CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1, open-label, 1-sequence crossover, drug-drug interaction study to assess the effect of repeated doses of cefiderocol on the pharmacokinetics of midazolam in healthy adult participants
Protocol Number:	2136R2118
Version Number:	Version 2 (Amendment 1)
Compound:	Cefiderocol (S-649266)
Brief Title:	Phase 1 drug-drug interaction study of cefiderocol
Study Phase:	Phase 1
Sponsor Name*:	Shionogi
Legal Registered Address:	Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA
Issue Date:	08 Mar 2022

Confidentiality Statement

This document and the information contained herein or attached hereto ("Confidential Material") are confidential and proprietary to Shionogi. This Confidential Material should only be viewed by those individuals or companies that have been given prior authorization to do so by Shionogi ("Authorized Users"). This Confidential Material should not be made available in any form to any person or company, other than the Authorized Users and their respective employees or associates on a need-to-know basis, without the written consent from Shionogi.

Sponsor Signatory:

Refer to electronic signature page
[redacted]
Shionogi & Co., Ltd.

Refer to electronic signature page
Date

Medical Monitor Name and Contact Information:

[redacted]
Shionogi Inc.
300 Campus Drive, Florham Park, NJ 07932 USA
Tel: [redacted]
Mobile: [redacted]

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 2 (Amendment 1)	08 Mar 2022
Version 1	22 Feb 2022

Version 2 (Amendment 1): (08 March 2022)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment is to remove urea from the clinical chemistry panel and to add fentanyl as a requirement in the drug screen.

A high-level description of the change(s) and brief rationale for specific items are outlined in the following:

Section # and Name	Description of Change	Brief Rationale
8.2.4 Clinical Safety Laboratory Tests 10.2 Appendix 10.2: Clinical Laboratory Tests (Table 10-1)	Removed urea from blood chemistry panel.	This change is because this analyte is not offered by the site laboratory.
10.2 Appendix 10.2: Clinical Laboratory Tests (Table 10-1)	Added fentanyl as requirement for drug screening.	This change is to ensure fentanyl testing is included in the drug screen.
6.1 Study Interventions Administered (Table 6-1)	Updated physical description of midazolam; added footnote to clarify that US FDA-approved, commercially-available midazolam syrup will be used in the study.	Updated information in Table 6-1 to match the midazolam product cited. These changes were made for clarification.
11 References	Changed citation for midazolam syrup.	Replaced citation for midazolam to a product listed on the https://dailymed.nlm.nih.gov website.
11 References	Reference to Zhanel et al 2019 removed and numbering of references was updated.	This change was made as this reference was not cited in the text.
10.9 Appendix 9: Protocol Amendment History	New section added.	This change was made in compliance with the protocol template when a protocol amendment is made.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

1. PROTOCOL SUMMARY

1.1 Synopsis

Study Title:

A Phase 1, open-label, 1-sequence crossover, drug-drug interaction study to assess the effect of repeated doses of cefiderocol on the pharmacokinetics of midazolam in healthy adult participants

Protocol Number:

2136R2118

Compound:

Cefiderocol (S-649266)

Brief Title:

Phase 1 drug-drug interaction study of cefiderocol

Rationale:

Cefiderocol is an injectable cephem antibiotic with a catechol group on the 3-position side chain developed as a treatment for aerobic, Gram-negative, bacterial infections. This study is being conducted to evaluate the potential for cefiderocol to affect the pharmacokinetics (PK) of midazolam (a cytochrome P450 3A [CYP3A] probe) in healthy adult participants.

Objectives and Endpoints:

Table 1-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of repeated doses of cefiderocol on the PK of midazolam, a CYP3A substrate, in healthy adult participants	• Midazolam: C_{max}, T_{max}, AUC, $t_{1/2,z}$, λ_z, CL/F, V_z/F, and MRT
Secondary	
• To evaluate the PK of cefiderocol after coadministration with midazolam • To evaluate the safety and tolerability of cefiderocol after coadministration with midazolam	• Cefiderocol: C_{max}, T_{max}, AUC, and CL • Physical examination findings, vital sign values, 12-lead ECG results, clinical laboratory test values, and TEAEs

λ_z = plasma terminal elimination rate constant; AUC = area under the plasma concentration-time curve; CL = total clearance; CL/F = apparent total clearance; C_{max} = maximum plasma concentration; CYP3A = cytochrome P450 3A; ECG = electrocardiogram; MRT = mean residence time; PK = pharmacokinetics; $t_{1/2,z}$ = terminal elimination half-life; TEAE = treatment-emergent adverse event; T_{max} = time to maximum plasma concentration; V_z/F = apparent volume of distribution in the terminal elimination phase

Overall Design:

This will be a Phase 1, open-label, 1-sequence crossover study in healthy adult participants.

Brief Summary:

The purpose of this study is to determine the effect of repeated doses of cefiderocol on the PK of midazolam.

The study will consist of a Screening Period (Days −28 to −3), including a Screening Visit; a Treatment Period (with confinement in the clinical research unit [CRU] from Days −2 to 16, single oral administration of midazolam 5 mg in the morning on Days −1 and 15, and intravenous infusion of cefiderocol 2 g every 8 hours [q8h] from Day 1 through Day 15 or 16 (depending on the start time of the first of the 3 administrations of cefiderocol, the final administration may occur in the early hours of Day 16), and discharge from the CRU on Day 16); and a Follow-up Period, including a Follow-up (Day 23 ± 2) or Early Termination Visit (see Figure 1-1 for study schema and Figure 1-2 for the Schedule of Activities [SoA]).

A total of 2 doses of midazolam and 45 doses of cefiderocol will be administered to each participant during the study.

Midazolam will be administered orally alone in the fasted state in the morning on Day −1. The intravenous infusion of cefiderocol q8h will be started in the morning on Day 1 and continue for 15 days. Midazolam and cefiderocol will be coadministered in the fasted state in the morning on Day 15 and then 2 additional doses of cefiderocol will be administered 8 and 16 hours after the coadministration of midazolam and cefiderocol.

Number of Participants:

It is planned that 14 participants will be enrolled to receive study intervention (cefiderocol and midazolam).

[**Note**: *Enrolled* means a participant has agreed to participate in the clinical study following completion of the informed consent process, the participant has completed all screening assessments, and the participant has met all eligibility requirements. A screened participant is one who has completed the informed consent process (the participant may subsequently withdraw consent and/or may not meet all eligibility criteria).]

Intervention Groups and Duration:

Study Intervention, Route, and Intervention Form:

- Cefiderocol 2 g; intravenous infusion over 3 hours
- Midazolam 2 mg/mL syrup, 5 mg (2.5 mL); oral administration in the fasted state

Study Intervention Duration:

- Midazolam 5 mg on Days -1 and 15
- Cefiderocol 2 g q8h for 15 days on Days 1 through 15 or 16

Study Duration:

- The total study duration for each subject (Screening, Treatment Period, and Follow-up Period complete for all 14 subjects) is approximately 7 to 8 weeks.

Data Monitoring/Other Committee: No

1.2 Schema

The study schematic is summarized in Figure 1-1.

See the SoA for detailed information on study assessments and timing in Figure 1-2 and Figure 1-3, respectively.

Figure 1-1 Study Schematic

Screening Period	**Confinement Period (includes Treatment Period)**			**Follow-up Period**
	Midazolam 5 mg in the morning on Day -1	Cefiderocol 2 g q8h on Days 1 to 14	Midazolam 5 mg plus cefiderocol 2 g in the morning on Day 15, and cefiderocol 2 g 8 and 16 hours after the coadministration	
4 weeks (Days -28 to -3)	2 days (Days -2[a] to -1)	14 days (Days 1 to 14)	2 days (Days 15 to 16[b])	7 days after discharge (Day 23 ± 2)

CRU = clinical research unit; q8h = every 8 hours

Midazolam 5 mg will be orally administered on Days -1 and 15 in the fasted state.

Cefiderocol 2 g will be intravenously infused over 3 hours q8h. The intravenous infusion of cefiderocol will be started in the morning on Day 1 and performed for 15 days. A total 45 doses of cefiderocol will be administered to each participant during the study.

a Admission to CRU on Day -2.

b Discharge from CRU on Day 16.

1.3 Schedule of Activities

Figure 1-2 Schedule of Activities

Procedure	Screening (Days -28 to -3)	Confinement Period (Day)																Discharge from CRU (Day 16)	Follow-up or Early Termination Visit (Day 23 ± 2)
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Administrative assessments																			
Informed consent	X																		
Inclusion and exclusion criteria	X		X[a]																
Demography	X																		
Medical history including prior medications[b]	X	X																	
Clinical Assessments																			
Weight and BMI	X	X																	
Complete physical examination[c]	X	X	X	X													X	X	X
Symptom-focused physical examination[d]					X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG for safety assessment[e]	X	X	X	X														X	X	
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events review	←==========→																		
Concomitant medication review	←==========→																		

Procedure	Screening (Days -28 to -3)	Confinement Period (Day)																Discharge from CRU (Day 16)	Follow-up or Early Termination Visit (Day 23 ± 2)
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Special situations (abuse, misuse, overdose, or medication error of study intervention cefiderocol/ midazolam)		←==========→																	X
Study intervention procedures																			
Cefiderocol administration[g]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Midazolam administration[h]			X															X		
Laboratory assessments																			
Drug, alcohol, and cotinine urine screen	X	X																		
Serological tests[i]	X																			
Pregnancy test[j]	X	X																		X
FSH test[k]	X																			
Laboratory tests[l]	X	X		X		X		X			X		X			X		X	X	X
PK blood samples for cefiderocol[m]						X			X			X			X			X	X	

Procedure	Screening (Days -28 to -3)	Confinement Period (Day)																Discharge from CRU (Day 16)	Follow-up or Early Termination Visit (Day 23 ± 2)
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
PK blood samples for midazolam[n]			X	X														X	X	

BMI = body mass index; CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; PK = pharmacokinetic; q8h = every 8 hours

a On Day −1, inclusion/exclusion criteria to be evaluated prior to administration of midazolam.

b Medical history will include a review of prior therapies in the previous 3 months.

c Height will be measured only at the Screening Visit. On the days in which study intervention is administered, complete physical examination to be performed 4 hours ± 30 minutes after dosing.

d Includes any system examination based on the nature of the participant's complaint and the investigator evaluation. The allowable time frame for assessment will be 60 minutes based on the administration time of cefiderocol in the morning on Day 1.

e Electrocardiography for safety assessment will be performed at the timepoints below. Allowable time frames for collection are ± 15 minutes after dosing of midazolam on Days -1 and 15 (−2 to 0 hours for the predose collection), and ± 30 minutes for the sample on Day 1 (24 hours after dosing of midazolam). At the Follow-up/Early Termination Visit, safety assessments can be performed at any time. The EGC measurements should be preceded by at least 5 minutes of rest.
- During the Screening Period
- On Day −2 (admission)
- On Day −1: before midazolam administration (0 hours) and 2 hours post midazolam
- On Day 1: 3 hours after the start of cefiderocol infusion in the morning (end-of-infusion)
- On Days 15: 3 hours after the coadministration (midazolam and start of cefiderocol infusion)
- At the Follow-up (Days 21 to 25) or Early Termination Visit

f Vital sign measurements include oral body temperature, pulse rate, respiratory rate, and blood pressure (3 consecutive readings) and will be collected at the timepoints below. Allowable time frame for collection is ± 20 minutes (−2 to 0 hours for the predose collection). The time window is ± 30 minutes for assessments done ≥ 24 hours after dosing of midazolam, except at the Follow-up/Early Termination Visit, at which safety assessments can be performed at any time. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest.
- During the Screening Period
- On Day -2 (admission)
- On Day -1: predose (0 hours) and 0.5, 1, 3, 5, and 8 hours after midazolam administration

- On Day 1: 24 hours after midazolam administration and 3 hours after the start of cefiderocol infusion in the morning (end-of-infusion)
- On Days 2 to 13: predose (0 hours) cefiderocol in the morning
- On Day 15: predose (0 hours) and 1, 3, 5, and 8 hours after coadministration (midazolam and start of cefiderocol infusion)
- On Day 16: 24 hours after the coadministration (midazolam and start of cefiderocol infusion)
- At the Follow-up (Days 21 to 25) or Early Termination Visit

g The intravenous infusion of cefiderocol q8h (± 15 minutes) will be started in the morning on Day 1 and performed for 15 days. A total of 45 doses of cefiderocol will be administered for each participant in the study.

h Midazolam 5 mg will be administered alone on Day -1 and administered within 5 minutes of the start of the first cefiderocol infusion on Day 15.

i Serological tests will include testing for positive hepatitis B surface antigen, positive hepatitis C virus antibody, and positive HIV antigen/antibody.

j Urine or serum pregnancy test will be for all females.

k Blood sample for serum FSH levels must be obtained to confirm female study participant's postmenopausal status if no documentation confirming postmenopausal status is available.

l Samples for laboratory tests, including hematology, blood chemistry, urinalysis, coagulation, and lipid profile tests, will be collected at the time points below. The time window is ± 30 minutes for assessments done ≥ 24 hours after dosing of midazolam, except at the Follow-up/Early Termination Visit, at which safety assessments can be performed at any time.
- During the Screening Period
- On Day −2 (admission)
- On Day 1: 24 hours after midazolam administration
- On Days 3, 8, 5, 10, and 13: predose (0 hours) cefiderocol in the morning
- On Days 15: predose (0 hours) midazolam in the morning
- On Day 16: 24 hours after midazolam administration
- At the Follow-up Visit (Days 21 to 25) or Early Termination Visit

m Blood samples for cefiderocol PK will be collected:
- On Days 3, 6, 9, and 12: predose (0 hours) cefiderocol in the morning
- On Day 15: predose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 16 hours after the coadministration (midazolam and start of cefiderocol infusion – if not simultaneous timings are based on midazolam administration)
- On Day 16: 24 hours after the coadministration (midazolam and start of cefiderocol infusion – if not simultaneous timings are based on midazolam administration)

The allowable time frame for predose collection on Days 3, 6, 9, 12, and 15 will be -15 to 0 minutes prior to the start of infusion. The allowable time frame for 3-hour postdose collection will be -5 to 0 minutes prior to the end of infusion. The allowable time frame for 8- and 16-hour postdose collection will be -5 to 0 minutes prior to the start of infusion. The allowable time frame for 24-hour postdose collection will be ± 20 minutes. The allowable time frame for other postdose collection will be ± 5 minutes.

n Blood samples for midazolam PK will be collected:
- On Day -1: predose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 16 hours after midazolam administration
- On Day 1: 24 hours after midazolam administration

- On Day 15: predose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 16 hours after the coadministration (midazolam and start of cefiderocol infusion – if not simultaneous timings are based on midazolam administration)
- On Day 16: 24 hours after the coadministration (midazolam and start of cefiderocol infusion – if not simultaneous timings are based on midazolam administration)

The allowable time frame for predose collection on Day -1 will be -2 to 0 hours. The allowable time frame for predose collection on Day 15 will be -5 to 0 minutes prior to midazolam and the start of the first cefiderocol infusion. The allowable time frame for 3-hour postdose collection on Day 15 will be -5 to 0 minutes prior to the end of first cefiderocol infusion. The allowable time frame for 8- and 16-hour postdose collection on Day 15 will be -5 to 0 minutes prior to the start of cefiderocol infusion. The allowable time frame for 24-hour postdose collection on Days 1 and 16 will be ± 20 minutes, and the 24-hour postdose collection on Day 1 will be prior to the start of cefiderocol infusion. The allowable time frame for other postdose collection will be ± 5 minutes.

Figure 1-3 Permitted Windows for Study Activities

Study Activity	Visit/Timepoint	Acceptable Window
Screening	Screening (Days -28 to -3)	28 to 1 days prior to confinement
Confinement	Days -2 through 16	≥ 10 hours prior to midazolam dose on Day -1 through ≥ 24 hours post midazolam dose on Day 15
Administration of midazolam	Day -1 Day 15	Morning after ≥ 10 hours fast After ≥ 10 hours fast and ≤ 5 minutes of start of first cefiderocol infusion on Day 15
Administration of cefiderocol	Day 1, after collection of 24-hour midazolam PK blood sample through Day 15/16	Every 8 hours ± 15 minutes (total of 45 infusions) fed or fasted
PK blood sampling for midazolam	Day -1 predose midazolam (0 hours)	≤ 2 hours before midazolam administration
	Day -1, post midazolam (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 16 hours)	± 5 minutes of scheduled time
	Day 1 post midazolam (24 hours)	± 20 minutes of scheduled time
PK blood sampling for cefiderocol	Days 3, 6, 9, and 12, predose start of cefiderocol infusion (0 hours)	≤ 5 minutes before start of first cefiderocol infusion of the day
PK blood sampling for midazolam and cefiderocol	Day 15, predose coadministration (0 hours)	≤ 5 minutes before midazolam (and start of first cefiderocol infusion on Day 15)
	Day 15, postdose coadministration (3 hours)	≤ 5 minutes of end of first cefiderocol infusion on Day 15
	Day 15, postdose coadministration (8 hours)	≤ 5 minutes of start of second cefiderocol infusion on Day 15
	Day 15, postdose coadministration (16 hours)	≤ 5 minutes of start of third cefiderocol infusion on Day 15
	Day 16, postdose coadministration (24 hours)	± 20 minutes of scheduled time
Complete physical examination	Day -2	≥ 10 hours prior to midazolam dose on Day -1
	Day -1, postdose midazolam (4 hours) Day 15, postdose coadministration (4 hours)	± 30 minutes of scheduled time
	Day 1, postdose cefiderocol (4 hours start of first infusion)	± 30 minutes of scheduled time
Symptom-focused physical examination	Days 2 to 14, as clinically indicated	Within 60 minutes (based on the start time of the first cefiderocol infusion on Day 1)

Study Activity	Visit/Timepoint	Acceptable Window
ECG	Day -2 Admission	No window specified
	Day -1, predose midazolam (0 hours)	≤ 2 hours before midazolam administration
	Day -1, postdose midazolam (2 hours)	± 15 minutes of scheduled time
	Day 1, postdose cefiderocol (3 hours after start of first infusion)	± 30 minutes of scheduled time
	Day 15, postdose coadministration (3 hours)	± 15 minutes of scheduled time
Vital signs	Day -2 Admission	No window specified
	Day -1, predose midazolam (0 hours)	≤ 2 hours before midazolam administration
	Day -1, postdose midazolam (0.5, 1, 3, 5, and 8 hours)	± 20 minutes of scheduled time
	Day 1, postdose midazolam (24 hours after) and postdose cefiderocol (3 hours after start of first infusion)	± 30 minutes of scheduled time
	Days 2 to 13, predose cefiderocol (0 hours, start of first infusion of each day)	≤ 2 hours before cefiderocol administration
	Day 15, predose coadministration (0 hours)	≤ 2 hours before coadministration
	Day 15, predose (0 hours) and postdose coadministration (1, 3, 5, and 8 hours)	± 20 minutes of scheduled time
Safety labs	Day -2 Admission	No window specified
	Day 1, postdose midazolam (24 hours)	± 30 minutes of scheduled time
	Days 3, 5, 8, 10, and 13	≤ 2 hours before first cefiderocol administration of the day
	Day 15, predose coadministration (0 hours)	≤ 2 hours before coadministration
	Day 16, postdose coadministration (24 hours)	± 30 minutes of scheduled time
Follow-up Visit	Day 23	± 2 days

ECG = electrocardiogram; PK = pharmacokinetic

2. INTRODUCTION

2.1 Study Rationale

Cefiderocol is an injectable cephem antibiotic with a catechol group on the 3-position side chain. Cefiderocol is a treatment for aerobic, Gram-negative, bacterial infections. This study is being conducted to evaluate the potential for cefiderocol on the PK of midazolam (a CYP3A probe) in healthy adult participants.

2.2 Background

Antibiotic resistance has been widely publicized and poses a serious threat to public health worldwide. Research efforts in recent years have become increasingly geared towards discovering and developing new classes of antibiotics with modes of action distinct from those of established agents and activity against resistant strains.

Cefiderocol exerts its antibacterial activity against Gram-negative bacteria by inhibiting cell wall synthesis. The molecular structure of cefiderocol offers several unique and important characteristics resulting in enhanced activity against carbapenem-resistant infections caused by Gram-negative bacteria, including Enterobacteriaceae and nonfermenters, independent of the underlying mechanism of carbapenem resistance.

Cefiderocol has been approved in the United States (US) for the treatment of adult patients with:

- Complicated urinary tract infections, including pyelonephritis caused by the following susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex
- Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii* complex, *E. coli*, *E. cloacae* complex, *K. pneumoniae*, *P. aeruginosa*, and *Serratia marcescens*

Cefiderocol has also been approved for use in similar indications for infections with Gram-negative microorganisms in other regions.

A detailed description of the chemistry, pharmacology, efficacy, and safety of cefiderocol is provided in the package insert [1].

2.3 Benefit/Risk Assessment

This Phase 1 study is being undertaken to assess the PK, safety, and tolerability of cefiderocol in healthy participants receiving midazolam; therefore, there is no expected benefit for the study participants.

Information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of cefiderocol are included in the package insert [1].

3. OBJECTIVES, ENDPOINTS

Table 3-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of repeated doses of cefiderocol on the PK of midazolam, a CYP3A substrate, in healthy adult participants	• Midazolam: C_{max}, T_{max}, AUC, $t_{1/2,z}$, λ_z, CL/F, V_z/F, and MRT
Secondary	
• To evaluate the PK of cefiderocol after coadministration with midazolam • To evaluate the safety and tolerability of cefiderocol after coadministration with midazolam	• Cefiderocol: C_{max}, T_{max}, AUC, and CL • Physical examination findings, vital sign values, 12-lead ECG results, clinical laboratory test values, and TEAEs

λ_z = plasma terminal elimination rate constant; AUC = area under the plasma concentration-time curve; CL = total clearance; CL/F = apparent total clearance; C_{max} = maximum plasma concentration; CYP3A = cytochrome P450 3A; ECG = electrocardiogram; MRT = mean residence time; PK = pharmacokinetics; $t_{1/2,z}$ = terminal elimination half-life; TEAE = treatment-emergent adverse event; T_{max} = time to maximum plasma concentration; V_z/F = apparent volume of distribution in the terminal elimination phase

4. STUDY DESIGN

4.1 Scientific Rationale for Study Design

This study design is in accordance Food and Drug Administration (FDA) Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling [2]. Midazolam was selected as the substrate for evaluation in this study from the list of recommended substrates of CYP3A in the FDA guidance document [2]. The clearance of midazolam is primarily mediated by CYP3A.

The study will be conducted in an open-label (un-blinded) manner as the primary purpose of the study is focused on PK parameter assessments, which are objective rather than subjective endpoints and therefore do not require blinding for unbiased interpretation.

The treatment schedule was defined based on the terminal elimination half-life of midazolam (approximately 3 hours, see midazolam package insert [3]). In order to ensure the maximal induction of the pathway, coadministration of cefiderocol and midazolam will be administered on Day 15. The FDA guidance states “The sponsor should administer inducers as multiple doses to ensure the maximal induction of a specific pathway. It may take about 2 weeks of daily drug administration to achieve the maximum level of induction in a specific pathway” [4]. The maximum duration of treatment for cefiderocol recommended in the product label is 14 days.

To ensure participant safety, participants will enter the CRU the day before first study intervention administration and remain in the CRU for at least 24 hours following coadministration of midazolam and cefiderocol. The safety assessments in this study are

standard measures for assessing the safety of participants exposed to study intervention in the clinical setting.

4.2 Justification for Dose

The study will evaluate the effect of cefiderocol on the PK of midazolam.

The doses of cefiderocol and midazolam to be used in this study are in accordance with the approved dosage and administration (see cefiderocol and midazolam package inserts [1, 3]).

4.3 End of Study Definition

The end of the study will be defined as the date of the last visit of the last participant in the study.

A participant will be considered to have completed study participation if he/she has completed all periods of the study through the Follow-up Visit.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants will be eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be 18 to 60 years of age inclusive, at the time of signing the informed consent form (ICF).

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation, including medical history, physical examination, clinical laboratory tests, vital sign measurements, and 12-lead electrocardiography (ECG) at the Screening Visit and upon admission to the CRU.

Weight

3. Body weight ≥ 50 kg and body mass index (BMI) within the range of ≥ 18.5 to ≤ 32.0 kg/m^2 at the Screening Visit.

Sex and Contraceptive/Barrier Requirements

4. Male or female
   a. If male, agrees to the following during the Treatment Period and for at least 3 months after the last dose of study intervention:

- Refraining from donating sperm

  Plus, either:

- Abstaining from heterosexual intercourse as the preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Must agree to use a male condom plus partner's use of a contraceptive method with a failure rate of < 1% per year as described in Table 10-2 when having penile-vaginal intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

b. Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:
  - Is not a WOCBP (see Section 10.4.1 [Appendix 4])

    OR
  - Is a WOCBP and using an acceptable contraceptive method as described in Section 10.4.2 (Appendix 4) during the Treatment Period (at a minimum until after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
  - A WOCBP must have a negative highly sensitive (see Section 10.2 [Appendix 2]) urine or serum pregnancy test during screening and within 24 hours before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1.3 (Appendix 1) that includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
2. Systolic blood pressure outside the range of 90 to 145 mm Hg, diastolic blood pressure outside the range of 50 to 95 mm Hg, pulse rate outside the range of 40 to 100 beats per minute, or blood pressure or pulse values considered clinically significant by the investigator at the Screening Visit or upon admission to the CRU. Abnormal values may be retested once.
3. Lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
4. Breast cancer within the past 10 years.
5. Alanine aminotransaminase (ALT) > 1.5 × upper limit of normal (ULN) at the Screening Visit or upon admission to the CRU.
6. Aspartate aminotransaminase (AST) > 1.5 × ULN at the Screening Visit or upon admission to the CRU.
7. Bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) at the Screening Visit or upon admission to the CRU.
8. Estimated glomerular filtration rate (eGFR) < 80 mL/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at the Screening Visit or upon admission to the CRU.
9. Chronic history of or current liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
10. QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for male participants or > 470 msec for female participants at the Screening Visit or upon admission to the CRU.
11. Risk factors for:
    a. Torsades de Pointes (eg, heart failure, cardiomyopathy, or family history of long QT syndrome or Brugada syndrome).
    b. Unexplained syncope, sick sinus syndrome, second- or third-degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, angina, prolonged QT interval, or conduction abnormalities.
12. Any condition requiring medication and/or other treatment, such as dietary restriction and physical therapy.

Prior/Concomitant Therapy

13. Past use of over-the-counter or prescription medication, including herbal medications, traditional Chinese medicines, vitamins, minerals, dietary supplements, and vaccines within 14 days (or 5 terminal half-lives, whichever is longer) prior to admission to the CRU (which will occur on Day –2) or intended use of any of the above throughout the study enrollment.
14. Used drugs or substances known to be inducers of cytochrome P450 (CYP450) enzymes and/or P-glycoprotein (P-gp) within 28 days prior to admission to the CRU (which will occur on Day –2; see Section 10.7 [Appendix 7] and Section 10.8 [Appendix 8]).

Prior/Concurrent Clinical Study Experience

15. Significant blood loss of ≥ 500 mL or blood or plasma donation within 56 days prior to the Screening Visit until completion of the study, or from the Screening Period until admission to the CRU through completion of the study.
16. Exposure to more than 4 new chemical entities within 12 months prior to dosing.
17. Current enrollment or past participation in any other investigational trial or exposure to another investigational drug within the last 28 days or 5 half-lives of the previously administered study intervention (date derived from last study procedure [blood collection or dosing] of previous trial), whichever is longer, prior to admission to the CRU.
18. Previous exposure to cefiderocol within 30 days prior to the first dose of study intervention.

Diagnostic Assessments

19. History of coronavirus disease 2019 (COVID-19) infection within 14 days prior to the Screening Visit or admission, or close contact with a COVID-19 patient in the 14 days prior to the Screening Visit or admission as reported by the participant and the participant's medical history.
20. Presence of hepatitis B surface antigen (HBsAg) at the Screening Visit or within 3 months prior to first dose of study intervention.
21. Positive hepatitis C antibody test result at the Screening Visit or within 3 months prior to first dose of study intervention. Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained.
22. Positive hepatitis C RNA test result at the Screening Visit or within 3 months prior to the first dose of study intervention. The test is optional and participants with negative hepatitis C antibody test will not be required to also undergo hepatitis C RNA testing.
23. Positive drug/alcohol screen at the Screening Visit or upon admission to the CRU.
24. Positive human immunodeficiency virus (HIV) antibody/antigen test at the Screening Visit.

25. Considered inappropriate for participation in the study for any reason by the investigator or subinvestigator.

Other Exclusions

26. Regularly consumes excessive amounts of alcohol, defined as > 3 glasses of alcoholic beverages per day (1 glass is approximately equivalent to: beer [284 mL/10 ounces (oz)], wine [125 mL/4 oz] or distilled spirits [25 mL/1 oz]).
27. History of drug or alcohol abuse/addiction.
28. Regularly consumes excessive amounts of caffeine, defined as > 6 servings of coffee, tea, caffeinated soft drinks, or other caffeinated beverages per day (1 serving is approximately equivalent to 120 mg of caffeine).
29. Used tobacco- or nicotine-containing products (including cigarette, pipe, cigar, chewing tobacco, nicotine patch, or nicotine gum) within 6 months prior to admission to the CRU or refuses to refrain from using tobacco- or nicotine-containing products throughout the study (including Follow-up Period).
30. Consumed alcohol or used alcohol-containing products within 72 hours prior to admission to the CRU or refuses to refrain from consuming such products through discharge on Day 16.
31. Used caffeine-containing products/medications (eg, coffee, tea, caffeinated soft drinks, other caffeinated beverages, or chocolate) within 24 hours prior to admission to the CRU or refuses to refrain from using such products through discharge on Day 16.
32. Consumed grapefruit, grapefruit juice, orange juice, and apple juice within 7 days prior to admission to the CRU or refuses to refrain from consuming such products throughout the study (including the Follow-up Period).
33. Sensitivity to heparin or heparin-induced thrombocytopenia.
34. Sensitivity to either of the study interventions, or components thereof, or drug or other allergy, including food allergy, that, in the opinion of the investigator or medical monitor, contraindicates participation in the study. Including history of penicillin hypersensitivity or allergy.
35. Female study participants who have a positive pregnancy test at the Screening Visit.
36. Female study participants who are lactating.
37. Poor venous access.

5.3 Lifestyle Considerations

Lifestyle considerations (including use of caffeine, alcohol, recreational drugs, and tobacco or nicotine, and meals and dietary restrictions) are included in the exclusions in Section 5.2.

5.3.1 Meals and Dietary Restrictions

1. Participants must refrain from consumption of grapefruit, grapefruit juice, orange juice, and apple juice from 7 days prior to admission to the CRU throughout the study (including the Follow-up Period).
2. During CRU stay, all foods/beverages will be provided by the study site staff, and all study participants will be given the same meals (except on the days of admission and administration of study intervention). From consent acquisition to the completion of the Follow-up (or Early Termination) examination, study participants must refrain from excess eating and excess drinking.
3. Midazolam will be administered in the fasting state. On Days -1 and 15, study participants will fast from all food and beverages, except water, for at least 10 hours prior to administration of midazolam on Days -1 and 15. No food will be allowed for at least 4 hours after administration of midazolam.

5.3.2 Caffeine, Alcohol, and Tobacco

1. Participants will abstain from ingesting caffeine-containing products (eg, coffee, tea, caffeinated soft drinks, other caffeinated beverages, or chocolate) from 24 hours prior to admission to the CRU through discharge on Day 16.
2. Participants will abstain from alcohol or use of alcohol-containing products from 72 hours prior to admission to the CRU through discharge on Day 16.
3. Use of tobacco and nicotine-containing products (including cigarette, pipe, cigar, chewing tobacco, nicotine patch, or nicotine gum) will not be allowed from 6 months prior to admission to the CRU until after the Follow-up/Early Termination Visit.

5.3.3 Activity

Participants will abstain from strenuous exercise from admission to the CRU until discharge from the CRU. Participants may participate in light recreational activities during the study (eg, watching television, reading).

5.4 Screen Failures

A screen failure is defined as a participant who consents to participate in the clinical study but who does not meet 1 or more criteria for participation in the study and are not subsequently entered in the Treatment Period of the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

At a minimum, the following information (if applicable) must be recorded in the electronic case report form (eCRF) for all screen failures: date of informed consent, baseline participant characteristics, all eligibility criteria not met, date of screen failure, reason for screen failure, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the discretion of the investigator. Rescreened individuals should be assigned a new participant number for every screening/rescreening event (eg, initial screening number: [redacted] rescreening number: [redacted], and these numbers should be linked.

Retesting of a participant for a specific test during the Screening Period will be allowed at the investigator's discretion and will not be considered rescreening.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

6.1 Study Interventions Administered

Table 6-1 details the study interventions.

Table 6-1 Study Interventions

Intervention name	Cefiderocol	Midazolam[a]
Type	Drug	Drug
Dosage form	Infusion solution: reconstitute in 0.9% normal saline to 2 g/100 mL	Syrup
Unit dose strength	1 g/vial	2 mg/mL
Dosage levels	2 g (100 mL) q8h from Days 1 through 15/16	5 mg (2.5 mL) once daily on Days −1 and 15
Physical description	White to off-white sterile lyophilized powder for reconstitution	Clear, red to purplish-red mixed-fruit flavored syrup (or equivalent)
Route of administration	IV administration over 3 hours	Oral
Use	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP
Dosing and administration instructions	Fed or fasted state Refer to the package insert for drug preparation and administration instructions [1]	Fasted state Refer to the package insert for drug preparation and administration instructions [3]
Sourcing	Provided centrally by the sponsor	Provided locally by the trial site
Packaging and labeling	Clear glass vials (NDC 59630-266-01) sealed with a rubber stopper and an aluminum seal with flip-off cap. 10 single dose vials/carton Labeled per package insert (or equivalent) [1]	118 mL amber bottle supplied with 1 press-in bottle adapter, 4 single-use, graduated, oral dispensers and 4 tip caps. Labeled per package insert (or equivalent) [3]

FDA = Food and Drug Administration; IMP = investigational medicinal product; IV = intravenous; NDC = national drug code; NIMP/AxMP = non-investigational medicinal product/ auxiliary medicinal product; q8h = every 8 hours; US = United States

a US FDA-approved, commercially-available midazolam syrup will be used in the study.

6.2 Preparation, Handling, Storage, and Accountability of Study Intervention

1. Cefiderocol (provided by the sponsor) should be stored refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light. Midazolam should be stored according to the package insert [3].
2. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
3. Only participants enrolled in the study may receive study intervention and only the investigator and authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label single-arm study. All study participants will receive the same study interventions, therefore randomization is not required.

6.4 Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee in the CRU, under medical supervision. The date and time of each dose administered will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. On Days −1 and 15, study site staff will examine each participant's mouth to ensure that the midazolam was ingested.

6.5 Dose Modification

Dose modification is not permitted in this study.

6.6 Prior/Concomitant Therapy

Participants must abstain from taking prescription or nonprescription drugs (including herbal medications, Chinese medicines, vitamins, minerals, and dietary supplements) and vaccines within 14 days (or 5 terminal half-lives, whichever is longer) before the start of study intervention until completion of the Follow-up/Early Termination Visit, unless, in

the opinion of the investigator and sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of not more than 1 g q8h (≤ 3 g/day), is permitted for simple analgesia at the investigator's discretion. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

6.7 Intervention After the End of the Study

There will be no study intervention following the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation from the study as a whole is detailed in Section 10.1.8 (Appendix 1).

7.1 Discontinuation of Study Intervention

The investigator will make every reasonable attempt to ensure a participant completes the study. However, it may be necessary for a participant to permanently discontinue study intervention. Reasons for discontinuation of study intervention may include AEs, participant request, investigator discretion, pregnancy, or protocol deviation.

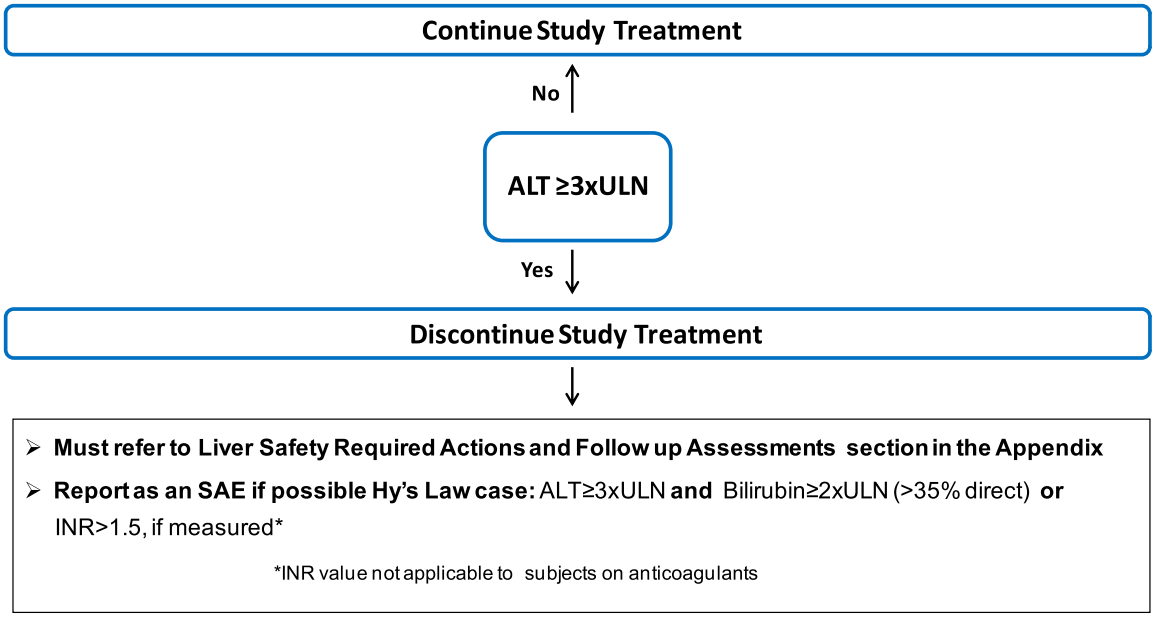
Discontinuation of study intervention is required if the participant meets any of the liver chemistry stopping criteria (Section 7.1.1) or if the participant becomes pregnant (Section 8.3.5).

If study intervention is permanently discontinued, the participant should complete the Follow-up/Early Termination Visit assessments before discharge from the CRU, and the participant should be asked to return for the Follow-up/Early Termination Visit for the final safety check. See the SoA (Figure 1-2) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Liver Chemistry Stopping Criteria

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria outlined in Figure 7-1 are met or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Figure 7-1 Liver Chemistry Stopping Criteria



ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Section 10.5 (Appendix 5).

7.2 Overall Design

This will be a Phase 1, open-label, 1-sequence crossover study in healthy adult participants.

The study will consist of a Screening Period (Days −28 to −3), including a Screening Visit; a Treatment Period (with confinement in the CRU from Days −2 to 16); and a Follow-up period including a Follow-up (Day 23 ± 2) or Early Termination Visit (see Figure 1-1).

Prospective study participants will be screened within 28 days prior to the first planned dose of midazolam administration. Subjects who meet the inclusion criteria and do not meet any exclusion criteria will be enrolled into the study. Participants who are enrolled in the study will be admitted to the CRU on Day −2.

A total of 2 doses of midazolam and 45 doses of cefiderocol will be administered to each participant during the study.

A single oral dose of midazolam 5 mg will be administered in the fasted state in the morning on Day −1. The intravenous infusion of cefiderocol 2 g q8h will be started in the morning on Day 1 and continue for 15 days. Midazolam and cefiderocol will be coadministered in the fasted state in the morning on Day 15 and then 2 additional doses

of cefiderocol will be administered 8 and 16 hours after the coadministration of midazolam and cefiderocol.

Study participants will be continuously monitored for safety during their entire CRU admission and will be discharged from the CRU on Day 16.

It is planned that 14 participants will be enrolled to receive study intervention (cefiderocol and midazolam).

Plasma samples for midazolam PK will be obtained prior to dosing on Day −1 through 24 hours postdose. Plasma samples for cefiderocol PK will be obtained predose on Days 3, 6, 9, and 12 to confirm trough levels. On Day 15, a 5-mg dose of midazolam and a 2-g dose of cefiderocol will be coadministered; PK sampling for both drugs will be obtained prior to dosing through 24 hours following coadministration.

7.2.1 QTc Stopping Criteria

Not applicable.

7.3 Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be discontinued at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. The sponsor may decide to replace a participant who withdraws for a nonsafety-related issue.

If the participant withdraws consent, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Figure 1-2). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. If the participant discontinues from the study during the Treatment Period (ie, while in the CRU), the participant should complete the Follow-up/Early Termination Visit assessments before discharge from the CRU, and the participant should be asked to return for the Follow-up/Early Termination Visit for the final safety check.

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if he/she fails to return for scheduled visits and is unable to be contacted by the site staff.

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

- The site staff must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant by phone and the contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have discontinued from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Figure 1-2). Protocol waivers or exemptions will not be allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator must maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 350 mL during study enrollment and treatment. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

Safety and tolerability will be evaluated based on physical examination findings, clinical laboratory test results, vital sign measurements (oral body temperature, pulse rate, respiratory rate, and blood pressure), 12-lead ECG results, and AE monitoring (see Section 10.2 (Appendix 2) for clinical laboratory tests to be performed and Section 10.3

(Appendix 3) for definitions of AEs, SAEs, assessment of intensity, assessment of causality, and procedures for recording, evaluating, follow-up, and reporting).

Planned timepoints for all safety assessments are provided in the SoA (Figure 1-2).

For any abnormal laboratory test results (hematology, blood chemistry, urinalysis, coagulation, or lipid profile tests) or other safety assessments (eg, physical examination, vital signs, ECGs) that worsen following exposure to the study intervention from baseline, the investigator will consider whether those results are clinically significant. Abnormal laboratory test results are defined as values outside the reference range. For test results which are abnormal at baseline and significantly worsen following the initiation of the study, the investigator must also consider whether those results are clinically significant. Any test results which are considered to be clinically significant by the investigator are to be recorded as AEs. If an abnormal laboratory finding is associated with disease or organ toxicity, the investigator should report only the disease or organ toxicity as an AE.

The investigator will consider test results to be clinically significant in the following circumstances (at their own discretion in the other circumstances):

- Test results that lead to any of the outcomes included in the definition of an SAE (see Section 8.3).
- Test results that lead to a change in study intervention dosing or discontinuation or discontinuation from the study.
- Test results that lead to a concomitant drug treatment or other therapy.
- Test results that require additional diagnostic testing (except for a confirmatory test) or other medical intervention.
- Test results that meet the management and stopping criteria for abnormal liver function tests identified in Section 7.1 and Section 10.5 (Appendix 5).

In addition, when any test results meet the management and stopping criteria for liver function abnormalities (Section 7.1 and Section 10.5 [Appendix 5]), the results of further assessments and required follow-up should be recorded in the Liver Event Form.

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height will be measured and recorded at Screening only. Weight and BMI will be measured and recorded at the Screening Visit and on Day −2 on admission to the CRU.

A symptom-focused physical examination relevant to the study participant's current condition will be performed as clinically indicated as specified in the SoA (Figure 1-2) for new or worsening AEs/symptoms.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Oral body temperature, pulse rate, respiratory rate, and blood pressure will be assessed; abnormal readings may be repeated once.
- Vital sign measurements (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). Each of the 3 blood pressure readings will be recorded on the eCRF.
- Blood pressure and pulse measurements will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3 Electrocardiography

A single 12-lead ECG will be obtained as outlined in the SoA (Figure 1-2) using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTc intervals. The EGC measurements should be preceded by at least 5 minutes of rest.

8.2.4 Clinical Safety Laboratory Tests

The following clinical laboratory tests will be performed for safety evaluation:

- Hematology: hemoglobin, hematocrit, red blood cell count and indices, white blood cell count and differential (absolute and relative), platelet count
- Blood chemistry: glucose, creatinine, eGFR CKD-EPI, blood urea nitrogen (BUN), BUN/creatinine ratio, uric acid, sodium, potassium, calcium, chloride, phosphorus, AST, ALT, gamma-glutamyl transferase (GGT), bilirubin (total, direct, indirect), alkaline phosphatase (ALP), creatine phosphokinase, lactate dehydrogenase (LDH), albumin, total protein, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)
- Urinalysis: specific gravity, pH, color, appearance, glucose, proteins, occult blood, nitrites, ketones, bilirubin. Microscopic examination of the sediment (casts, erythrocytes, leukocytes) may be obtained based on the investigator's judgement in the event of significant abnormal findings. Cefiderocol may result in false-positive results in dipstick tests (urine protein, ketones, or occult blood).
- Coagulation: activated partial thromboplastin time (APTT), prothrombin time (PT), and international normalized ratio (INR)

See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA (Figure 1-2) for the timing and frequency. All protocol-required laboratory

assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA.

The investigator must review the laboratory test results, document this review, and record any clinically significant changes occurring during the study as an AE. Clinically significant abnormal laboratory findings are described in Section 10.3 (Appendix 3). The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Pregnancy Testing

- Urine or serum pregnancy testing will be required for all females during the Screening Period and upon admission to the CRU.
- Pregnancy testing will be repeated at the Follow-up or Early Termination Visit.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3 (Appendix 3).

All AEs reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) must be captured in source documents.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on all AEs/SAEs considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or withdraw from the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

When an AE occurs, the investigator should take appropriate medical measures such as treatment, if necessary.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the date of signing of the ICF until the Follow-up or Early Termination Visit (Day 23 ± 2) at the time points specified in the SoA (Figure 1-2).

All SAEs will be recorded and reported to the clinical research organization (CRO)/sponsor or designee immediately and under no circumstance should this exceed 24 hours from the time point when the investigator first becomes aware of the SAE, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study (out of period specified in the SoA (Figure 1-2), and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor by phone, email, or fax as detailed in Section 10.3 (Appendix 3).

Investigator assessment of causality must be included with all SAEs reported to the sponsor. Serious adverse events with missing investigator causality will be followed up by the CRO/sponsor urgently until response is provided to the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator will be required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Section 10.3 (Appendix 3).

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the CRO/sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

The sponsor must prepare investigator safety reports for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forward to investigators as necessary.

8.3.5 Pregnancy

The investigator must collect pregnancy information for all pregnancies in female participants and female partners of male participants after start of study intervention until 3 months after the last dose.

If a pregnancy is reported, the investigator will record pregnancy information on the paper Pregnancy Form and submit it to the CRO/sponsor within 24 hours of learning of the pregnancy and should follow the procedures, which require completion of the paper Pregnancy Form, as outlined in Section 10.4.3 (Appendix 4).

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

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study prior to administration of study intervention will be withdrawn from the study; if a female

participant becomes pregnant after administration of study intervention, the participant will be encouraged to complete the study.

8.3.6 Adverse Events of Special Interest

Not applicable.

8.3.7 Special Situations - Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error of the study intervention (Special Situations, as defined below) must be reported to the sponsor (medical monitor) by the investigator via electronic data capture (EDC) using a Special Situations Report Form as soon as possible. In the event that EDC is not available, the site may submit paper reports to the medical monitor via email. If there are associated SAEs, the investigator must also complete and submit an SAE submission via EDC as well.

- Abuse - persistent or sporadic, intentional excessive use of a study intervention(s), which is accompanied by harmful physical or psychological effects.
- Misuse - intentional and inappropriate use of a study intervention(s) other than as directed or indicated at any dose.
- Overdose - intentional or unintentional intake of study intervention(s) in excess of the assigned dose in the protocol.
- Medication Error - any unintended error in the prescribing, dispensing or administration of a study intervention(s) (including intercepted error).

Treatment of Overdose

For this study, any dose of study intervention greater than the daily dose of study intervention within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until all AEs or abnormalities have resolved or are stable.
3. Obtain a plasma sample for PK analysis daily from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.4 Pharmacokinetics

Plasma samples will be used to evaluate the PK of cefiderocol/midazolam. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Each plasma sample will be divided into 2 aliquots (1 for PK analysis and 1 for back-up).

The following volumes will be collected at each timepoint as specified in the SoA (Figure 1-2):

- Approximately 3 mL will be collected for measurement of plasma concentrations of cefiderocol.
- Approximately 5 mL will be collected for measurement of plasma concentrations of midazolam.

Samples collected for analyses of concentration cefiderocol/midazolam may also be used to evaluate safety related to concerns arising during or after the study. At visits during which samples for the determination of PK and clinical laboratory assessments will be taken, 1 sample of sufficient volume can be used.

Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

Pharmacokinetic parameters and definitions are provided in Section 9.3.2.1. Further details will be provided in the statistical analysis plan (SAP).

8.5 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.6 Genetics/Pharmacogenomics

Genetics will not be evaluated in this study.

8.7 Biomarkers

Biomarkers will not be evaluated in this study.

8.8 Immunogenicity Assessments

Immunogenicity assessments will not be evaluated in this study.

8.9 Health Economics and Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to the first participant's first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

There is no formal statistical hypothesis in this study since it will be a Phase 1 study to assess the effect of cefiderocol on the PK of midazolam (a CYP3A probe), safety, and tolerability, in healthy adult study participants.

9.2 Analysis Populations

For the purposes of analysis, the following analysis populations are defined (Table 9-1):

Table 9-1 Analysis Populations

Participant Analysis Population	Description
Enrolled analysis population	Enrolled means a participant has agreed to participate in the clinical study following completion of the ICF process, the participant has completed all screening assessments, and the participant has met all eligibility requirements. A screened participant is one who has completed the ICF process and all screening assessments (the participant may subsequently withdraw consent and/or may not meet all eligibility criteria).
Safety analysis population	All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
PK analysis populations	The PK concentration population includes all study participants who receive at least 1 dose of cefiderocol or midazolam, and have at least 1 evaluable concentration of cefiderocol or midazolam. This population will be used for the concentration listing. The PK parameter population includes all study participants with at least 1 PK parameter estimated appropriately. This population will be used for PK parameter listing and summary. This population will also be used for plotting of the concentration-time data, the concentration summary and statistical analysis.

ICF = informed consent form; PK = pharmacokinetic

The safety analysis set will be used to analyze the endpoints and assessments related to safety, and the PK analysis set will be used for the PK analyses.

9.3 Statistical Analyses

Summary statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum) will be generated for continuous variables and the number and percentage of subjects within each category will be presented for categorical variables.

All analyses and tabulations will be performed by using both SAS Version 9.4 and WinNonlin Version 8.1 or higher.

Disposition

Among the study participants enrolled into the study, the number and percentage who complete the study and who prematurely discontinue from the study will be summarized. In addition, reasons leading to study discontinuation will be summarized. The number of study participants included in each analysis population (safety, PK concentration, and PK parameter populations) will also be presented.

Demographics, Treatment Compliance, and Prior and Concomitant Therapies

Demographic and baseline characteristics will be summarized with descriptive statistics for the Safety Population.

The study intervention exposure and compliance will be listed.

Prior therapies for drugs will be coded using the World Health Organization (WHO) Drug Dictionary. Study participants who have received prior therapy will be listed for the Safety Population.

Concomitant therapies for drugs will be coded using the WHO Drug Dictionary. Study participants who received concomitant therapy will be listed for the Safety Population.

9.3.1 Safety Analyses

All safety analyses will be performed on the Safety analysis population.

The number of treatment-emergent adverse events (TEAEs) and the number (percentage) of study participants who had any TEAEs will be summarized for Day -1 (to predose on Day 1), Days 1 (postdose) through Day 15 (predose), and Day 15 post dose through End of Follow-up. The summarization of treatment-related TEAEs will be performed in a similar manner. The number of study participants who experience any TEAEs and incidence by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term will be presented.

For clinical laboratory tests (hematology, blood chemistry, urinalysis, coagulation, and lipid profile tests), vital sign measurements (oral body temperature, pulse rate, respiratory rate, and blood pressure), and 12-lead ECG results, summary statistics for each parameter and for the change from baseline (latest observation prior to first administration) to each time point will be calculated.

Physical examination findings will be summarized by visit.

9.3.2 Pharmacokinetic Analysis

All PK analyses will be performed on the PK analysis population.

Plasma Concentrations

Plasma concentrations of midazolam and cefiderocol will be listed and summarized by treatment and nominal sampling time with the number of nonmissing observations (N), arithmetic mean (mean), standard deviation (SD) and coefficient of variation (CV%, calculated by SD/mean × 100), geometric mean and coefficient of variation for geometric mean (geometric CV%), and median, minimum, and maximum values at each sampling time. The geometric CV% will be calculated according to a formula geometric CV% = $[\exp(sd^2)-1]^{1/2} \times 100$, where sd is the standard deviation for natural log (ln)-transformed data. Time course profiles for plasma concentrations will be presented by appropriate graphics.

For summary of plasma concentration, plasma concentration below the lower limit of quantitation (BLQ) will be treated as zero (0) for calculations of mean, SD, CV%, median, minimum, and maximum values and treated as missing for calculation of geometric mean and geometric CV% mean values.

9.3.2.1 Pharmacokinetic Parameters

The following PK parameters will be calculated, whenever possible, from plasma concentration data of midazolam from 0 to 24 hours after the administration of midazolam on Days -1 and 15 and plasma concentration data of cefiderocol from 0 to 8 hours after the coadministration of midazolam and cefiderocol on Day 15 by noncompartmental methods. Other parameters may be computed, as appropriate, upon review of the data. The estimated PK parameters will be computed for each study participant using the actual sample collection times recorded during the study

Pharmacokinetic parameters of midazolam

C_{max} (ng/mL)	Maximum plasma concentration on Days -1 and 15
T_{max} (hr)	Time to maximum plasma concentration on Days -1 and 15
$AUC_{0\text{-last}}$ (ng·hr/mL)	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing on Days -1 and 15, calculated by Linear Up/Log Down Trapezoidal Method
$AUC_{0\text{-inf}}$ (ng·hr/mL)	Area under the plasma concentration-time curve extrapolated from time zero to infinity defined as $AUC_{0\text{-last}} + (C_{last}/\lambda_z)$, where C_{last} is the last measurable plasma concentration and λ_z is the plasma terminal elimination rate constant on Days -1 and 15
$t_{1/2,z}$ (hr)	Terminal elimination half-life, where $t_{1/2,z} = \ln(2)/\lambda_z$ on Days -1 and 15

λ_z (hr^{-1})	Terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase on Days -1 and 15
MRT (hr)	Mean residence time, where MRT = $AUMC_{0\text{-}inf}/AUC_{0\text{-}inf}$ and $AUMC_{0\text{-}inf}$ is the area under the first moment curve extrapolated to infinity on Days -1 and 15
CL/F (L/hr)	Apparent total clearance estimated according to: CL/F = Dose/$AUC_{0\text{-}inf}$ on Days -1 and 15
V_z/F (L)	Apparent volume of distribution in the terminal elimination phase, estimated according to: V_z/F = Dose/$AUC_{0\text{-}inf}/\lambda_z$ on Days -1 and 15

Pharmacokinetic parameters of cefiderocol

C_{max} (µg/mL)	Maximum plasma concentration on Day 15
T_{max} (hr)	Time to maximum plasma concentration on Day 15
$AUC_{0\text{-}\tau}$ (µg·hr/mL)	Area under the plasma concentration-time curve over the dosing interval τ (8 hours) on Day 15, calculated by Linear Up/Log Down Trapezoidal Method
CL (L/hr)	Total clearance estimated according to: CL = Dose/$AUC_{0\text{-}\tau}$ on Day 15

The estimated PK parameters except for T_{max} will be summarized by treatment with N, mean, SD, coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum values. The T_{max} will be summarized by analyte and study intervention with N, mean, SD, CV%, median, minimum, and maximum values. If the number of PK parameter data is < 3, the data will not be summarized.

If the number of data points used to calculate λ_z is < 3 or the calculated coefficient of determination (R^2) value for λ_z is < 0.800, then that study participant's λ_z, and $AUC_{0\text{-}inf}$, $t_{1/2,z}$, MRT, CL/F, and V_z/F derived from λ_z will be flagged in the data listing, and excluded from the descriptive and statistical analysis. If λ_z cannot be determined, then $AUC_{0\text{-}inf}$, $t_{1/2,z}$, MRT, CL/F, and V_z/F will not be estimated.

In addition to the parameters listed above, the extrapolated percent of $AUC_{0\text{-}inf}$ (AUC_{extr}), calculated as AUC_{extr} (%) = 100 × ($AUC_{0\text{-}inf}$ − $AUC_{0\text{-}last}$)/$AUC_{0\text{-}inf}$, will be determined. If the AUC_{extr} is greater than 20%, then $AUC_{0\text{-}inf}$, MRT, CL/F, and V_z/F derived from $AUC_{0\text{-}inf}$ will be flagged in the data listing and excluded from the descriptive statistics and statistical analysis.

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis at the discretion of the PK study director. Any such exclusion will be clearly represented in the study report along with justification for exclusion.

For the calculations of PK parameters, BLQ before the occurrence of the first quantifiable concentration will be treated as zero, and BLQ after the first occurrence of the quantifiable concentration will be treated as missing.

The $AUC_{0-\tau}$ at steady state will be calculated with observed plasma concentrations from time 0 to τ (actual time) on Day 15 without extrapolation or interpolation. The actual time for the predose (0 hours) on Day 15 will be replaced with 0. If observed plasma concentration at τ on Day 15 is BLQ, area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing (AUC_{0-last}) will be used as $AUC_{0-\tau}$.

Pharmacokinetic calculations will be performed by using WinNonlin Version 8.1 or higher.

9.3.2.2 Effect of Repeated Doses of Cefiderocol on the Pharmacokinetics of Midazolam

When data are available, the effect of cefiderocol on the PK of midazolam will be assessed. An analysis of variance (ANOVA) will be performed using SAS Proc Mixed for ln-transformed C_{max}, AUC_{0-last}, and AUC_{0-inf} of midazolam. In case of unbalanced data, the Kenward-Roger method will be used to compute the denominator degrees of freedom for the tests of a fixed effect in the analysis. The point estimates and their 90% confidence intervals (CIs) will be generated for the differences between midazolam coadministered with cefiderocol and midazolam alone for ln-transformed C_{max}, AUC_{0-last}, and AUC_{0-inf}. The point estimates and their 90% CIs will be back-transformed to obtain the corresponding geometric least squares mean ratios and 90% CIs as the following ratio:

(midazolam coadministered with cefiderocol) / (midazolam alone)

The following linear mixed effects model will be used:

ln (Parameter) = Treatment + Subject + Random error

Where Treatment is a fixed effect of treatment, Subject is a random effect of study participant, and Random error is a random residual error.

The drug interaction will be assessed by whether the 90% CIs for C_{max}, AUC_{0-last}, and AUC_{0-inf} of midazolam are completely contained within the range of 0.8000 to 1.2500.

The comparison of C_{max}, AUC_{0-last}, and AUC_{0-inf} between midazolam alone and midazolam coadministered with cefiderocol will be graphically represented.

The effect of cefiderocol on the PK of midazolam will be concluded based on the point estimates and 90% CIs of the ANOVA model and visual inspection of the corresponding plots.

9.4 Interim Analysis

Not applicable for this study.

9.5 Sample Size Determination

The sample size is 14 eligible healthy adult study participants enrolled in the study.

No formal calculations were performed to determine sample size for this study.

Note: “Enrolled” means a participant has agreed to participate in the clinical study following completion of the informed consent process, the participant has completed all screening assessments, and the participant has met all eligibility requirements. A screened participant is one who has completed the ICF process and all screening assessments (the participant may subsequently withdraw consent and/or may not meet all eligibility criteria).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 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 (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. Competent authority notification, review and approval may be required as appropriate according to local country requirements.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants as appropriate according to local country requirements.
- For studies to be submitted as part of an European Union (EU) marketing authorisation application (MAA), the sponsor will select a Clinical Study Report (CSR) Coordinating Investigator who will sign the CSR.

- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

- Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.
- The information on financial disclosure for investigators will be addressed in a separate agreement between the sponsor and the investigator.

10.1.3 Informed Consent Process

- The investigator or his/her representative must explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and privacy and data protection requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date that written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed ICF(s) must be provided to the participant.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant directly identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

All information regarding cefiderocol supplied by the sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical trial will be used toward the development of cefiderocol and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

The sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the sponsor's approval requirements.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF by the investigator or authorized designee unless 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.
- Guidance on completion of eCRFs will be provided.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the clinical monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained. 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. Records will be retained for the longest of the following periods: at least 2 years after approval

of the last marketing application; 3 years after formal discontinuation of the clinical development of the investigational product or after discontinuation of the study.

10.1.7 Source Documents

- Source documents provide evidence of the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are defined as original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, study participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, study participant files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical study).
- The investigator must maintain accurate documentation (source data) that supports the information recorded in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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.

10.1.8 Study and Site Start and Closure

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date on which the first participant signs the ICF and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

The study site will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, data have been collected, and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no (evaluated after a reasonable amount of time) recruitment of participants by the investigator
- Total number of participants included earlier than expected

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

10.1.9 Publication Policy

- All information regarding cefiderocol supplied by the sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and must not use it for other purposes without consent from the sponsor.
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-required Safety Laboratory Assessments

Laboratory Tests	Parameters			
Hematology	• Platelet count • Red blood cell (RBC) count • Hemoglobin • Hematocrit	RBC indices: • Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • % Reticulocytes	• White blood cell (WBC) count WBC differential counts: • Neutrophils • Lymphocytes • Monocytes	• Eosinophils • Basophils
Blood chemistry[a]	• Blood urea nitrogen • Creatinine • Blood urea nitrogen/creatinine • Uric acid • Glucose (fasting)	• Potassium • Sodium • Calcium • Chloride • Phosphorus	• Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Alkaline phosphatase[b] • Gamma glutamyl transferase • Lactate dehydrogenase	• Creatine phosphokinase • Total, indirect, and direct bilirubin • Total protein • Albumin • C-reactive protein • Erythrocyte sedimentation rate • Estimated glomerular filtration rate
Lipid profile	• Cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein			
Coagulation tests	• Activated partial thromboplastin time, prothrombin time, international normalized ratio (INR)			
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal) Cefiderocol may result in false-positive results in dipstick tests (urine protein, ketones, or occult blood).			

Laboratory Tests	Parameters
Pregnancy testing	• Highly sensitive urine or serum human chorionic gonadotropin pregnancy test (for women)
Other screening tests	• Follicle stimulating hormone (as needed in women of non-childbearing potential only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates and fentanyl) • Serology (human immunodeficiency virus antibody, hepatitis B surface antigen, and hepatitis C virus antibody)

SAE = serious adverse event; ULN = upper limit of normal

a Details of liver chemistry stopping criteria and actions and suggested follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.5 (Appendix 5). All events of ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 × ULN and INR > 1.5 (if INR measured), which may indicate severe liver injury, must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

b If alkaline phosphatase is elevated, consider fractionating.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, after the participant has signed the informed consent, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) after the participant has signed the informed consent.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, blood chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition. • New condition detected or diagnosed after study intervention administration even though they may have been present before the initiation of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Hospitalization for preplanned and elective procedures to treat a pre-existing condition that did not worsen after initiation of study will not be considered an AE, and therefore will not be considered an SAE despite requiring hospitalization. These procedures will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section. The exception is when the participant experiences another event during/following the procedure. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the initiation of the study that do not worsen.

10.3.2 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the CRO/sponsor in lieu of completion of the required form and AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the CRO/sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the CRO/sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

- In the case of a death, the cause of death should be reported instead of "Death" as death is an outcome and not the SAE. If the cause of death is unknown, "Death" can be reported until the cause of death is determined, at which time the cause of death should be reported.

Assessment of Severity

- The investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
  - Severe: An event that prevents normal everyday activities.
    An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the severity of an event; both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - The relationship of an event to the study intervention will be determined by the investigator according to the following criteria:
    - Related: An AE which can be reasonably explained as having been caused by the study intervention. For example, the occurrence of the AE can be explained by any of the following: a pharmacological effect of the study intervention (eg, a similar event had been reported previously); an increase/decrease of the dose affects the occurrence or seriousness of the AE; or all other causative factors (eg, medical history, concomitant medication etc.) can be ruled out after careful analysis of sufficient information.
    - Not related: An AE which cannot be reasonably explained as having been caused by the study intervention.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- The investigator should provide rationale for the causality assessment in the eCRF or if reporting via paper, the rationale for causality should be provided in the narrative section of SAE form.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the CRO/sponsor. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the CRO/sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the CRO/sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

All SAEs must be reported to the CRO/sponsor in detail (via EDC [or the SAE form if EDC is not available]) within 24 hours from the time point when the investigator first becomes aware of the SAE.

SAE Reporting to the CRO/sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to CRO/sponsor will be EDC.
- If EDC is unavailable, then the site will use the paper SAE form (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after EDC has been taken off-line, then the site can report this information on a paper SAE form (see next table) or to the sponsor's medical monitor/sponsor's safety group by telephone.

SAE Reporting to the CRO/sponsor via Paper SAE Form (if EDC is unavailable)

- Facsimile transmission of the paper SAE form is the preferred method to transmit this information to the sponsor's safety group/medical monitor. Data collected using the paper SAE data collection tool will be sent to sponsor as follows:

  Safety Fax Number: [redacted]

  E Email address: [redacted]
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the paper SAE form sent by overnight mail or courier service.

  Safety telephone number: [redacted]
- Initial notification via telephone does not replace the need for the investigator to complete and sign the paper SAE form within the designated reporting timeframes.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Definition of Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented tubal ligation
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, investigator discretion should be applied to determining study entry.

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

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement will be insufficient.

10.4.2 Contraception Guidance

Male Study Participants

Male study participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the Treatment Period and for at least 3 months after the last dose of study intervention:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 10-2 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study intervention.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the Treatment Period.

Table 10-2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods that are User Dependent[a] Failure rate of < 1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation[b] • Oral • Injectable
Highly Effective Methods that are User Independent[a] Failure rate of < 1% per year when used consistently and correctly.
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

b Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the Treatment Period and for at least 3 months after the last dose of study intervention.

10.4.3 Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the CRO/sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and neonate will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the paper Pregnancy Form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will immediately discontinue study intervention.

10.5 Appendix 5: Liver Safety: Actions and Suggested Follow-up Assessments

Phase 1 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Phase 1 Liver Chemistry Stopping Criteria and Follow-up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>Alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN)
If ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN (>35% direct bilirubin) or international normalized ratio (INR) > 1.5, report as a serious adverse event (SAE)[a,b]
See additional actions and follow-up assessments below</td></tr>
<tr><th colspan="2">Required Actions and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to the Contract Research Organization (CRO)/sponsor within 24 hours
• Complete the liver event case report form (CRF), and complete an SAE data collection tool if the event also met the criteria for an SAE[2]
• Perform liver function follow-up assessments
• Monitor the participant until liver function test abnormalities resolve, stabilize, or return to baseline (see MONITORING)
MONITORING:
If ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5
• Repeat liver function tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin, and INR) and perform liver function follow-up assessments within 24 hours.
• Monitor participant twice weekly until liver function test abnormalities resolve, stabilize, or return to baseline.
• A specialist or hepatology consultation is recommended.
If ALT ≥ 3 × ULN AND bilirubin < 2 × ULN and INR ≤ 1.5:
• Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver function follow-up assessments within 24 to 72 hours</td><td>• Viral hepatitis serology[c]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis after the most recent dose[d]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
• Fractionate bilirubin, if total bilirubin ≥ 2 × ULN
• Complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the adverse event (AE) CRF
• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF
• Record alcohol use on the liver event alcohol intake CRF
If ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins</td></tr>
</table>

• Monitor participants weekly until liver function abnormalities resolve, stabilize, or return to baseline	• Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) [5]) **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRFs

a Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick which is indicative of direct bilirubin elevations suggesting liver injury.

b All events of ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and INR > 1.5 may indicate severe liver injury and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). The INR stated threshold value will not apply to participants receiving anticoagulants.

c Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

d A PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.6 Appendix 6: Abbreviations

λz	plasma terminal elimination rate constant
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-inf}}$	area under the plasma concentration-time curve extrapolated from time zero to infinity
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing
$AUC_{0\text{-}\tau}$	area under the plasma concentration-time curve over the dosing interval τ
BLQ	below the lower limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent total clearance
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CYP3A	cytochrome P450 3A
CV%	coefficient of variation
ECG	electrocardiogram/electrocardiography
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	institutional ethics committee
INR	international normalized ratio
IRB	institutional review board
Mean	arithmetic mean
MRT	mean residence time
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
$t_{1/2,z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.7 Appendix 7: Examples of Pharmacological Inducers of CYP450 Enzymes

	Strong Inducers	Moderate Inducers	Weak Inducers
CYP1A2	--	phenytoin, rifampin, ritonavir, smoking, teriflunomide	--
CYP2B6	carbamazepine	efavirenz, rifampin	nevirapine, ritonavir
CYP2C8	--	rifampin	--
CYP2C9	--	enzalutamide, rifampin	apalutamide, aprepitant, carbamazepine, ritonavir
CYP2C19	rifampin	apalutamide, efavirenz, enzalutamide, phenytoin	ritonavir
CYP3A	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, phenobarbital, primidone	armodafinil, modafinil, rufinamide

CYP = cytochrome P450; FDA = Food and Drug Administration

Source: FDA Guidance: Drug Development and Drug Interactions - Table of Substrates, Inhibitors and Inducers [6]

10.8 Appendix 8: Examples of Common Pharmacological Inducers of P-glycoprotein

- Rifampin
- Phenytoin
- Carbamazepine
- St. John's wort extract
- Rifabutin
- Quercetin
- Curcumin

10.9 Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

10.10 Appendix 10: Investigator's Signature

Study Title:	A Phase 1, open-label, 1-sequence crossover, drug-drug interaction study to assess the effect of repeated doses of cefiderocol on the pharmacokinetics of midazolam in healthy adult participants
Study Number:	2136R2118
Date of Original:	22 Feb 2022
Date of Latest Amendment:	08 Mar 2022

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____
[enter name and credentials] [enter title]
[enter affiliation]

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the sponsor.

11. REFERENCES

1. Fetroja (cefiderocol) [package insert]. Florham Park, NJ: Shionogi Inc.; 2020.
2. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), “Guidance for industry: drug interaction studies - study design, data analysis, and implications for dosing and labeling.” September 2006.
3. Midazolam HCl Syrup [prescribing information]. Minneapolis, MN: Perrigo. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0be63f63-6a93-4782-8f9c-d13ca5ae44bd.
4. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), “FDA guidance for industry: clinical drug interaction studies - cytochrome p450 enzyme- and transporter-mediated drug interactions.” January 2020. Available at: https://www.fda.gov/media/134581/download.
5. James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009;37:1779-84.
6. FDA Guidance: Drug Development and Drug Interactions - Table of Substrates, Inhibitors and Inducers. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Content current as of 10 Mar 2020.

Electronic Signature Page for VV-CLIN-087865 v1.0

Final Approval	[redacted] 07-Mar-2022 21:23:25 GMT+0000

Electronic Signature Page for VV-CLIN-087865 v1.0