to collect 24-hour excreta samples on up to 2 further occasions on a nonresidential basis to allow extrapolation of urinary and fecal excretion. If needed, the 2 additional 24-hour nonresidential collections will start on the morning of Days 22 and 29 (to be brought into the study site at the end of the collection interval on Days 23 and 30, respectively). If on the second occasion the subject has still not met the desired criterion, then the subject will be discharged from the study, per investigator and sponsor decision.

Number of Subjects

Up to 8 subjects will be enrolled and studied as a single group in order that 6 subjects complete the study.

Diagnosis and Main Criteria for Inclusion

Healthy male subjects aged between 35 and 55 years (inclusive) with a body mass index between 18.0 and 32.0 kg/m^2 (inclusive).

Investigational Medicinal Products, Dose, and Mode of Administration

Each subject will receive a single oral dose of [redacted] mg of ^{14}C-bemcentinib as two [redacted]-mg capsules containing approximately [redacted] µCi ([redacted] MBq) on the morning of Day 1, 30 minutes after starting a standard high-fat breakfast.

Duration of Subject Participation in the Study

Planned screening duration: approximately 4 weeks.

Planned study duration (screening to outpatient visit [if required]): a maximum of approximately 9 weeks.

Statistical Methods

Pharmacokinetic parameters will be derived by standard noncompartmental analysis.

Pharmacokinetic and safety parameters will be listed and summarized. No formal statistical analysis will be performed.

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LIST OF ABBREVIATIONS

AE	adverse event
ALARA	as low as (is) reasonably achievable
API	active pharmaceutical ingredient
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
$AUC_{0-tlast}$	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
CSR	clinical study report
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CYP	cytochrome P450
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICRP	International Commission on Radiological Protection
IFN	interferon
IMP	investigational medicinal product
P-gp	P-glycoprotein
PK	pharmacokinetic
SAE	serious adverse event
$t_{½}$	apparent plasma terminal elimination half-life
t_{max}	time of the maximum observed plasma concentration

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

Bemcentinib, formerly known as BGB324 and R428, is being developed for the treatment of a range of solid tumors and myeloid malignancies, as well as SARS-CoV-2 infection (COVID-19). BerGenBio ASA (BerGenBio)-sponsored and investigator-led studies are ongoing in patients with non-small cell lung cancer, metastatic melanoma, acute myeloid leukemia (AML), myelodysplastic syndrome, metastatic pancreatic cancer, glioblastoma, malignant mesothelioma, and COVID-19. Bemcentinib is being administered in various studies as monotherapy and in combination with erlotinib, cytarabine, decitabine, pembrolizumab, docetaxel, cisplatin, nab-paclitaxel, gemcitabine, and dabrafenib/trametinib.

In previous and ongoing studies bemcentinib is taken orally, initiated at a dose of 400 mg once daily for a 3-day loading period, followed by a maintenance dose of 200 mg daily.

Bemcentinib is a small molecule AXL kinase inhibitor which has demonstrated potent and selective inhibition of AXL in biochemical and cell-based kinase inhibition assays. In the oncology setting bemcentinib has been shown in vitro to inhibit cell proliferation in a number of different cell lines and induce apoptosis and cell death in acute myeloid leukemia cell lines. Bemcentinib showed pharmacological efficacy as a single agent and in combination with targeted chemo- or immune-checkpoint inhibitors in vivo in a variety of hematologic and primary and metastatic solid tumor models. As a single agent, bemcentinib inhibited tumor growth and prolonged survival in human acute myeloid leukemia xenograft models and syngeneic bone marrow transplantation mouse models and affected the expansion and survival of myelodysplastic cells. AXL is a recognized therapeutic target for the treatment of cancer and is an important negative regulator of type I interferon (IFN) responses that are important for both anti-cancer treatments and cellular anti-viral responses.

The AXL pathway is a mechanism utilized by several enveloped viruses to enter host cells and dampen viral immune response. The AXL receptor mediates entry of enveloped viruses such as Zika and Ebola through "apoptotic mimicry". Phosphatidylserine on the viral envelope is tethered to AXL by its bound ligand, growth arrest-specific 6, leading to virus internalization. Viruses also activate AXL signal transduction that dampens key anti-viral type I IFN responses. Preclinical data show that AXL-mediated internalization and Type 1 IFN suppression extend to SARS-CoV-2 and that bemcentinib acts on 2 host pathways to inhibit coronavirus replication, namely prevention of viral entry and enhanced anti-viral IFN response.

1.2. Summary of Nonclinical Pharmacokinetics

Nonclinical repeat dose toxicity studies were performed using daily oral gavage doses of bemcentinib administered to mice, rats, dogs, and monkeys. For oral administration, bemcentinib was prepared as a suspension in 0.5% (weight/volume [w/v]) hydroxypropyl

methyl cellulose in 0.15% (w/v) polysorbate 80, unless otherwise stated. Bemcentinib was not well tolerated in dogs due to significant gastrointestinal toxicity. Based upon the high plasma exposure and reasonable tolerability to bemcentinib in range-finding studies, mice and monkeys were selected for repeat dose Good Laboratory Practice (GLP) toxicity studies.

Single doses of bemcentinib were administered to male and female Sprague Dawley rats to identify the maximum tolerated dose. Bemcentinib was administered by oral gavage at doses of 100, 200, 600, and 1000 mg/kg (equivalent to 600, 1200, 3600, and 6000 mg/m^2) to 3 rats/sex/group. All animals survived until scheduled euthanasia. Minimal bemcentinib-related changes were identified, with no bemcentinib-related effects identified as gross findings.

Repeat dose studies with bemcentinib were conducted in mice, rats, dogs, and monkeys. Bemcentinib was administered orally once daily for 10 days (rats and dogs) in non-GLP studies and for 28 days in GLP studies in mice and monkeys. Once and twice daily dosing for a total of 9 days was also investigated in a non-GLP monkey study. In the 28-day GLP studies, the treatment period was followed by a treatment-free recovery period of 14 or 16 days, in monkeys and mice respectively, in order to assess the reversibility of any treatment-related effects and for evidence of delayed toxicity. Initial toxicology work was conducted in line with International Council for Harmonisation S9 guidelines to support the initial oncology. Additionally, a 26-week GLP study was also conducted in the mouse along with a 39-week GLP study conducted in monkeys.

Pharmacokinetic (PK) studies were conducted both in vitro and in vivo, to elucidate the PK profile of bemcentinib and support clinical pharmacology investigations. Bemcentinib has good in vitro permeability and is a poor substrate for P-glycoprotein (P-gp), suggesting good systemic availability after oral dosing. Animal studies in which bemcentinib was dosed orally and intravenously showed high bioavailability indicating that bemcentinib is extensively absorbed from the gastrointestinal tract.

Protein binding of bemcentinib in human plasma was approximately 90% and 91.8% in mice, which was similar to that observed in rats, dogs and monkeys. The volume of distribution at steady state for bemcentinib was large (30-32 L/kg) and consistent across species, while clearance was moderate to high (19 - 43 mL/min/kg) with some variability. The time of the maximum observed plasma concentration (t_{max}) occurred late in the rat (8.9-13.3 hours), dog (14.0-18.0 hours), and monkey (6.7-28 hours). Data generated during a mouse absorption, distribution, metabolism, and excretion study indicate that bemcentinib is extensively distributed into tissue and that tissue concentrations were higher in comparison to plasma with a half-life of elimination between 11 and 14 hours.

Incubation of bemcentinib with human liver cells demonstrate that bemcentinib is a low-turnover compound in hepatocytes (half-life [$t_{1/2}$] >240 mins) and that in liver microsomes cytochrome P450 (CYP)3A4 and flavin containing dimethylaniline monoxygenase 1 are responsible for metabolism. Bemcentinib was found to inhibit CYP3A4 and CYP2D6 and to induce CYP3A4 and there is a moderate risk of interactions with co-administered drugs that are CYP3A4 or CYP2D6 substrates. Bemcentinib was found to weakly inhibit OATP1B1 and OCT1 and moderately inhibit P-gp and breast cancer resistance protein.

Bemcentinib was found to be an in vitro substrate of breast cancer resistance protein and MDR1 ABC (efflux) transporters under monolayer assay conditions.

1.3. Summary of Clinical Experience

To date, 1 Phase I study (BGBC001) has been completed in healthy volunteers and another Phase I food and gastric effect study (BGBC018) has completed recruitment and is in the final stages of reporting. Two Phase Ib/II company-sponsored clinical studies (BGBC003 and BGBC008) are currently ongoing in patients with advanced cancers. Another Phase Ib/II company-sponsored clinical study in non-small cell lung cancer (BGBC004) has completed patient recruitment and the clinical study report (CSR) is currently being finalized. One Phase II study (BGBC007) evaluating bemcentinib in combination with pembrolizumab in patients with triple negative breast cancer was terminated due to pre-defined futility.

There was also 1 company-sponsored study (BGBC020) and 1 investigator-led study (BGBIL019) evaluating bemcentinib plus standard of care in patients hospitalized with COVID-19 that have completed patient recruitment. Both studies have had last patient last visit and the final CSRs are being developed. In addition, 3 investigator-led studies in the oncology setting are ongoing, and 3 have completed patient enrollment.

Clinical study BGBC001, a Phase 1 first-in-human study that investigated the safety and PK of bemcentinib, has completed. Single ascending oral doses of bemcentinib in the range of 50 to 1500 mg were administered under fasted conditions to 32 healthy male subjects aged 18 to 45 years. Seven of these subjects were also administered bemcentinib at the same dose under fed conditions.

Bemcentinib was shown to have a predictable PK profile and long plasma half-life, allowing for different dosing options. Modelling of the PK data from this study has indicated that the most effective approach to rapidly achieving steady state is to administer a series of loading doses followed by a lower daily maintenance dose.

The administration of a single oral dose of bemcentinib was well tolerated up to 1000 mg. A single oral dose of 1500 mg was not well tolerated as demonstrated by the review of AEs. There were no serious adverse events (SAEs) reported in this study and all AEs resolved spontaneously. There were no clinically significant changes from screening in laboratory safety parameters, no clinically significant changes in vital signs, and no clinically significant abnormalities in electrocardiogram (ECG) parameters during the study. The most commonly occurring AEs were gastrointestinal disorders, particularly diarrhea and nausea.

In clinical study BGBC001, systemic exposure to bemcentinib increased approximately dose proportionately. The geometric mean $t_{1/2}$ was 45.6 to 88.7 hours. Between-subject variability in systemic exposure (area under the plasma concentration-time curve [AUC] from time 0 extrapolated to infinity [$AUC_{0-\infty}$] and maximum observed plasma concentration [C_{max}]) to bemcentinib at 100 to 1500 mg (PK parameters were only available in 2 subjects at 50 mg) was generally high (geometric coefficient of variation of 25.8% to 96.7% for $AUC_{0-\infty}$ and C_{max}, respectively), most probably reflecting a variable extent of absorption. The median t_{max} was 8 to 23 hours for doses ranging from 50 to 1500 mg, reflecting a slow absorption process. The geometric mean value for C_{max} after 200 and 400 mg single doses were 36.8 and

69.1 ng/mL, respectively. The geometric mean value for $AUC_{0-\infty}$ after 200 and 400 mg single doses were 3240 and 6290 h*ng/mL, respectively.

Following administration of bemcentinib with food to subjects who had previously received bemcentinib, there was an increase in systemic exposure in 3 subjects (50% or more), no appreciable change in 3 subjects, and an apparent reduction in systemic exposure (40%) in 1 subject. While C_{max} and AUC from time 0 to 48 hours under fed conditions were 29% and 21% greater, respectively, compared to fasted conditions, the 95% confidence intervals of the ratio (fed/fasted) included 100%, indicating lack of statistically significant effect of food on bemcentinib with Formulation 1. In a separate healthy volunteer food effect study (BGBC018) where 24 subjects received a single dose of 400 mg bemcentinib, the C_{max} and AUC from time 0 to the time of the last quantifiable concentration ($AUC_{0-tlast}$) were increased by 60% and 70%, respectively, under fed conditions compared to fasted conditions. There was also a 60% reduction in the coefficient of variation in the fed state compared to fasted.

1.4. Study Rationale

The purpose of this study is to determine mass balance recovery and identification of potential metabolites of bemcentinib which will enable the planning and design of future studies. The previously established ^{14}C labeling site of the active moiety of bemcentinib, which was used in the preclinical package for the radioburden calculation, is believed to provide the potential to monitor all of the unknown metabolites representing >10% of the parent compound as well as to determine the mass balance recovery (urine and feces).

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 treatments, although there may also be some discomfort from collection of blood samples and other study procedures. The radioactive dose is an acceptable dose to give to healthy male subjects. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with bemcentinib may be found in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

Table 1 shows the objectives and endpoints of the study.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary: • to determine the mass balance recovery (urine and feces) and route and rate of elimination of ^{14}C-bemcentinib • to determine the PK of total radioactivity in plasma and whole blood and of bemcentinib in plasma after a single oral dose of ^{14}C-bemcentinib in healthy male subjects.	• total radioactivity recovery (fe_{t1-t2}) in urine and feces • PK parameters including, but not limited to, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, t_{max}, and $t_{1/2}$ for bemcentinib in plasma and total radioactivity in plasma and whole blood and urinary recovery of bemcentinib (fe_{t1-t2}).
Secondary: • to determine the metabolite profile of ^{14}C-bemcentinib in plasma, urine, and feces • to identify the chemical structure of the major* metabolites of bemcentinib *based on the MIST guidelines: >10% of bemcentinib parent exposure in plasma after oral administration • to assess safety and tolerability of ^{14}C-bemcentinib when administered to healthy subjects.	• quantitative metabolic profiles of bemcentinib in plasma and excreta • identification of bemcentinib major metabolites in plasma (>10% relative total drug related exposure) and excreta (>10% of excreted dose) • incidence and severity of AEs • incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results • 12-lead ECG parameters • vital signs measurements • physical examinations.

Abbreviations: AE = adverse event; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; ECG = electrocardiogram; fe_{t1-t2} = percentage of the dose administered recovered over the time interval t1 to t2; MIST = Metabolites in Safety Testing; PK = pharmacokinetics; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of the maximum observed concentration.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase 1, open-label, nonrandomized, single oral dose study in healthy male subjects.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to dose administration. Up to 8 subjects will be enrolled to ensure that 6 subjects complete the study. Subjects will be admitted into the study site on Day -1. On the morning of Day 1, all subjects will receive a single oral dose of [redacted] mg containing approximately [redacted] µCi ([redacted] MBq) of ^{14}C-bemcentinib, 30 minutes after starting a standard high-fat breakfast.

Subjects will be confined to the study site until at least Day 8. Subjects will be discharged from the study site on Day 8 if the following discharge criteria are met:

- ≥90% mass balance recovery, and
- <1% of the total radioactive dose is recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods.

If these discharge criteria are not met by Day 8, subjects will be required to remain resident until discharge criteria are met, up to Day 15. If criteria are not met by Day 15, subjects may be asked to collect 24-hour excreta samples on up to 2 further occasions on a nonresidential basis to allow extrapolation of urinary and fecal excretion. If needed, the 2 additional 24-hour nonresidential collections will start on the morning of Days 22 and 29 (to be brought into the study site at the end of the collection interval on Days 23 and 30, respectively). If on the second occasion the subject has still not met the desired criterion, then the subject will be discharged from the study, per investigator and sponsor decision.

Subjects experiencing emesis during the first 4 hours postdose may be discharged on the same day from the study site, provided there are no safety concerns, and after discharge study procedures are performed.

The total duration of study participation for each subject (from screening to outpatient visit [if required]) is anticipated to be a maximum of approximately 58 days.

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

A Schedule of Assessments is presented in Appendix 6.

3.2. Discussion of Study Design

This study will be open-label because the primary endpoints of the study are considered objective. Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Subjects over 35 years of age will be used to minimize the risk to fertility in healthy subjects.

Female subjects will be excluded to align with regulatory guidance. The 'as low as (is) reasonably achievable' (ALARA) principle prescribed by the International Commission on Radiological Protection (ICRP)[2] recommends that radiation exposure to subjects should be kept ALARA; therefore, if no specific reason exists to include females (ie, no available data suggest metabolism of the ^{14}C-bemcentinib is different in females versus males), then the radiation exposure to female subjects should ideally be kept at zero by not including females in this radioactivity study and only enrolling and dosing male subjects.

Oral administration was chosen since this is the intended clinical route of administration. Based on the nonclinical data and the known PK of ^{14}C-bemcentinib, the sample collection timing and duration of this study are considered adequate to achieve the study objectives.

3.3. Selection of Doses in the Study

A single dose level of [redacted] mg, approximately [redacted] µCi ([redacted] MBq) of ^{14}C-bemcentinib, will be administered to each subject. This administration is considered adequate to define the disposition of ^{14}C-bemcentinib and will deliver a committed effective radiation dose of 0.997 mSv to each subject.

The committed effective radiation doses to be received by the subjects as a consequence of the administration have been calculated based on the results of a preclinical mass balance study and a quantitative whole body autoradiography study.[3] The effective radiation dose is defined as being within dose limits for members of the public (Category II study, World Health Organization)[4] with a minor associated risk (risk Category IIb, ICRP).[2]

A [redacted]-mg dose of bemcentinib is within the anticipated clinical dose range and is considered to be high enough to fully characterize the single oral dose PK of the parent compound.

Bemcentinib will be dosed after a high-fat breakfast as previous studies have shown a higher exposure to bemcentinib in the fed state and less variability in the PK of bemcentinib.

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 of any race, between 35 and 55 years of age, inclusive.
2. Body mass index between 18.0 and 32.0 kg/m^2, inclusive, and a total body weight between 50 and 100 kg, inclusive.
3. In good health, determined by no clinically significant findings from medical history, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at screening and check-in and from the physical examination at check-in, as assessed by the investigator (or designee).
4. No clinically significant abnormalities in 12-lead ECG determined within 28 days before dose of IMP including average PR > 220 ms and QT interval corrected for heart rate using Fridericia's formula >450 ms.
5. No history of clinically significant dysrhythmias (long QT features on ECG, sustained bradycardia, left bundle branch block, or ventricular arrhythmia), atrial fibrillation, or history of familial long QT syndromes.
6. Will agree to use contraception as detailed in Appendix 4.
7. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.
8. History of a minimum of 1 bowel movement per day.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

Medical conditions

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. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2).

Prior/concomitant therapy

5. Administration of a COVID-19 vaccine in the past 30 days prior to dosing.
   Note: further details regarding COVID-19 testing (including procedures for subjects who test positive at any time throughout clinical research unit confinement) are specified in a separate document.
6. 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 check-in, unless deemed acceptable by the investigator (or designee).
7. Use or intend to use any prescription medications/products within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
8. 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).
9. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to check-in, unless deemed acceptable by the investigator (or designee).

Prior/concurrent clinical study experience

10. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days prior to dosing.
11. Subjects who have participated in any clinical study involving a radiolabeled investigational product within 12 months prior to check-in.
12. Have previously completed or withdrawn from this study or any other study investigating bemcentinib, and have previously received bemcentinib.

Diet and lifestyle

13. Alcohol consumption of > 28 units per week for males. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
14. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at screening or check-in.
15. History of alcoholism or drug/chemical abuse within 2 years prior to check-in.
16. Use of tobacco- or nicotine-containing products within 3 months prior to check-in, or positive cotinine at screening or check-in.
17. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in.

Other exclusions

18. Receipt of blood products within 2 months prior to check-in.
19. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
20. Poor peripheral venous access.
21. Subjects with exposure to significant diagnostic or therapeutic radiation (eg, serial X-ray, computed tomography scan, barium meal) or current employment in a job requiring radiation exposure monitoring within 12 months prior to check-in.
22. Subjects who, in the opinion of the investigator (or designee), should not participate in this study.

Subjects may previously have been screened on a generic basis to determine their eligibility for inclusion in Phase 1 clinical studies conducted at the study site. If generic screening was performed within the specified study screening window, selected study-specific procedures will be repeated either at an additional screening visit or on admission to the study site on Day -1.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Subjects will be assigned a subject number prior to dosing. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103).

A replacement subject (see Section 4.4) will be assigned a subject number corresponding to the number of the subject he is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by screening identification number or subject number only on all study documentation. A list identifying the subjects by subject 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 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 from the study, efforts will be made to perform all discharge assessments, if possible (Appendix 6). Other applicable safety-related procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, 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.

The replacement of subjects withdrawn from the study will be discussed between the investigator and sponsor.

4.5. Study Termination

The study may be discontinued at the discretion of the investigator (or designee), sponsor, or sponsor's 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 TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Active pharmaceutical ingredient (API), as an off-white to colored solid (with a target clinical specific activity of [redacted] µCi/mg) will be supplied by the sponsor and radiolabeled API

(powder) will be supplied by the sponsor from ALMAC (UK), along with the batch number, Good Manufacturing Practice certificate, and certificates of analysis.

The study site will manufacture and label the IMP from bulk API and excipient supplies, such that each unit dose contains a total of [redacted] mg bemcentinib as two [redacted]-mg capsules containing approximately [redacted] µCi ([redacted] MBq) of ^{14}C-bemcentinib. A certificate of release authorized by a Qualified Person from a listed country or United Kingdom will also be issued for the IMP prior to administration to subjects.

The sponsor will supply a sufficient quantity of the applicable API (target of [redacted] mCi) for the manufacture of the unit doses at the study site. All excipients and capsules will be sourced by the study site. Specific instructions regarding dose preparation and storage of materials will be mutually agreed upon between the sponsor and the appropriate clinical staff and will be presented in a separate document.

The API and IMP will be stored according to the instructions on the label at the study site in a location that is locked with restricted access. The IMP label will be the responsibility of Labcorp, and the API label will be the responsibility of the sponsor.

5.2. Study Treatment Administration

Each dose of ^{14}C-bemcentinib will be administered orally with 240 mL of room temperature water. All subjects will fast overnight (at least 8 hours) and will consume a standard high-fat breakfast 30 minutes prior to dosing. Subjects will refrain from consuming water for 1 hour prior to dosing. Subjects will refrain from consuming water until 2 hours postdose, excluding the amount of water consumed at dosing, and will fast until 4.5 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Subjects will be dosed in numerical order while standing and will not be permitted to lie supine for 2 hours after administration of ^{14}C-bemcentinib except as necessitated by the occurrence of an AE(s) and/or study procedures.

Except when they are using the toilet, study subjects will be observed for approximately 4 hours postdose to ensure that they are not experiencing AEs, becoming nauseated, or experiencing emesis.

5.3. Randomization

This is a nonrandomized study. The study has a single treatment group.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after oral administration, visual inspection of the mouth 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 the study supplies 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 unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the sponsor or disposed of 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 discharge, unless the investigator (or designee) and/or sponsor have given their prior consent.

A mild laxative (ie, Milk of Magnesia®, Colace®) may be used to help with bowel movements if necessary. 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 its 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 confined at the study site, subjects will receive a standardized, high-fiber diet at scheduled times that do not conflict with other study-related activities. Prune juice may be administered on an as-needed basis to aid in normal bowel function and will not be considered a concomitant medication. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests.

Subjects will consume a high-fat breakfast (contents are detailed in Table 2) before dosing. Subjects should start the meal 30 minutes prior to administration of the IMP. Study subjects should eat this meal in 30 minutes or less. The drug product should be administered 30 minutes after start of the meal.

Table 2: High-fat Breakfast Content

High-fat Breakfast
120 g fried eggs (2 eggs) in vegetable oil
50 g bacon (2 rashers)
72 g toasted white bread (2 slices)
13 g butter (2 pats)
108 g hash brown (3 each)
240 g whole milk
Total calories: 973 kcal

This high-fat meal contains the equivalent of approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until discharge.

Caffeine-containing foods and beverages will not be allowed from 36 hours before check-in until discharge.

Consumption of alcohol will not be permitted from 36 hours prior to check-in until discharge.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to check-in until discharge.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before check-in until discharge 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 3 months prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 3 months after discharge.

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 samples for PK assessments
- urine and fecal collections for PK assessments
- any other procedures.

7.1. Pharmacokinetic Assessments

Table 3 shows the PK assessments to be carried out.

Table 3: Pharmacokinetic Assessments

Sample	Radioanalysis	Pharmacokinetics (bemcentinib)	Metabolite profiling
Whole blood	X		
Plasma	X	X	X
Urine	X	X	X
Feces	X		X

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6 for determination of bemcentinib concentration, total radioactivity, and metabolite profiling and identification.

Approximately 1 × 2 mL blood sample will be collected for total radioactivity in whole blood and approximately 1 × 6 mL blood sample will be collected for total radioactivity in plasma. Approximately 1 × 4 mL blood sample will be collected for bemcentinib concentration in plasma. Approximately 1 × 10 mL blood sample will be collected for metabolite profiling and identification in plasma.

7.1.2. Pharmacokinetic, Total Radioactivity, and Metabolite Urine and Feces Collection and Processing

Urine will be collected over the time intervals indicated in the Schedule of Assessments in Appendix 6 for determination of bemcentinib concentration, total radioactivity, and metabolite profiling and identification. Procedures for collection, processing, and shipping of urine collections will be detailed in a separate document.

Feces will be collected over the time intervals indicated in the Schedule of Assessments in Appendix 6 for determination of total radioactivity, and, where possible, metabolite profiling and identification. If possible, a single baseline fecal sample will be collected from after check-in on Day -1 until just prior to dose administration on Day 1. Procedures for collection, processing, and shipping of fecal collections will be detailed in a separate document.

7.1.3. Vomitus Sample Collection

For subjects experiencing emesis within 4 hours following oral dosing, vomitus will be collected. Attempts will be made to collect vomitus from subjects experiencing emesis after 4 hours postdose. All vomitus collected will be stored for possible analysis as deemed appropriate.

7.1.4. Analytical Methodology

Plasma and urine concentrations of bemcentinib will be determined using a validated analytical procedure. Urine, and feces total radioactivity will be determined with liquid scintillation counting. Whole blood and plasma total radioactivity will be determined by accelerated mass spectrometry. Profiling and identification of metabolites in plasma, urine, and, where possible, feces will be conducted using standard laboratory procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Safety and Tolerability Assessments

7.2.1. Adverse Events

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

The condition of each subject will be monitored from the time of signing the ICF to 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.

Any AEs and remedial action required will be recorded in the subject’s source data. 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 treatment.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the investigator (or designee) to have stabilized. 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 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 breath test at the times indicated in the Schedule of Assessments in Appendix 6.

Additional clinical laboratory evaluations will 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 clinical laboratory safety evaluations is required.

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, 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.

All measurements will be performed singly, and repeated once if outside the relevant clinical reference range.

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 once if the investigator deems a repeat is indicated.

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 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

No formal statistical assessment of sample size has been conducted. The sample size chosen for this study is common in human radiolabeled studies and is considered sufficient to achieve the objectives of the study. Up to 8 subjects will be enrolled and studied as a single group in order that 6 complete the study.

8.2. Analysis Populations

8.2.1. Safety Population

The safety population will include all subjects who received a dose of radiolabeled study treatment (^{14}C-bemcentinib).

8.2.2. Pharmacokinetic Population

The PK population will include all subjects who received a dose of radiolabeled study treatment (^{14}C-bemcentinib) and have at least 1 valid PK concentration.

8.2.3. All Subjects Population

The all subjects population will include all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

8.3. Pharmacokinetic Analyses

Pharmacokinetic parameters of bemcentinib in plasma and urine, and total radioactivity in plasma and whole blood will be determined using standard noncompartmental methods, where data allow. Full details of PK parameters will be presented in the statistical analysis plan for this study.

Pharmacokinetic parameters will be listed and summarized. No formal statistical analysis will be performed.

The mass balance recovery of total radioactivity (percentage of the dose administered recovered in urine, feces, and total excreta) will be calculated by the radioanalysis laboratory.

8.4. Safety Analysis

Safety parameters will be listed and summarized. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

8.5. Interim Analysis

No formal interim analyses are planned for this study.

9. REFERENCES

1. BerGenBio. Bemcentinib, formerly known as BGB324 – Investigator's Brochure (Version 16). 27 April 2022.

2. ICRP, 1992. Radiological Protection in Biomedical Research. ICRP Publication 62, *Ann. ICRP*, 22(3).

3. Study 8442959: Absorption, Distribution, Metabolism, and Excretion of Bemcentinib (BGB324) After a Single Oral Administration of ^{14}C-Bemcentinib (BGB324) to Mice, Madison, Wisconsin, United States of America.

4. World Health Organization, 1977. Use of ionising radiation and radionuclides on human beings for medical research, training and nonmedical purposes. Technical report series No. 611, Geneva.

10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

Assessment of Severity

The investigator (or designee) will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at discharge will be followed up, where possible, until

resolution or until the unresolved AE is judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the discharge visit can be closed out as ongoing at the investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, investigator's brochure for an unapproved IMP).

Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of the study treatment and considered by the investigator to be possibly related to the study treatment, will be reported to the sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the electronic case report form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Serious AEs that occur between the time of signing the informed consent form and until 28 days after the dose of study treatment, regardless of relationship to the study treatment, must be reported within 24 hours of knowledge of the event to the sponsor or designee. In addition, if the investigator learns at any time of an SAE which is believed to be related to the study treatment then this must be reported to the sponsor, even if more than 28 days have elapsed since the dose of study treatment.

Serious AE reporting will be conducted as described in the safety management plan. The SAE form will collect all relevant data concerning the AE, including: details of the nature of the symptoms, time of onset, duration, and severity, together with an investigator's (or designee's) opinion of the relationship to study treatment, and any action taken in relation to the planned administration of study treatment. In addition, the investigator should provide relevant medical history, concomitant medications, laboratory or diagnostic test reports, details of any treatment for the SAE, and all other pertinent medical information.

Pregnancy

Pregnancy (paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin[a] Total CO_2 Total protein Troponin I Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[b]:	**Drug screen:**	
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test[c] Alcohol[c]	

[a] Direct and total bilirubin will always be measured
[b] Only analyzed at screening
[c] Screening and Day -1 check-in

Appendix 3: Total Blood Volume

The following blood volumes are the maximum that will be withdrawn for each subject.

		Up to Day 15	
	Volume per blood sample (mL)	**Maximum number of blood samples**	**Total amount of blood (mL)**
Clinical Laboratory evaluations	7.5	3	22.5
Serology	3.5	1	3.5
Whole blood for pharmacogenetic profiling	2	1	2
Whole blood for total radioactivity	2	28	56
Plasma for total radioactivity	6	28	168
Plasma for bemcentinib	4	28	112
Plasma for metabolite profiling	10	22	220
Total:			584

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 600 mL.

Appendix 4: Contraception Guidance

Contraception Guidance

Male Subjects

Male subjects with partners of childbearing potential must use a highly effective method of contraception (ie vasectomy) or 2 effective methods of contraception from check-in until 90 days after receiving the IMP dose. Acceptable methods of contraception for female partners include:

Highly effective:

- Combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal and transdermal) associated with inhibition of ovulation
- Progestogen-only hormonal contraception (oral, injectable and implantable) associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- Vasectomy (surgery that has been performed 90 days prior to the screening visit, with verbal confirmation of surgical success) – *male subjects.*

Effective:

- Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action)
- Male or female condom with spermicide.

To prevent exposure of any partner (male or female) during non-vaginal intercourse to the semen from a male subject who has been exposed to the IMP, the following contraception must be used:

- Condom.

The chosen contraception method(s) must be followed from the IMP dose until at least 90 days after receiving the IMP dose. Male subjects (even with a history of vasectomy) must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study and for 90 days after receiving the IMP dose. Male subjects must not donate sperm from receiving the IMP dose and for at least 90 days after receiving the IMP dose.

Sexual Abstinence and Same-sex Relationships

A subject who practices total abstinence is required to identify contraceptive methods he will use in the event of sexual activity. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the informed consent form becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

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 Council for 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 must be submitted to an ethics committee (EC) by the investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC 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 or any nonsubstantial changes, as defined by regulatory requirements.

The study will additionally be approved by the Administration of Radioactive Substances Advisory Committee.

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 treatment, 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 study site personnel, subjects will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy of the ICF will be given to the subject.

Subjects must be re-consented 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 the 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 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 study-related data may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

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, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Labcorp Drug Development is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a project management plan. Additional details of quality checking to be performed on the data may be included in a data management plan.
- 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 the study site archive for at least 5 years after the end of the study 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 Code of Federal Regulations Part 11-compliant electronic data capture system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to Labcorp Drug Development electronically, will be integrated with the subject's eCRF data in accordance with the data management plan.

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 electronic data capture 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.

Publications

The sponsor holds all publication rights to the data obtained from this study. Before any data from this study are published on the initiative of the investigator, a manuscript will be sent to the sponsor for review and approval at least 30 days prior to submission to the publisher.

Appendix 6: Schedule of Assessments

Study Procedures	Screening	Day -1	Days 1 to 8[a]	Discharge[b] Days 8 to 15	Outpatient Visit Days 22 to 29
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographic data	X				
Medical history	X	X[c]			
Urinary drug screen	X	X			
Alcohol breath test	X	X			
Cotinine test	X	X			
Serology	X				
Height and body weight	X				
Blood sampling for pharmacogenetic profiling[d]			Day 1 (predose)		
Study residency:					
Check-in		X			
Check-out				X	
Nonresidential visit	X				X
Study treatment administration:					
^{14}C-bemcentinib			Day 1 oral administration (0 hours) (30 minutes after starting a high-fat breakfast)		
Pharmacokinetics:					
Blood sampling for bemcentinib concentration (plasma)			Predose, 15 and 30 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours following the oral dose	192, 216, 240, 264, 288, 312, and 336 hours postdose	
Blood sampling for total radioactivity (whole blood and plasma)			Predose, 15 and 30 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours following the oral dose	192, 216, 240, 264, 288, 312, and 336 hours postdose[a]	

Study Procedures	Screening	Day -1	Days 1 to 8[a]	Discharge[b] Days 8 to 15	Outpatient Visit Days 22 to 29
Blood sampling for metabolite profiling and identification (plasma[g])			Predose, 15 and 30 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hours following the oral dose		
Urine collection for bemcentinib[j] concentration, total radioactivity, and metabolite profiling[g] and identification			Predose (-3 to 0 hours)[h], 0 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168 hours postdose[i]	168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288, 288 to 312, and 312 to 336 hours postdose[a]	Days 22 to Day 23, Days 29 to Day 30[e]
Fecal collection for total radioactivity and metabolite profiling[g] and identification			Predose (from check-in to 0 hours)[h], 0 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168 hours postdose[i]	168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288, 288 to 312, and 312 to 336 hours postdose[a]	Days 22 to Day 23, Days 29 to Day 30[e]
Safety and tolerability:					
Adverse event recording	X	X	Ongoing	X	X
Prior/concomitant medication monitoring	X	X	Ongoing	X	X
Clinical chemistry, hematology, and urinalysis	X	X		X	
Blood pressure and pulse rate[f]	X	X	Predose and 2, 4, 8, 24, and 48 hours postdose	X	
Oral body temperature	X	X		X	
12-lead electrocardiogram	X	X	Predose and 2 and 24 hours postdose	X	
Physical examination		X		X[k]	

[a] Additional 24-hour collections (urine and feces) for radioanalysis may continue up to Day 15 if mass balance recovery is not adequate or radioactivity is still being eliminated in excreta. Subjects will be discharged when the following criteria are met: ≥90% mass balance recovery and <1% of the total radioactive dose is recovered in excreta (urine and feces) in 2 consecutive 24-hour periods. If this is the case, subjects will be asked to remain resident within the clinical research unit for a further period (up until Day 15).

[b] Discharge will be from Day 8 to Day 15 depending on radioactivity elimination.

[c] Interim medical history.

[d] On Day 1, a blood sample will be collected and stored for subsequent assessment of the pharmacogenetic profile of bemcentinib in order to explore the influence of pharmacogenetic factors on the pharmacokinetics and safety.

[e] If discharge criteria (mass balance recovery) is not adequate (≤90% mass balance recovery, and >1% of the total radioactive dose is recovered in excreta [urine and feces] in 2 consecutive 24-hour periods) are not met by Day 8, subjects will be required to remain resident until discharge criteria are met, up to Day 15. If criteria are not met by Day 15, subjects may be asked to collect 24-hour excreta samples on up to 2 further occasions on a nonresidential basis to allow extrapolation of urinary and fecal excretion. If needed, the 2 additional 24-hour nonresidential collections will start on the morning of Days 22 and 29 (to be brought into the study site at the end of the collection interval on Days 23 and 30, respectively). If on the second occasion the subject has still not met the desired criterion, then the subject will be discharged from the study, per investigator and sponsor decision.

[f] Blood pressure and pulse rate will be measured singly followed by at least 5 minutes in the supine position.

[g] Plasma samples for metabolite profiling will be selected after confirming the total radioactivity time profile. Urine and fecal samples for metabolite profiling will be selected after confirming total radioactivity time profile in excreta.

[h] For the predose timepoint for urine and fecal collection, a single sample will be collected within 3 hours and 24 hours prior to dosing, respectively.

[i] Collection may cease after 168 hours (Day 8) if <1% of the total radioactive dose is recovered in excreta (urine and feces) in 2 consecutive 24-hour collection periods and if mass balance recovery is ≥90% (if 2 of the 3 recovery criteria are fulfilled, the investigator and sponsor will decide whether they require the subject to return to the unit).

[j] Analysis of pharmacokinetics will be performed on urine samples collected up to and including 168 hours postdose, only.

[k] Symptom-directed physical examination.