2. SYNOPSIS

Sponsor: Shionogi Inc. **Name of Finished Product:** Cefiderocol (S-649266) **Name of Active Ingredient:** Cefiderocol (S-649266)	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Study Title:

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of Single-Ascending Doses of S-649266 (Part 1) and a Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Period Crossover Study to Assess the Effect of S-649266 on the QT/QTc Interval (Part 2) in Healthy Adult Subjects

Investigator: [redacted]

Study Site: [redacted]

Publication (reference): None

Studied Period (years):
[redacted] Jun 2016 (first subject first visit) to
Oct 2016 (last subject last visit)

Study Phase: 1

Objectives:

Part 1:

Primary objective:

To evaluate the safety and tolerability of single 3-g and 4-g doses of cefiderocol (S-649266), each administered by intravenous (IV) infusion over 3 hours, in healthy adult subjects.

Secondary objective:

To evaluate the pharmacokinetics of single 3-g and 4-g doses of cefiderocol, each administered by IV infusion over 3 hours, in healthy adult subjects.

Part 2:

Primary objective:

To evaluate the effect of a single 2-g dose of cefiderocol administered by IV infusion over 3 hours (therapeutic dose) and a single 4-g dose of cefiderocol administered by IV infusion over 3 hours (supratherapeutic dose) on the QT interval corrected using Fridericia's formula (QTcF) in healthy adult subjects.

Secondary objectives:

1. To describe changes in other electrocardiograph (ECG) parameters including heart rate (HR) and duration of PR, RR, and QRS intervals in healthy adult subjects.

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2. To evaluate the pharmacokinetics of a single 2-g dose of cefiderocol administered by IV infusion over 3 hours in healthy adult subjects.
3. To confirm sensitivity of the ECG study assessments to detect an effect on QTcF interval in healthy subjects using moxifloxacin as a positive control.
4. To evaluate the safety and tolerability of single 2-g and 4-g doses of cefiderocol, each administered by IV infusion over 3 hours in healthy adult subjects.

Exploratory objective:

To conduct linear pharmacokinetic (PK)/corrected QT (QTcF) interval modeling to explore the potential relationship between the pharmacokinetics of cefiderocol and the QTcF interval.

Methodology:

Part 1:

This was a randomized, double-blind, placebo-controlled, single-ascending dose study in healthy adult male and female subjects. The study consisted of 2 dose groups, Group A and Group B, in which 8 subjects each were to be randomly assigned to receive either a single 3-g (Group A) or 4-g (Group B) dose of cefiderocol or placebo, administered intravenously over 3 hours, in a 3:1 ratio (6 active, 2 placebo). An assessment of the safety and tolerability of cefiderocol from Part 1 was performed before initiation of study drug administration in Part 2.

Part 2:

This was a randomized, double-blind (with respect to cefiderocol only), placebo- and active-controlled, single dose, 4-period crossover study in healthy adult male and female subjects. Subjects were randomly assigned to 1 of 4 treatment sequences according to a 4-period Williams square design to receive the following treatments in a crossover manner: a single 2-g dose of cefiderocol infused over 3 hours (Treatment A), a single 4-g dose of cefiderocol infused over 3 hours (Treatment B), a single administration of matching placebo infused over 3 hours (Treatment C), and a single oral 400-mg dose of moxifloxacin (Treatment D). Treatments A, B, and C were administered in a double-blind manner. Treatment D was administered in an open-label manner.

Number of subjects (planned and analyzed):

Part 1:

A total of 16 subjects, 8 subjects in each dose group (Group A and Group B), were planned and randomized to receive study treatments.

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Part 2:

Forty-four subjects were originally planned (to complete 40 subjects) and were randomized; due to a higher than expected dropout rate, an additional 4 subjects were enrolled as replacement subjects and received the same treatment sequence as the subjects whom they replaced for an overall total of 48 subjects randomized.

Diagnosis and main criteria for inclusion: Healthy adult male or female subjects, 18 to 50 years of age, inclusive, with a body mass index from ≥ 18.5 to ≤ 30.0 kg/m^2 at the screening visit.

Test product, dosage, route of administration, lot number:

Part 1:

- Cefiderocol (S-649266), 3-g and 4-g doses, IV administration (Lot number: [redacted])

Part 2:

- Cefiderocol (S-649266), 2-g and 4-g doses, IV administration (Lot number: [redacted])

Reference product, dosage, route of administration, lot number:

Part 1:

- Placebo matched to cefiderocol (S-649266), normal saline, IV administration (Lot number: [redacted])

Part 2:

- Placebo matched to cefiderocol (S-649266), normal saline, IV administration (Lot number: [redacted])
- Moxifloxacin hydrochloride (positive control), 400-mg tablets, oral administration (Lot number: [redacted])

Duration of treatment:

Part 1:

1 day: single dose for each dose group (Group A and Group B).

Part 2:

1 day: single dose in each treatment period (Treatment Period 1, 2, 3, and 4).

Criteria for evaluation:

Pharmacodynamics (Part 2 only): In each treatment period, continuous cardiac monitoring was implemented to assess the potential effects of cefiderocol on ECG parameters, including HR and RR, PR, QRS, QT, and QTcF intervals.

Derived QTc variables:

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QTcF: The QT interval, in units of milliseconds (msec), corrected using Fridericia's formula, was the primary ECG parameter used for assessment of the potential effect of cefiderocol on QTc interval prolongation.

Derived QTc differences:

dQTcF interval: The baseline-adjusted QTcF (dQTcF) interval for each post initiation of the infusion timepoint for the 2-g and 4-g doses of cefiderocol was the primary parameter used for assessment of the potential effect of cefiderocol on QTc interval prolongation and was defined as the difference between the mean triplicate QTcF interval values at each post initiation of the infusion timepoint and the mean predose (baseline) triplicate QTcF interval value. The same definition was applied to the sensitivity analysis for the 400-mg moxifloxacin treatment.

ddQTcF interval: The primary study endpoint was the time-matched placebo- and baseline-adjusted QTcF (ddQTcF) interval for each post initation of the infusion timepoint for the 2−g and 4−g doses of cefiderocol and was defined as the mean dQTcF interval value at each postdose timepoint minus the mean dQTcF interval value for placebo at corresponding post initiation of the infusion timepoints for each subject: ddQTcF = (dQTcF [2-g or 4-g dose of cefiderocol] – dQTcF [placebo]). The definition was applied to the sensitivity analysis for the 400-mg moxifloxacin treatment.

For the secondary endpoints (HR and RR, PR and QRS intervals), corresponding derived variables were also calculated.

Pharmacokinetics (Part 1 and Part 2): The plasma PK parameters of cefiderocol were calculated on the basis of concentration-time profiles for all evaluable subjects in each dose group (Group A and Group B in Part 1) or for each dose (2−g or 4−g dose in Part 2). The following plasma PK parameters of cefiderocol were calculated using non-compartmental analyses (data permitting):

- C_{max}: Maximum observed plasma concentration
- T_{max}: Time of maximum observed plasma concentration
- $AUC_{0\text{-}last}$: Area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration after dosing
- $AUC_{0\text{-}inf}$: Area under the concentration-time curve extrapolated from time zero to infinity
- AUC_{extr}: Extrapolated percent of the area under the concentration-time curve extrapolated from time zero to infinity
- λ_z: Terminal elimination rate constant
- $t_{1/2,z}$: Terminal elimination half-life
- CL: Total clearance

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- V_z: Volume of distribution in the terminal elimination phase

Safety (Part 1 and Part 2): Safety was monitored by repeated assessments of safety parameters, including physical examinations, vital sign measurements, 12-lead ECGs, clinical laboratory tests, and reporting of adverse events (AEs).

Statistical methods:

Pharmacodynamics (Part 2 only): The ddQTcF interval was the primary endpoint used to investigate potential QTc interval prolongation associated with cefiderocol. A mixed-effects model was used to evaluate the primary endpoint and included terms for treatment, period, timepoint, treatment-by-post initiation of the infusion-timepoint interaction, sequence as a fixed effect and subjects nested within sequence as a random effect. Baseline QTcF interval and sex were also included in the model as covariates. A spatial power law covariance structure (a time-dependent first-order autoregressive covariance designed for unequally-spaced timepoints) was used for the model and the mean and upper bound of the 95% one-sided confidence interval (CI) of the ddQTcF interval for each post initiation of the infusion timepoint was used for the primary statistical comparison. If the model did not converge, then unstructured or compound symmetry structures were assessed, in that order.

If the upper bound of the 95% one-sided CI for the mean difference in the dQTcF interval between cefiderocol and placebo at each post initiation of the infusion timepoint treatments (or ddQTcF interval) excluded 10 msec, then it was concluded that there was no clinically meaningful prolongation of the QTc interval.

The relationship between ddQTcF and plasma cefiderocol concentrations was investigated by mixed-effects model.

Pharmacokinetics (Parts 1 and 2): Plasma cefiderocol and moxifloxacin concentrations were summarized using descriptive statistics (number of nonmissing observations, arithmetic mean [mean], standard deviation, percent coefficient of variation [CV%], geometric mean, [CV%]for geometric mean, median, minimum, and maximum) by timepoint and treatment. Mean plasma concentration-time profiles were plotted by treatment on linear and semilogarithmic scales using nominal time points. Individual concentration-time profiles and spaghetti plots with subject concentration-time profiles overlaid, using linear and semilogarithmic scales, with respective treatments presented, are included in the appendices. All calculated PK parameters were presented in a data listing. Dose dependency and independency of PK parameters were assessed by an analysis of variance (ANOVA) model.

Safety (Parts 1 and 2): All safety data were presented in data listings. Treatment-emergent AEs, including serious AEs, were summarized. Clinical laboratory results and changes from baseline were summarized by treatment and timepoint using

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descriptive statistics or counts and percentages. Shifts from baseline in clinical laboratory results were summarized by treatment and timepoint using the number and percentage of subjects with results below, within, and above reference ranges. Vital sign and safety 12-lead ECG results and changes from baseline were summarized by treatment and postdose timepoint using descriptive statistics. The ECG interpretations were summarized for each treatment and timepoint using counts and percentages.

SUMMARY OF RESULTS

Part 1:

Safety: There were a total of four (4) TEAEs reported by 4 different subjects in Part 1 of the study. Two (2) of the four (4) TEAEs (headache and phlebotomy pain) were reported after administration of a 3−g dose of cefiderocol and the other TEAEs (phlebotomy pain and right wrist numbness) were reported after infusion of placebo. The TEAE of headache, reported by Subject [redacted] after administration of the 3−g dose of cefiderocol, was considered by the investigatory to be related to study drug. There were no TEAEs reported after administration of the 4−g dose of cefiderocol. All AEs in Part 1 of the study were mild in severity and resolved without intervention by the end of the study.

There were no deaths, SAEs, or AEs leading to study discontinuation reported. There were no clinically significant abnormal findings observed for ECG parameters, vital sign measurements or clinical laboratory test results.

Pharmacokinetics: Plasma cefiderocol concentrations were quantifiable from 0.5 hours through the 16-hour timepoint after initiation of the infusion in all subjects who received a 3-g dose (Group A) and through the 24-hour time point in all subjects who received a 4−g dose (Group B). After administration of a single 3−g dose (Group A) and 4−g dose (Group B), the plasma C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values of cefiderocol increased in a dose-proportional manner The geometric mean $t_{1/2,z}$, CL, and V_z values for cefiderocol were comparable (ie, independent of the cefiderocol dose) .

Part 2:

Pharmacodynamics: No clinically significant prolongation of the QTcF interval were observed after administration of either the 2-g (therapeutic dose) or 4-g (2 times the therapeutic dose [supratherapeutic dose]) dose of cefiderocol. The 90% CI for the ddQTcF interval was in the positive range and excluded zero at 6 timepoints after initiation of the infusion for the 2-g dose of cefiderocol and at a single timepoint after initiation of the infusion for the 4-g dose of cefiderocol; however, all point estimates for the ddQTcF interval were below 5 msec and the upper bound of the 90% CI were well below 10 msec at each timepoint after initiation of the infusion. Thus, single 2−g and 4−g doses of cefiderocol did not prolong the ddQTcF interval to a level of regulatory concern and met the criteria associated with a negative thorough QT/QTc

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study stipulated in the International Council for Harmonisation (ICH) E14 Guidance for Industry, Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Department of Health and Human Services, 2005) [2].

Adequate assay sensitivity was demonstrated in the mixed-effects model for the ddQTcF interval, as the lower bounds of the 90% CI of the mean ddQTcF interval exceeded 5 msec at all 3 prespecified postdose time-points for the moxifloxacin treatment after application of the Hochberg procedure. The changes from baseline in HR were similar for the cefiderocol treatments and placebo and were not clinically significant. Heart rate increased modestly for the moxifloxacin treatment. The relatively minor changes from baseline in PR and QRS intervals were similar for the placebo, cefiderocol, and moxifloxacin treatments and were not clinically significant. There were no trends in the abnormal diagnostic statements before and during treatment suggestive of a treatment effect. In addition, concentration-effect modeling showed a slightly negative slope and predicted modestly negative values for the ddQTcF interval at the C_{max} for cefiderocol.

Safety: There were a total of 45 TEAEs reported by 19 different subjects in Part 2 of the study. Of these, a total of 28 of the TEAEs were considered by the investigator to be related to study drug, 8 of which occurred after administration of a 2−g dose of cefiderocol, 12 of which occurred after administration of the 4−g dose of cefiderocol, 4 of which occurred after administration of 400-mg dose of moxifloxacin, and 4 of which occurred after administration of placebo to cefiderocol. The drug-related TEAEs for the 2−g dose of cefiderocol included vessel puncture site pain (IV site pain), chest discomfort, headache, dizziness (lightheaded), pain in extremity (hand pain), and pain (body aches). The drug-related TEAEs for the 4−g dose of cefiderocol included infusion site pain, dyspnea (shortness of breath), headache, infusion site irritation, laboratory test abnormal (elevated AST/ALT enzymes), dyspepsia, diarrhoea, dizziness (lightheaded), and abdominal pain upper (stomach ache). The drug-related TEAEs for the 400−mg dose of moxifloxacin included, dizziness (lightheaded), headache, and atrioventricular block second degree [possible atrioventricular (AV) block second degree]. The drug related TEAEs for placebo included vomiting, nausea, and dizziness (lightheaded).

All AEs in Part 2 of the study were mild in severity and resolved without intervention by the end of the study, except for 1 subject (Subject [redacted]) who had an ongoing TEAE of anemia, was prescribed ferrous sulfate and ascorbic acid (Vitamin C), and instructed to follow up with her primary care physician and 1 subject (Subject [redacted]) who had elevated AST and ALT levels after receiving a 4−g dose of cefiderocol, a 400-mg dose of moxifloxacin, a 2-g dose of cefiderocol, and placebo to cefiderocol in Treatment

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Period 1, 2, 3 and 4, respectively, and who continued to be followed until his values returned to nearly within normal limits. There were no clinically significant abnormalities in vital sign measurements or ECG parameters, except for 1 subject (Subject [redacted]) with a TEAE of possible second degree AV block (Mobitz 1). One subject (Subject [redacted]) was discontinued from the study due to elevated AST, ALT, and LDH levels after receiving a 4-g dose cefiderocol, placebo to cefiderocol, and a 2-g dose of cefiderocol in Treatment Periods 1, 2 and 3, respectively. There were no deaths or SAEs reported in Part 2 of the study.

Pharmacokinetics: Plasma cefiderocol concentrations were quantifiable from 0.5 hours through the 16-hour timepoint after initiation of the infusion in all subjects who received a 2−g dose and through the 24-hour timepoint after initiation of the infusion for all subjects who received a 4-g dose. After administration of a 2−g- or 4−g dose, the plasma C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ values of cefiderocol increased in a dose-proportional manner. The cefiderocol geometric mean $t_{½,z}$, CL, and V_z were comparable (ie, independent of the cefiderocol dose). Moxifloxacin concentrations were quantifiable in all subjects by 2 hours postdose.

CONCLUSIONS

Part 1:

- Single 3-g and 4-g doses of cefiderocol, each administered by IV infusion over 3 hours, were generally safe and well tolerated in healthy adult subjects.
- After administration of a single 3−g and 4−g doses of cefiderocol, the PK parameters of cefiderocol were consistent with a linear PK profile (the geometric mean C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ values increased dose proportionally. .

Part 2:

- After administration of single 2−g and 4−g doses, cefiderocol did not prolong the ddQTcF interval to a level of regulatory concern and met the criteria associated with a negative thorough QT/QTc study stipulated in the ICH E14 Guidance.
- Assay sensitivity was confirmed by the moxifloxacin treatment ddQTcF response (the lower bounds of the 90% CI of the mean ddQTcF interval exceeded 5 msec at all 3 prespecified postdose time-points).
- The changes from baseline in HR were similar after administration of single 2-g or 4−g doses of cefiderocol or placebo and were considered not to be clinically significant.

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- The relatively minor changes from baseline in PR and QRS intervals after administration of single 2-g or 4−g dose of cefiderocol and placebo were similar and considered not to be clinically significant.
- Concentration-effect modeling showed a slightly negative slope and predicted modestly negative values for the ddQTcF interval at the C_{max} for both doses of cefiderocol indicating that no positive association between the C_{max} for cefiderocol and ddQTcF interval were observed.
- After administration of a single 2−g and 4−g doses, the PK parameters of cefiderocol were consistent with a linear PK profile (the geometric mean C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ values increased dose proportionally. .
- Single 2-g and 4-g doses of cefiderocol, each administered by IV infusion over 3 hours, were generally safe and well tolerated in healthy adult subjects.

Date of Report: 03 Oct 2017