# 2. SYNOPSIS

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**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

**Investigators and Study Centers:** This study was conducted at 1 site in the United States.

**Publication (reference):** Not applicable

**Study Period:**
First participant enrolled: [redacted] May 2022
Last participant completed: [redacted] Jul 2022

**Phase of Development: 1**

**Objectives:**

| 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, $t_{1/2,z}$, $\lambda_z$, CL/F, $V_z$/F, and MRT |
| **Secondary** | |
| • To evaluate the PK of cefiderocol after coadministration with midazolam<br>• To evaluate the safety and tolerability of cefiderocol after coadministration with midazolam | • Cefiderocol: $C_{max}$, $T_{max}$, AUC, and CL<br>• Physical examination findings, vital sign values, 12-lead ECG results, clinical laboratory test values, and TEAEs |

$\lambda_z$ = 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

**Methodology:**
The purpose of this study was to determine the effect of repeated doses of cefiderocol on the pharmacokinetics (PK) of midazolam. The study consisted 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

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administration of midazolam 5 mg in the morning on Days −1 and 15, and intravenous (IV) infusion of cefiderocol 2 g every 8 hours [q8h] from Days 1 through 15 or 16; and a Follow-up Period, including a Follow-up (Day 23 ± 2) or Early Termination Visit. A total of 2 doses of midazolam and 45 doses of cefiderocol were administered to each participant during the study.

Midazolam was administered orally alone in the fasted state in the morning on Day −1. The IV infusion of cefiderocol q8h was started in the morning on Day 1 and continued for 15 days. Midazolam and cefiderocol were coadministered in the fasted state in the morning on Day 15, with 2 additional doses of cefiderocol administered 8 and 16 hours after the coadministration of midazolam and cefiderocol.

**Number of Participants (Planned and Analyzed):**

Planned: 14 participants were planned to be enrolled to receive study intervention.

All 14 (100%) enrolled participants were included in the Safety Analysis Population, PK Concentration Population, and PK Parameter Population.

Diagnosis and Main Criteria for Inclusion:

1. Key Inclusion criteria
   - Age 18 to 60 years inclusive, at the time of signing the informed consent form
   - 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
   - Body weight ≥ 50 kg and body mass index within the range of ≥ 18.5 to ≤ 32.0 kg/m$^2$ at the Screening Visit
   - Agreed to comply with contraceptive requirements per protocol
2. Key Exclusion criteria
   - 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; or constituting a risk when taking the study intervention; or interfering with the interpretation of data
   - 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

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clinically significant by the investigator at the Screening Visit or upon admission to the CRU.

- Lymphoma, leukemia, or any malignancy within the past 5 years, except basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years, or breast cancer within the past 10 years
- Alanine aminotransaminase > 1.5 × upper limit of normal (ULN) at the Screening Visit or upon admission to the CRU
- Aspartate aminotransaminase> 1.5 × ULN at the Screening Visit or upon admission to the CRU
- 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
- Estimated glomerular filtration rate < 80 mL/min per 1.73 $m^2$ as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation at the Screening Visit or upon admission to the CRU
- Chronic history of or current liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
- 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
- Risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, or family history of long QT syndrome or Brugada syndrome), unexplained syncope, sick sinus syndrome, second- or third-degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, angina, prolonged QT interval, or conduction abnormalities
- 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
- Presence of hepatitis B surface antigen, positive hepatitis C antibody test result, or positive hepatitis C RNA 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 may have been enrolled if a confirmatory negative hepatitis C RNA test was obtained.

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- Positive drug/alcohol screen at the Screening Visit or upon admission to the CRU; history of drug or alcohol abuse/addiction
- Positive human immunodeficiency virus antibody/antigen test at the Screening Visit
- Considered inappropriate for participation in the study for any reason by the investigator or subinvestigator
- Regularly consumed excessive amounts of alcohol, caffeine, and/or tobacco- or nicotine-containing products as defined in the protocol. Consumed these substances within 72 hours, 24 hours, or 6 months, respectively, prior to admission to the CRU or refused to refrain from consuming such products as defined in the protocol.
- Consumed grapefruit, grapefruit juice, orange juice, and apple juice within 7 days prior to admission to the CRU or refused to refrain from consuming such products throughout the study (including the Follow-up Period)

**Test Products, Dose and Mode of Administration, Lot Numbers:**

| Study Intervention | Dose and Mode of Administration | Lot Numbers |
|---|---|---|
| Cefiderocol | IV infusion over 3 hours, 2 g (100 mL) every 8 hours for 15 days on Days 1 through 15/16 | [redacted] |
| Midazolam | Orally administered syrup 5 mg (2.5 mL) once daily on Days −1 and 15 | [redacted] |

**Duration of Treatment:**

Cefiderocol: Every 8 hours for 15 days on Days 1 through 15/16

Midazolam: Once daily on Days −1 and 15

**Reference Therapy, Dose and Mode of Administration, Lot Number:**

None

**Criteria for Evaluation:**

**Efficacy Assessment:**

Not applicable; efficacy was not assessed in this study.

**Safety Assessments:**

Safety and tolerability were evaluated based on physical examination findings, clinical laboratory test results, vital sign measurements (oral body temperature, pulse rate,

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respiratory rate, and blood pressure), 12-lead ECG results, and adverse event (AE) monitoring.

**Pharmacokinetics Assessments:**

The following estimated PK parameters for cefiderocol were computed for each participant using the actual sample collection times recorded during the study.

| **Pharmacokinetic Parameters for Midazolam** | |
|---|---|
| $C_{max}$ (ng/mL) | Maximum plasma concentration on Days -1 and 15 |
| $T_{max}$ (h) | Time of the maximum plasma concentration on Days -1 and 15 |
| $AUC_{0\text{-last}}$ (ng·h/mL) | Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing on Days -1 and 15 |
| $AUC_{0\text{-inf}}$ (ng·h/mL) | Area under the concentration-time curve extrapolated from time 0 to infinity, calculated as $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + [C_{last}/\lambda_z]$, where $C_{last}$ is the last measured concentration and $\lambda_z$ is the plasma terminal elimination rate constant on Days -1 and 15 |
| $AUC_{extr}$ (%) | The percentage of $AUC_{0\text{-inf}}$ based on extrapolation, calculated as: $AUC_{extr}$ (%) = 100 × ($AUC_{0\text{-inf}}$ − $AUC_{0\text{-last}}$)/$AUC_{0\text{-inf}}$ |
| $\lambda_z$ (1/h) | Terminal elimination rate constant, where $\lambda_z$ 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 |
| $t_{1/2,z}$ (h) | Terminal elimination half-life, where $t_{1/2,z} = (\ln 2)/\lambda_z$ on Days -1 and 15 |
| CL/F (L/h) | Apparent total clearance, where CL/F = Dose/$AUC_{0\text{-inf}}$ on Days -1 and 15 |
| Vz/F (L) | Apparent volume of distribution in the terminal elimination phase, where Vz/F = Dose/$AUC_{0\text{-inf}}/\lambda_z$ on Days -1 and 15 |
| MRT (h) | 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 |
| **Pharmacokinetic Parameters for Cefiderocol** | |
| $C_{max}$ (µg/mL) | Maximum plasma concentration on Day 15 |
| $T_{max}$ (h) | Time of the maximum plasma concentration on Day 15 |
| $AUC_{0\text{-}\tau}$ (µg·h/mL) | Area under the plasma concentration-time curve over the dosing interval τ (8 hours) on Day 15 |
| CL (L/h) | Total clearance, where CL = Dose/$AUC_{0\text{-}\tau}$ on Day 15 |

**Statistical Methods:**

**Pharmacokinetic Analyses:**

Plasma concentrations of midazolam and cefiderocol were listed and summarized by treatment (midazolam alone, midazolam + cefiderocol, cefiderocol alone) and nominal

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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% was 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. Predose concentrations of cefiderocol were also summarized by study day (Days 3, 6, 9, and 12).

Mean and individual concentration-time profiles were created using linear and semi-logarithmic scales. Mean concentration-time profiles were created using nominal time and individual concentration-time profiles were created using actual time.

When data were available, the effect of cefiderocol on the PK of midazolam were assessed. An analysis of variance (ANOVA) was performed using SAS Proc Mixed for ln-transformed $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of midazolam. In the case of unbalanced data, the Kenward-Roger method was 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) were generated for the differences between midazolam coadministered with cefiderocol and midazolam alone for ln-transformed $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$. The point estimates and their 90% CIs were back-transformed to obtain the corresponding geometric least squares mean ratios and 90% CIs.

The drug interaction was assessed by whether the 90% CIs for $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of midazolam were completely contained within the range of 0.8000 to 1.2500. The comparison of $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ together with $T_{max}$ $\lambda_z$, $t_{1/2,z}$, CL/F, $V_z$/F, and MRT between midazolam alone and midazolam coadministered with cefiderocol were graphically represented via pair plots between treatments of individual and mean (standard deviation) data for each parameter. The effect of cefiderocol on the PK of midazolam was concluded based on the point estimates and 90% CIs of the ANOVA model and visual inspection of the corresponding plots.

**Safety Analyses:**

Adverse events were classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities, Version 25.0. Overall incidence and the number of treatment-emergent adverse events (TEAEs), treatment-related TEAEs, serious adverse events (SAEs), serious treatment-related TEAEs, TEAEs leading to withdrawal, and TEAEs leading to death were tabulated by system organ class,

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preferred term, maximum severity, and relationship to study intervention. All TEAEs were also listed.

All clinical laboratory data were listed. For clinical laboratory tests, summary statistics for each parameter and for the change from baseline to each time point were calculated. Clinically significant laboratory measurements recorded throughout the study were listed.

Descriptive statistics for observed values and changes from baseline were presented by visit for vital signs, ECG parameters, and physical examination findings. All data were also listed.

**Summary of Results:**

**Efficacy:** Not applicable

**Safety:**

No unexpected safety events were reported in this study. Elevation in liver tests (elevated liver transaminases) and urticaria (rash) are reported as common adverse reactions in the FETROJA® (cefiderocol) prescribing information. No specific safety events trends were observed. With the exception of 1 participant who was discontinued due to reaching the predefined protocol-specified liver chemistry stopping criteria (elevated liver transaminases) and 1 participant with study intervention discontinuation due to an adverse event of urticaria, the study intervention was well tolerated by the study participants.

- Fourteen participants were enrolled in the study and received a median of 16.0 days (range: 6 to 16 days) of cefiderocol.
- In the overall Safety Analysis Population, 11 (78.6%) participants experienced 53 TEAEs. The most frequently reported preferred terms were infusion site extravasation (7 participants, 50.0%); infusion site pain, infusion site phlebitis (4 participants, 28.6%); and abdominal pain, diarrhea, nausea, catheter site pain, headache, and somnolence (each reported for 2 participants, 14.3%).
- All TEAEs were mild in severity, with the exception of 1 participant (7.1%) who experienced moderate transaminases increased while receiving cefiderocol alone.
- Four (28.6%) participants experienced 12 cefiderocol-related TEAEs, and 2 (14.3%) participants experienced 3 midazolam-related TEAEs.
- No SAEs, adverse events leading to withdrawal from the study related to cefiderocol or midazolam, or deaths were reported.

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- Three participants experienced TEAEs leading to withdrawal of study intervention; all events resolved. One event of transaminases increased was moderate in severity; all other events were mild in severity. Two of the 3 participants had TEAEs leading to withdrawal of study intervention that were considered related to cefiderocol.
- No trends or notable changes were observed in laboratory test results, vital sign measurements, physical examination findings, or ECG parameters.

**Pharmacokinetics:**

The mean midazolam concentration-time profile after administration of midazolam with cefiderocol was similar to that after administration of midazolam alone.

The ratios of geometric means based on least squares mean (midazolam + cefiderocol/midazolam alone) and the 90% CI for $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were 1.0865 (0.9724, 1.2141), 1.1174 (0.9784, 1.2762), and 1.1239 (0.9887, 1.2776), respectively. These slight changes in exposure to midazolam after administration of midazolam with cefiderocol are not clinically meaningful.

**CONCLUSION**

**Pharmacokinetics Conclusions:**

The PK of midazolam was not clinically meaningfully altered after coadministration with cefiderocol, suggesting that repeated doses of cefiderocol do not affect the PK of CYP3A substrates.

**Date of Report:** 02 January 2023

**Date of Amendment 1:** 17 March 2023