16.1.1. Protocol and Amendments

Protocol

A Phase I, Open-label Study of the Metabolism and Excretion of [^{14}C]-Zidebactam (WCK 5107) Following a Single Intravenous Infusion in Healthy Male Subjects

Protocol Status: Final
Protocol Date: 13 November 2017

Investigator Product: Zidebactam

Protocol Reference Number: W-5107-103
Covance Study Number: 8375685
IND Number:116002

Sponsor:
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SPONSOR APPROVAL

I have read the protocol and approve it.

Ashima Bhatia

Ashima Bhatia, MD
Senior Vice President
Global Research and Development
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14 NOV 2017

Date

SPONSOR APPROVAL

I have read the protocol and approve it.

14/Nov/2017

Rakesh Chugh, MD
Senior General Manager
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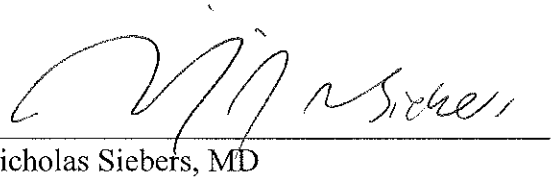
Date

INVESTIGATOR AGREEMENT

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



Nicholas Siebers, MD
Principal Investigator

15 NOV 2017
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STUDY IDENTIFICATION

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SYNOPSIS

Title of study: A Phase I, Open-label Study of the Metabolism and Excretion of [^{14}C]-Zidebactam (WCK 5107) Following a Single Intravenous Infusion in Healthy Male Subjects.

Objectives:

The primary objectives of the study are:

- To determine mass balance and routes of elimination of [^{14}C]- zidebactam following administration of a single 1g (approximately 200 μCi) radiolabeled intravenous (IV) infusion of zidebactam in healthy male subjects
- To assess the pharmacokinetics (PK) of a single IV infusion of zidebactam using [^{14}C]-labeled zidebactam
- To determine the whole blood and plasma concentrations of total radioactivity following a single IV infusion of [^{14}C]-zidebactam
- To determine the urinary and fecal recovery of the total administered radioactive dose

The secondary objectives of the study are:

- To characterize and identify metabolites of [^{14}C]-zidebactam in plasma, urine, and feces, as applicable
- To determine plasma and urine concentrations of non-radiolabeled zidebactam
- To assess the safety and tolerability of zidebactam

Study design:

This will be an open-label, nonrandomized, metabolism and excretion study of [^{14}C]-zidebactam administered as a 1g (approximately 200 μCi) IV infusion over 1 hour, administered in a fasted state. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharged.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to Check-in (Day -1). Subjects will be considered enrolled in the study after they have signed the informed consent form.

Subjects will be discharged from the CRU starting on Day 5 if ≥90% of the radioactive dose is recovered AND ≤1% of the radioactive dose is recovered in urine and feces (combined) for 2 consecutive 24 hour collection intervals. Subjects that do not meet discharge criteria will continue to stay in the CRU until either they have met discharge criteria or until the maximum stay is reached on Day 7.

Number of subjects:

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

Diagnosis and main criteria for inclusion:

Healthy male subjects aged 18 to 55 years, inclusive, with a body mass index between 18.5 and 29.9 kg/m^2, inclusive, at Screening.

Investigational products, dose, and mode of administration:

Subjects will receive an IV infusion of 1g [^{14}C]- zidebactam (200 μCi) over a period of 1 hour.

Duration of subject participation in the study:

Planned Screening Duration: 28 days

Length of Confinement: Check-in on Day -1, discharge as early as Day 5 and/or as late as Day 7.
Follow-up phone call: 4 ± 2 days post discharge.
Planned Study Duration: approximately 10 to 14 days.
Total duration (including Screening): Approximately 42 days maximum.

Endpoints:

Pharmacokinetics:

Blood, urine and feces will be collected at specified timepoints or intervals starting on Day -1 through discharge from the CRU. The following PK parameters will be calculated using noncompartmental methods, based upon the plasma concentration of zidebactam and ^{14}C total radioactivity in plasma and whole blood: area under the concentration-time curve (AUC) from time zero extrapolated to infinity ($AUC_{0-\infty}$), AUC from time zero to the last quantifiable concentration maximum observed concentration (C_{max}), time of C_{max}, apparent terminal elimination half-life ($t_{1/2}$), total systemic clearance (zidebactam only), volume of distribution during the terminal elimination phase (zidebactam only), volume of distribution at steady state (zidebactam only), AUC of plasma zidebactam relative to AUC of plasma total radioactivity, AUC of whole blood total radioactivity to AUC of plasma total radioactivity .

The following PK parameters will be calculated based on zidebactam concentration and total radioactivity in urine: amount excreted in urine (A_{eu}), cumulative $A_{eu,}$ percentage excreted in urine (f_{eu}), cumulative $f_{eu,}$ renal clearance (zidebactam only).

The following PK parameters will be calculated based on total radioactivity in feces: amount excreted in feces (A_{ef}), cumulative $A_{ef,}$ percentage excreted in feces (f_{ef}), and cumulative $f_{ef.}$

Other PK parameters may be included.

Safety:
Safety variables include clinical laboratory evaluations, electrocardiograms, physical examinations, vital signs, and adverse event (AE) assessments.

Statistical methods:

Pharmacokinetic parameters will be summarized using descriptive methodology, and AEs will be listed and summarized using descriptive methodology. No formal statistical analysis will be performed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
A_{ef}	amount excreted in feces
A_{eu}	amount excreted in urine
ALARA	as low as (is) reasonably achievable
API	active pharmaceutical ingredient
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{0-t}	area under the concentration-time curve from time zero to the last quantifiable concentration
CFR	Code of Federal Regulations
CL	total clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSA	clinical study agreement
EDC	electronic data capture
ECG	electrocardiogram
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
f_{ef}	percentage excreted in feces
f_{eu}	percentage excreted in urine
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDYF?	How Do You Feel?
HIV	Human Immunodeficiency Virus
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
MAD	multiple-ascending dose

NCE	new chemical entity
PK	pharmacokinetic(s)
RBC	red blood cell
SAD	single-ascending dose
SAE	serious adverse event
$t_{1/2}$	apparent terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	time of maximum observed concentration
WBC	white blood cell

1. INTRODUCTION

1.1. Overview

Zidebactam (WCK 5107) is a New Chemical Entity (NCE) exhibiting a dual mechanism of action as a β-lactamase inhibitor and an enhancer specifically binding to Gram-negative penicillin binding protein 2. A combination of cefepime, a 4th generation cephalosporin β-lactam, and zidebactam (WCK 5222) is being developed as an intravenous (IV) injectable formulation for the treatment of Gram-negative bacterial infections. WCK 5222 has been shown to be active against a variety of bacteria representing a diversity of resistance mechanisms. In view of the complementary properties of cefepime and zidebactam, a cefepime-zidebactam combination is expected to provide highly synergistic composition for treating infections caused by a wide variety of bacteria, including those producing one or more β-lactamases.

This study is an evaluation of the metabolism and excretion of zidebactam in healthy human subjects following a single dose of 1 g (approximately 200 μCi) of [^{14}C]-zidebactam administered as an IV infusion. As coadministration with cefepime has been demonstrated to have no effect on the pharmacokinetics (PK) of zidebactam (Section 1.3.2), cefepime will not be administered in this study.

Refer to the Investigator's Brochure (IB)[1] for more detailed information on the background of zidebactam and cefepime-zidebactam.

1.2. Summary of Nonclinical Pharmacokinetics

Preclinical pharmacokinetic and safety studies have been conducted in mice, rats, and dogs using single and multiple doses. Zidebactam exposure was dose-proportional, either alone, or in combination with cefepime, following subcutaneous administration in rodents and IV administration in dogs. Zidebactam was rapidly eliminated in all 3 species, with a maximum apparent terminal elimination half-life ($t_{1/2}$) of 2.1 h (standard deviation ±0.5 h) observed following a single IV dose of 10 mg/kg in dog.

Zidebactam was primarily excreted as unchanged drug in urine, in all 3 species, with 2 trace urinary metabolites detected in dogs and one trace urinary metabolite in rodents. No zidebactam or metabolites were detected in fecal samples from any of the 3 species, suggesting that zidebactam is cleared by urinary excretion alone. The pharmacokinetic and safety profile of cefepime is well established as the drug has been licensed since 1996; however no pharmacokinetic interactions between zidebactam and cefepime were observed in the 3 animal species studied following single or multiple dose administration of the cefepime-zidebactam combination.

1.3. Summary of Clinical Experience

Cefepime-zidebactam or zidebactam alone have been administered to a total of 107 healthy adult human subjects in 3 completed Phase I studies, including a single-ascending dose (SAD) study

(74 subjects) and 2 multiple-ascending dose (MAD) studies (33 subjects). In the SAD study, zidebactam alone was administered as single doses ranging from 250 mg to 3000 mg to healthy adult subjects in the US. Subjects in 2 crossover cohorts (2 dose levels of zidebactam) received cefepime and zidebactam both alone and in combination. Two Phase I studies in healthy subjects, and 1 in subjects with normal or impaired renal function, have been conducted and not yet reported. The studies in healthy subjects aimed to assess the effect of a single supratherapeutic IV dose of 2 g cefepime and 4 g zidebactam on QT/corrected QT interval and to assess and compare the plasma, epithelial lining fluid and alveolar macrophage concentrations following a seven combined IV doses of 2 g cefepime and 1 g zidebactam. The open-label Phase I study in subjects with normal or impaired renal function administered a single IV dose of cefepime-zidebactam.

1.3.1. Safety

No deaths, serious adverse events (SAEs), or discontinuations due to adverse events (AEs) were reported in the conducted SAD study. Across the study and all cohorts, 22 (29.7%) subjects reported 42 treatment-emergent adverse events (TEAEs), the majority of which were mild in severity; only 2 subjects had TEAEs of moderate severity (both headache). Three subjects (37.5%) administered 1 g zidebactam as a 1 hour infusion reported 6 TEAEs, of which 1 was considered drug related (headache). No subject had a severe TEAE. Headache was the most commonly reported TEAE (10.8% subjects across all cohorts).

No deaths or SAEs were reported in either MAD study and all TEAEs were mild in severity. In the zidebactam MAD study, the most frequently reported TEAEs were infusion site swelling (4 subjects), infusion site erythema (4 subjects), and headache (4 subjects). In the cefepime-zidebactam MAD study, the most frequently reported TEAEs were headache (6 subjects), infusion site pain (5 subjects), and infusion site swelling (3 subjects). Discontinuations due to AEs were reported for 4 subjects in the cefepime-zidebactam MAD study due to drug eruption, diarrhea, abdominal pain, and *Clostridium difficile* colitis.

No deaths or SAEs were noted in the completed, unreported studies, and no AEs leading to discontinuation were noted in the QT or renal impairment studies. No effect on QT was noted following administration of cefepime-zidebactam. Refer to the IB[1] for more detailed information regarding safety and tolerability of zidebactam.

1.3.2. Pharmacokinetics

Following single-ascending IV infusion doses of zidebactam from 250 mg to 3000 mg, the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) ranged from 44.3 to 458 µg•h/mL and maximum concentration (C_{max}) from 16.5 to 174 µg/mL; the AUC and C_{max} increased in a dose-proportional manner. The $t_{½}$ ranged from 1.84 to 2.39 h and appeared to be independent of dose. Median time to C_{max} (t_{max}) was 1.00 and 3.00 h in the 60-minute and 180-minute infusion cohorts, respectively. For the crossover cohorts, $AUC_{0-\infty}$, C_{max}, $t_{½}$, and related PK parameters were consistent for both cefepime and zidebactam. The ratio of C_{max} and ratio of AUC for each drug given in combination divided by each drug administered alone were close to unity (range 0.88 to 0.99), indicating no relevant PK interaction between the 2 drugs at the

evaluated dose combinations. Renal clearance accounted for the majority of plasma clearance, which appeared to be independent of dosage regimen (for zidebactam the 2 crossover cohorts) and treatment sequence (when each drug was given alone versus in combination). The majority (>80%) of the administered dose of zidebactam and cefepime was excreted as unchanged drug within the first (0 to 6 hour) collection interval, with complete dose recovery within 24 hours postdose.

In the MAD studies, sequential cohorts received multiple IV infusions of either zidebactam alone (1 g or 2 g every 8 hours) for 7 days or the cefepime-zidebactam combination (2 g cefepime and 1 g zidebactam, or 2 g cefepime, and 2 g zidebactam, every 8 hours) for 10 days. Exposure parameters for zidebactam ($AUC_{0-\infty}$, C_{max}) were comparable for each dosing interval within each dosing day and between dosing days. In the zidebactam alone MAD study, $AUC_{0-\infty}$ ranged from 150 to 343 µg•h/ml and C_{max} from 59.5 to 129 µg/ml. In the cefepime-zidebactam MAD study, $AUC_{0-\infty}$ for zidebactam ranged from 152 to 402 µg•h/ml and C_{max} from 57.2 to 130 µg/ml, whereas cefepime $AUC_{0-\infty}$ ranged from 341 to 508 µg•h/ml and C_{max} from 130 to 160 µg/ml. The majority of the administered doses of zidebactam and cefepime were excreted unchanged in urine.

1.4. Study Rationale

Knowledge of the metabolism and excretion of parent drug and its metabolites is useful for evaluating the Metabolites in Safety Testing requirements elucidated in the FDA Guidance[2] and International Conference on Harmonisation M3[3] and the likelihood of effects of renal or hepatic impairment on the disposition of zidebactam and the likelihood for drug-drug interactions with zidebactam. The results from this study may guide future study designs using special populations or evaluating the potential for drug-drug interactions.

The purpose of this study is to determine the excretion kinetics of zidebactam and to identify and characterize metabolites present in plasma, urine, and feces in healthy male subjects following a single dose of 1 g (approximately 200 µCi) of [^{14}C]-zidebactam administered as an IV infusion. Data from this study may be used to guide the design of future studies conducted in special populations or to address potential drug-drug interactions.

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 (Section 3.3). More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with zidebactam may be found in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

The primary objectives of the study are:

- To determine mass balance and routes of elimination of [^{14}C]- zidebactam following administration of a single 1g (approximately 200 μCi) radiolabeled IV infusion of zidebactam in healthy male subjects
- To assess the PK of a single IV infusion of zidebactam using [^{14}C]-labeled zidebactam
- To determine the whole blood and plasma concentrations of total radioactivity following a single IV infusion of [^{14}C]- zidebactam
- To determine the urinary and fecal recovery of the total administered radioactive dose.

2.1.2. Secondary Objectives

The secondary objectives of the study are:

- To characterize and identify metabolites of [^{14}C]-zidebactam in plasma, urine, and feces, as applicable
- To determine plasma and urine concentrations of non-radiolabeled zidebactam
- To assess the safety and tolerability of zidebactam.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary PK endpoints of zidebactam and total radioactivity derived from the whole blood and plasma concentration-time profiles following IV administration of [^{14}C]- zidebactam are as follows:

- area under the concentration-time curve (AUC) from time zero extrapolated to infinity ($AUC_{0-\infty}$)
- AUC from time zero to the last quantifiable concentration (AUC_{0-t})
- maximum observed concentration (C_{max})
- time of C_{max} (t_{max})
- apparent terminal elimination half-life ($t_{1/2}$)
- total systemic clearance (zidebactam only; CL)
- volume of distribution during the terminal elimination phase (zidebactam only; V_z)
- volume of distribution at steady state (zidebactam only; V_{ss})

- AUC of plasma zidebactam relative to AUC of plasma total radioactivity (AUC Plasma zidebactam/ Total Radioactivity Ratio)
- AUC of whole blood total radioactivity to AUC of plasma total radioactivity (AUC Blood/Plasma Ratio).

The primary PK outcome endpoints of zidebactam and total radioactivity derived from urine collections are as follows:

- amount excreted in urine (A_{eu})
- cumulative A_{eu}
- percentage excreted in urine (f_{eu})
- cumulative f_{eu}
- renal clearance (zidebactam only; CL_R).

The primary PK outcome endpoints of total radioactivity derived from feces collections are as follows:

- amount excreted in feces (A_{ef})
- cumulative A_{ef}
- percentage excreted in feces (f_{ef})
- cumulative f_{ef}.

Other PK parameters may also be added.

2.2.2. Secondary Endpoints

The secondary metabolite endpoints are as follows:

- metabolic profile of [^{14}C]-zidebactam
- identification of [^{14}C]-zidebactam metabolites.

The secondary safety outcome measures for this study are as follows:

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

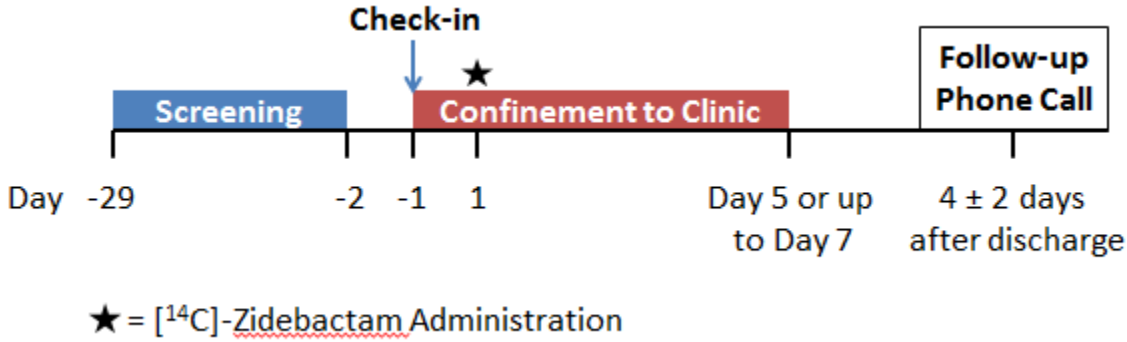
3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be an open-label, nonrandomized, metabolism and excretion study of [^{14}C]-zidebactam administered as a 1g (approximately 200 µCi) IV infusion over 1 hour in up to 8 healthy male subjects following at least an 8-hour fast from food (not including water).

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to Check-in (Day 1). Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until Clinic Discharge. Up to 8 subjects will be dosed on Day 1 to ensure that 6 subjects complete the study. Subjects will be discharged from the CRU starting on Day 5 if ≥90% of the radioactive dose is recovered AND ≤1% of the radioactive dose is recovered in urine and feces (combined) for 2 consecutive 24 hour collection intervals. Subjects that do not meet discharge criteria will continue to stay in the CRU until either they have met discharge criteria or until the maximum stay is reached on Day 7.

Blood, urine, and fecal samples will be collected at specified times during the study for PK, metabolite profiling, and radioanalysis. Safety will be evaluated using the following assessments: physical examinations, 12-lead ECGs, vital signs, How Do You Feel? (HDYF?) inquiries, and clinical laboratory evaluations (Appendix 2). All AEs will be recorded throughout the study (ie, from the time of signing the informed consent until completion of the Follow-up phone call).

The total duration of study participation for each subject (from Screening through Follow-up phone call) is anticipated to be a maximum of approximately 42 days.

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 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 5.

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.

Female subjects will be excluded to align with regulatory guidance. The "as low as (is) reasonably achievable" (ALARA) principle prescribed by both the FDA and Nuclear Regulatory Commission (2007)[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 study drug is different in females versus males), then the radiation exposure to female subjects should be kept at zero potential by not including females in radioactivity studies and only enrolling and dosing male subjects.

IV administration was chosen since this is the intended clinical route of administration. Based on the nonclinical data and the known plasma PK and excretion pattern of zidebactam, 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

The chosen single 1 g IV dose of zidebactam provides pharmacokinetically- and pharmacodynamically relevant concentrations in healthy subjects. Safety data from previous Phase 1 studies has demonstrated that single IV doses of 1 g have been well tolerated in healthy subjects.

The planned radioactive dose of approximately 200 μCi of [^{14}C]-zidebactam is expected to provide a sufficient radioactive signal to achieve the study objectives with minimal radiation risk to subjects. Based upon whole-body dosimetry studies conducted in rat, the maximum whole-body radiation dose expected in a human male subject following administration of a single 200 μCi (7.4 MBq) IV dose of [^{14}C]-zidebactam was estimated (by conversion of dosimetry report, which was based on a 100 μCi dose) to be 3.8 mrem (0.038 mSv).[4] This value is well below the FDA exposure limit of 3000 mrem after a single dose for human isotope studies.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

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

1. Males, of any race, between 18 and 55 years of age, inclusive.
2. Body mass index between 18.5 and 29.9 kg/m^2, inclusive at Screening and Check-in (Day -1).
3. In good health, determined by no clinically significant findings from medical history, physical examination (at Check-in [Day -1]), 12-lead ECG, vital signs measurements, and

clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, Gilbert's syndrome] is not acceptable) at Screening or Check-in as assessed by the Investigator (or designee).

4. Blood pressure between 90 and 140 mmHg systolic, inclusive, and not higher than 90 mmHg diastolic, unless deemed not clinically significant by the Investigator (or designee).
5. Subjects will agree to use contraception as detailed in Section 6.6.
6. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.
7. 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:

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 alcoholism or drug/chemical abuse within 1 year prior to Check-in (Day -1).
4. Alcohol consumption of >28 units per week for males. One unit of alcohol equals 12 oz. (360 mL) of beer, 1½ oz. (45 mL) of liquor, or 5 oz. (150 mL) of wine.
5. Positive urine drug screen at Screening, or positive alcohol breath test or positive urine drug screen at Check-in.
6. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2). Subjects whose results are compatible with prior immunization may be included at the discretion of the Investigator.
7. Participation in a clinical study involving administration of an investigational drug (NCE) in the past 30 days or within 5 half-lives (if known), whichever is longer, prior to Check-in.
8. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's Wort, within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
9. Use or intend to use any prescription medications/products within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
10. 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).

11. 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).
12. Consumption of foods and beverages containing poppy seeds, grapefruit, or Seville oranges from 7 days prior to Check-in and for the duration of the study.
13. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in, as determined by medical history and cotinine test.
14. Unwilling to refrain from strenuous exercise from 48 hours prior to Check-in (Day -1) and for the duration of the study.
15. Unwilling to refrain from consumption of caffeine- or xanthine-containing products for 48 hours prior to Check-in (Day -1) and for the duration of the study.
16. Consumption of alcohol 48 hours prior to Check-in (Day -1) and for the duration of the study.
17. Receipt of blood products within 2 months prior to Check-in.
18. Donation of blood from 56 days prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening until after the Follow-up phone call.
19. Poor peripheral venous access.
20. Have previously completed or withdrawn from this study or any other study investigating zidebactam, and have previously received the investigational product.
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 have participated in a radiolabeled drug study where exposures are known to the Investigator within the previous 4 months prior to admission to the clinic for this study or participated in a radiolabeled drug study where exposures are not known to the Investigator within the previous 6 months prior to admission to the clinic for this study. The total 12-month exposure from this study and a maximum of 2 other previous radiolabeled studies within 4 to 12 months prior to this study will be within the Code of Federal Regulations (CFR) recommended levels considered safe, per US Title 21 CFR 361.1: less than 5,000 mrem whole-body annual exposure with consideration given to the half-lives of the previous radiolabeled study drugs received.
23. 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 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 101, 102, 103).

Subjects will be identified by either their Screening 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 the study, 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 (eCRF). If a subject is withdrawn, efforts will be made to perform all discharge assessments, if possible (Appendix 5). Other safety 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
- cancellation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Active pharmaceutical ingredient (API; nonradiolabeled powder) will be supplied by the Sponsor and radiolabeled API (powder) will be supplied by Arcinova, along with the batch/lot numbers and Certificates of Analysis. A Covance CRU licensed pharmacist will manufacture and label the investigational medical product (IMP) from bulk supplies, such that each unit dose contains a total of 1 g zidebactam containing approximately 200 μCi of [^{14}C]-zidebactam. The completed drug product will be released by GMP Quality Assurance under GMP conditions or by a second licensed pharmacist if under non-GMP conditions prior to administration to subjects.

The Sponsor will supply a sufficient quantity of the applicable API for the manufacture of the unit doses at Covance CRU. All excipients will be sourced by Covance. Specific instructions regarding dose preparation 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 CRU in a location that is locked with restricted access.

5.2. Study Treatment Administration

Appropriate unit doses will be administered to consecutively numbered subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at specific times, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. For each dose, the subject's actual dosing time will be recorded in the source documents and transcribed into the eCRFs.

On Day 1, following at least an 8-hour fast from food (not including water), subjects will receive an IV infusion of [^{14}C]-zidebactam over a period of 1 hour. Subjects will be asked to be semi-supine/supine for the IV dosing. For each subject, the start, and end of infusion time, as well as any dosing interruptions, will be documented in the source data.

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.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

All doses will be administered under the supervision of suitably qualified study site staff.

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.

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 and/or in accordance with local/state/federal guidelines governing waste disposal of investigational drugs.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from participation in a clinical study involving administration of an investigational drug (NCE) in the past 30 days, or 5 half-lives (if known), whichever is longer, prior to Check-in.

Subjects will refrain from use of any prescription medications/products, or any medications/products known to alter drug absorption, metabolism or elimination processes from 14 days prior to Check-in (Day -1) or 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).

A mild laxative (ie, Milk of Magnesia®, Colace®) may be used to help with bowel movements if necessary and will not be considered a concomitant medication. 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, until the follow-up phone call, without prior approval of the Investigator (or designee), unless its use is deemed necessary in a medical emergency. 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 clinical laboratory evaluations.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in (Day -1) and for the duration of the study.

Caffeine- or xanthine-containing foods and beverages will not be allowed from 48 hours prior to Check-in (Day -1) and for the duration of the study.

Consumption of alcohol will not be permitted from 48 hours prior to Check-in and for the duration of the study.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in (Day -1) and for the duration of the study.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 48 hours prior to Check-in (Day -1) and for the duration of the study. Subjects 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 56 days prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until after the Follow-up phone call.

6.6. Contraception

Male subjects will be surgically sterile for at least 90 days or when sexually active with female partners of childbearing potential will be required to use a male condom with spermicide from Check-in until 90 days after the last dose of study drug.

Sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the last dose of study drug. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the last dose of study drug.

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

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 ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

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 order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- ECGs
- blood samples for PK, total radioactivity, and metabolites
- start and end of urine, collections for PK assessments
- vital signs measurements
- blood and urine samples for clinical laboratory evaluations
- physical examinations

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic, Total Radioactivity, and Metabolite 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 5 for determination of zidebactam plasma concentrations, total radioactivity whole blood and plasma concentrations, and metabolite profiling, and identification. Blood samples will be collected from the contralateral arm to the arm/hand used for dose administration on Day 1. Procedures for collection, processing, and shipping of blood samples will be detailed in a separate document.

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 Table 1 for determination of zidebactam 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 Table 1 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 predose administration on Day 1. Procedures for collection, processing, and shipping of feces collections will be detailed in a separate document.

7.1.3. Analytical Methodology

Plasma and urine concentrations of zidebactam will be determined using a validated analytical procedure.

Total radioactivity concentrations will be determined in whole blood, plasma, urine, and feces using liquid scintillation counting. 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 serious AEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to the follow up phone call. 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 and follow-up phone call. 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. Nonserious AE information should also be collected from the start of a washout period or other observational period intended to establish a baseline status for the subjects. 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 up, where possible, until resolution. 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, coagulation and serology) at the times indicated in the

Schedule of Assessments in Appendix 5. Clinical laboratory evaluations are listed in Appendix 2.

Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

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 5.

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, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 5. 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 5.

Single 12-lead ECGs may be repeated once if outside the clinical reference range at the request of the Investigator or designee.

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 abbreviated physical examinations will be performed at the timepoints specified in the Schedule of Assessments in Appendix 5.

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. Pharmacokinetic Population

The PK population will include all subjects who received [^{14}C]-zidebactam and have evaluable PK data.

8.2.2. Safety Population

The safety population will include all subjects who received [^{14}C] -zidebactam and have at least 1 postdose safety assessment.

8.3. Pharmacokinetic Analyses

The plasma and urine PK parameters of zidebactam and whole blood, plasma, urine, and fecal PK parameters of total radioactivity will be calculated using standard noncompartmental methods. Additional noncompartmental PK parameters may be determined where appropriate.

Pharmacokinetic parameters will be summarized using descriptive methodology. No formal statistical analysis will be performed.

8.4. Safety Analysis

All AEs will be listed and summarized using descriptive methodology. No formal statistical analysis will be performed. The incidence of AEs will be presented by severity and by association with the study drug as determined by the Investigator (or designee). Each AE will be coded using the Medical Dictionary for Regulatory Activities.

8.5. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

1. Wockhardt. Cefepime-Zidebactam – Investigator's Brochure (Version 02). 18 August 2016.

2. US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER); Guidance for Industry, Safety Testing of Drug Metabolites; Availability. *Federal Register*. 2008; 73 (31): 8884-8885.

3. ICH Harmonised Tripartite Guideline M3: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals; July 1997. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf. 2009.

4. Crossman, L; Murphy, B; Holdsworth, C; Potchioiba, MJ. Covance 8337156. [14C]-WCK 5107: Absorption, Distribution, Metabolism, and Excretion in the Rat. Covance Laboratories, Inc.; Madison, Wisconsin; 2016.

10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An 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 an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether, or not related to the study drug.

Assessment of Severity

The Investigator 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 will make a determination of the relationship of the AE to the study drug using a 2-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, and/or has no reasonable temporal relationship with administration of the study drug
- **Related**: The AE follows a reasonable temporal sequence from administration of the study drug, and does not have another apparent clinical cause

Action Taken for Adverse Events

The Investigator or designee will record the action taken for the AE in the eCRF. Actions taken will include:

- **Dose not changed**: The medication schedule was not changed
- **Drug withdrawn**: The medication schedule was modified through termination of the prescribed regimen of medication
- **Subject withdrawn from study**

- **Not applicable**
- **Unknown**

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 IMP or study procedures at Discharge will be followed up, where possible, until resolution. 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 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, IB for an unapproved IMP).

Serious Adverse Events

An 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.

Definition of Life-threatening

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 CRU. 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 eCRF. 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

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and are serious and unexpected. Food and Drug Administration-reportable AEs will be reported by the study site to the Sponsor, Medical Monitor assigned by the Sponsor, and the responsible Institutional Review Board (IRB).

The Sponsor and Medical Monitor will be notified in writing (eg, facsimile) within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported.

Subsequently, a written confirmation or summary of the AE (using FDA Form 3500A or equivalent) will be sent to the Sponsor within 3 working days of the original notification.

The IRB will be notified of any FDA-reportable AEs within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

The responsibility for reporting SAEs will be transferred to the Sponsor 30 days after the end of the study.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Gamma-glutamyl transferase Glucose Phosphorus Potassium Sodium Total bilirubin[a] Total CO_2 (measured as bicarbonate) Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology[b]:	**Drug Screen[c]:**	**Coagulation**
Anti-hepatitis B surface antibody Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Cotinine Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Alcohol breath test[d]	International normalized ratio Prothrombin time

[a] Direct bilirubin will be analyzed if total bilirubin is elevated
[b] Only analyzed at Screening
[c] Only analyzed at Screening and Check-in
[d] Alcohol testing is not included at Screening

Appendix 3: Total Blood Volume

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

		Up to Day 7[a]	
	Volume per blood sample (mL)	**Maximum number of blood samples**	**Total amount of blood (mL)**
Clinical laboratory evaluations	10.7	4	42.8
Serology	4	1	4
Plasma for zidebactam concentration	4	22	88
Whole blood and plasma for total radioactivity	4	22	88
Plasma for metabolite profiling and identification	10	10	100
Total:			322.8

[a] Subjects could be discharged on Day 5 if the discharge criteria are met or may be resident within the Clinical Research Unit for additional 24-hour collections (blood, urine, and feces) for total radioactivity up to Day 7.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed the volume of a normal blood donation

Appendix 4: 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) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an 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 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will additionally be approved by the Radiation Safety 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 drug, 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 CRU personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

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 or full date of birth in 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 **S**ponsor, by appropriate IRB 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 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.
- Covance 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 risk management register. 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 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.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each subject who signs an ICF and 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.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals patient to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process shall occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution, and Investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor shall have 60 days to respond with any requested revisions, including without limitation, the deletion of confidential information. The Investigator shall act in good faith upon requested revisions, except the Investigator shall delete any confidential information from such proposed publications. The Investigator shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 5: Schedule of Assessments

Table 1: Schedule of Assessments

Study Procedures	Screening	Check-in	Treatment Period				Clinic Discharge / ET	Follow-up Phone Call
	Days -29 through -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5 or up to Day 7	4 ± 2 days after discharge
Informed Consent	X							
Demographics	X							
Medical History	X	X[a]						
Height, Weight, and BMI	X	X[b]						
Hepatitis and HIV Screen	X							
Alcohol and Drug Screen[c]	X	X						
Cotinine Screen	X	X						
Confined to the Clinical Site		X	X	X	X	X	X	
Physical Examination		X					X[d,m]	
12-Lead ECG[e]	X	X					X[m]	
Vital Signs[f]	X	X	X	X	X	X	X	
Clinical Laboratory Evaluations	X	X		X			X[m]	
HDYF? Inquiry[g]		X	X	X	X	X	X	X
AE Evaluations	X	X	X	X	X	X	X	X
Review of Concomitant Medications and Procedures	X	X	X	X	X	X	X	X
[^{14}C]-Zidebactam Administration[h]			X					
Blood Samples for PK and Total Radioactivity Analysis[i]			X	X	X	X	X	
Blood Samples for Metabolite Profiling and Identification[j]			X	X	X	X	X (Day 5 only)	
Urine Samples[k]		X	X	X	X	X	X	
Fecal Samples[l]		X	X	X	X	X	X	

AE = adverse event; BMI = body mass index; CBC = complete blood count; ECG = electrocardiogram; HDYF? = How Do You Feel? Inquiry; HIV = human immunodeficiency virus; PK = pharmacokinetics; UA = urinalysis

[a] Interim medical history only.

[b] Height measured at Screening only. BMI to be recalculated on Day -1.

[c] Drug screen does not include alcohol testing at Screening but does include an alcohol breath test at Check-in.

[d] Abbreviated physical examination only.

[e] Single 12-lead ECGs will be obtained at Screening, Check-in (Day -1), and prior to Clinic Discharge. The ECGs will be collected after the subject has been resting in a supine position for at least 5 minutes. The 12-lead ECGs will be performed before blood draws on appropriate days and when blood draw and ECG timepoints coincide, ECGs will be performed prior to the blood draws and as close to the scheduled timepoint as possible.

[f] Vital signs (oral temperature, respiratory rate, and supine blood pressure and pulse) will be obtained at Screening; Check-in (Day -1); on Day 1 at predose (0 Hour) and 1, 3, and 12 hours postdose; daily at 24-hour intervals; and prior to Clinic Discharge. Vital signs measurements will be performed with the subject supine and after the subject has rested for at least 5 minutes. When the timepoints for blood draws and vital signs measurements coincide, the vital signs measurements will be collected prior to the blood draws and as close to the scheduled timepoint as possible.

[g] How Do You Feel? inquiry performed at Check-in, each postdose vital signs measurement, and during the Follow-up phone call.

[h] Single IV dose of [^{14}C]-zidebactam at 1g (approximately 200 µCi) will be administered as an IV infusion over 1 hour.

[i] Blood samples for PK and radioanalysis will be collected prior to start of infusion and 0.25, 0.5, 1 (just prior to end of infusion), 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, and 96 hours after the start of infusion. If subject is not discharged on Day 5, additional blood samples will be collected every 24 hours until Clinic Discharge.

[j] Blood samples for metabolite identification and profiling will be collected at prior to start of infusion and 1 (just prior to end of infusion), 2, 4, 8, 12, 24, 48, 72, and 96 hours post start of infusion.

[k] Urine samples will be collected at -12 hours through 0 hour (predose) and at the following collection intervals: 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, and 72 to 96 hours after start of infusion. If subjects are not eligible for discharge on Day 5, urine will continue to be collected for 24-hour intervals until the subject meets discharge criteria or until the maximum stay (Day 7).

[l] If possible, a baseline fecal sample will be collected after Check-in (Day -1) until just prior to dosing on Day 1. All postdose fecal samples will then be collected daily (24-hour intervals) from Days 1 through 5 (96 hours postdose) to determine total [^{14}C]-radioactivity in feces and/or for metabolite profiling/identification. If subjects are not eligible for discharge, fecal samples will continue to be collected for 24-hour intervals until either the subject meets discharge criteria or until the maximum stay (Day7).

[m] Assessment to be completed at Clinic Discharge or Early Termination only.