Effect of Cefiderocol, a Siderophore Cephalosporin, on QT/QTc Interval in Healthy Adult Subjects

Carlos Sanabria, MD[1]; Elizabeth Migoya, PharmD[2,*]; Jay W. Mason, MD[3]; Stephanie H. Stanworth, MS[1]; Takayuki Katsube, PhD[4]; Mitsuaki Machida, MS[4]; Yukitoshi Narukawa, PhD[4]; and Tsutae Den Nagata, MD, PhD[4]

[1]Spaulding Clinical Research, LLC, West Bend, WI, USA; [2]Shionogi Inc, Florham Park, NJ, USA; [3]Mason Cardiac Safety Consulting, Reno, NV, USA; and [4]Shionogi & Co, Ltd, Osaka, Japan

ABSTRACT

Purpose: Cefiderocol is a novel siderophore cephalosporin with potent activity against gram-negative bacteria, including multidrug-resistant strains. This Phase I study was conducted to assess the tolerability of single-ascending doses of cefiderocol (part 1) and the effect of cefiderocol on cardiac repolarization, assessed using the electrocardiographic corrected QT interval (QTcF) and other ECG parameters (part 2), in healthy adult subjects.

Methods: Part 1 was a randomized, double-blind, placebo-controlled, single-ascending dose study in healthy adult male and female subjects. Part 2 was a 4-period crossover study in which subjects received a single 2-g dose of cefiderocol (therapeutic dose), a single 4-g dose of cefiderocol (supratherapeutic dose), or saline (placebo), each infused over 3 hours, and a single oral 400-mg dose of moxifloxacin. In each treatment period, continuous cardiac monitoring was used to assess the effects of cefiderocol on ECG parameters. The QT interval corrected using the Fridericia formula (QTcF) was the primary ECG parameter; the time-matched placebo- and baseline-adjusted (dd)-QTcF interval was the primary end point. The plasma pharmacokinetic properties of cefiderocol were calculated on the basis of concentration−time profiles in all evaluable subjects.

Findings: All point estimates for the ddQTcF interval were <5 ms and the upper bound of the 90% CIs were <10 ms at each timepoint after the initiation of the cefiderocol 3-hour infusion. Concentration-effect modeling showed a slightly negative slope and predicted modestly negative values of the ddQTcF interval at the C_{max} of cefiderocol. Both doses of cefiderocol were well tolerated. All adverse events were mild in severity, with no deaths or serious adverse events reported.

Implications: Overall, therapeutic and supratherapeutic doses of cefiderocol had no apparent clinically significant effect on the QTcF. (*Clin Ther*. 2019;41:1724−1736)

Keywords: carbapenem resistance, cefiderocol, gram-negative bacterial infection, siderophore.

INTRODUCTION

Drug-induced QT prolongation might be associated with the development of torsades de pointes arrhythmia, depending on underlying risk factors, and could potentially be fatal.[1] A wide range of drugs, including antiarrhythmic drugs, calcium channel blockers, psychoactive drugs, and antihistamines, have been shown to cause QT prolongation.[2] Among antibiotics, quinolones and macrolides have been associated with QT

Accepted for publication July 8, 2019
https://doi.org/10.1016/j.clinthera.2019.07.006
0149-2918/$ - see front matter

* Current affiliation: Myovant Sciences, Brisbane, California.

prolongation, although no such effect has been observed with β-lactams to date, including carbapenems and cephalosporins.[2–8] The likelihood of QT prolongation is related to the affinity of a drug for a specific cardiac myocyte potassium channel encoded by the human ether-à-go-go–related gene (hERG), although other factors such as dose, route of administration, duration of exposure, and patient factors also play a role.[3]

Cefiderocol is a novel parenteral siderophore cephalosporin that uses the bacterial iron-transport system to gain entry into gram-negative bacterial cells.[9] Cefiderocol has high stability against hydrolysis by all known classes of carbapenemases,[10] and potent *in vitro* activity against infection with gram-negative fermenters and nonfermenters, including multidrug-resistant strains,[11–13] the treatment of which is a recognized unmet medical need.[14–16] The noninferiority and tolerability of cefiderocol versus imipenem/cilastatin was demonstrated in a randomized, double-blind, Phase II clinical study of the treatment of patients with complicated urinary tract infections (ClinicalTrials.gov identifier: NCT02321800).[17] The pharmacokinetics (PK) and tolerability profiles of cefiderocol, at a dose of up to 2 g infused over 1 hour, have been well described in previous Phase I, single- and multiple-ascending–dose clinical studies.[18,19] Cefiderocol exhibits linear PK properties over a dose range of 0.1 to 2 g and is primarily excreted unchanged into urine, with a $t_{1/2}$ of 2 to 3 hours.[18,19] There is little plasma accumulation of cefiderocol with every-8-hour dosing, and steady state is attained within 1 day after the initiation of multiple-dose administration.[18,19]

A comprehensive evaluation of cardiac tolerability is a regulatory requirement for ensuring the safe conduct of drug-development programs.[20] As part of a thorough QT/QTc study, testing of a supratherapeutic dose to accommodate circumstances in which systemic drug concentrations would be increased, such as drug interactions, food effect, or overdose, is recommended.[20] Since the tolerability of doses of cefiderocol that exceed 2 g had not previously been evaluated, in part 1 of the present study, the tolerability of single 3- and 4-g doses of cefiderocol infused over 3 hours in healthy adult subjects was assessed. After the completion of part 1, part 2 of the study was conducted to evaluate the effects of a single 2-g therapeutic dose infused over 3 hours and a single 4-g supratherapeutic dose of cefiderocol infused over 3 hours on the QT interval corrected using the Fridericia formula (QTcF) in healthy adult subjects.

SUBJECTS AND METHODS

Study Design and Subjects

Part 1 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, in which 8 subjects each were to be randomly assigned to receive either a single 3- or 4-g dose of cefiderocol or placebo, administered intravenously over 3 hours, in a 3:1 ratio (6 active, 2 placebo) (Figure 1). The tolerability of cefiderocol was assessed in part 1 before the initiation of study drug administration in part 2 (Figure 1).

Part 2 was a single-dose, randomized, double-blind (with respect to cefiderocol and placebo only), placebo- and active-controlled, 4-period crossover study in healthy adult male and female subjects (Figure 1). The current regulatory guideline from the US Food and Drug Administration recommends that a standard, thorough QT/QTc study include both a placebo and a positive control to provide a robust assessment of the potential of a compound to prolong the QTc interval relative to a quantifiable effect within the context of the same study.[20] Moxifloxacin was selected as the positive control in the present study because it provides a reproducible peak QTc interval prolongation of 8 to 15 ms after a single oral 400-mg dose.[21] Subjects were randomly assigned to 1 of 4 treatment sequences according to a 4-sequence Williams Latin square design to receive the following treatments in a crossover manner: a single 2-g dose of cefiderocol infused over 3 hours, a single 4-g dose of cefiderocol infused over 3 hours, a single administration of matching placebo infused over 3 hours, and a single oral 400-mg dose of moxifloxacin. Cefiderocol and placebo were administered in a double-blind manner; moxifloxacin was administered in an open-label manner.

The study included 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. Subjects had no clinically significant history or presence of abnormal ECG findings, in the opinion of the investigator. Subjects who satisfied the eligibility criteria were entered into either part 1 or 2 of the

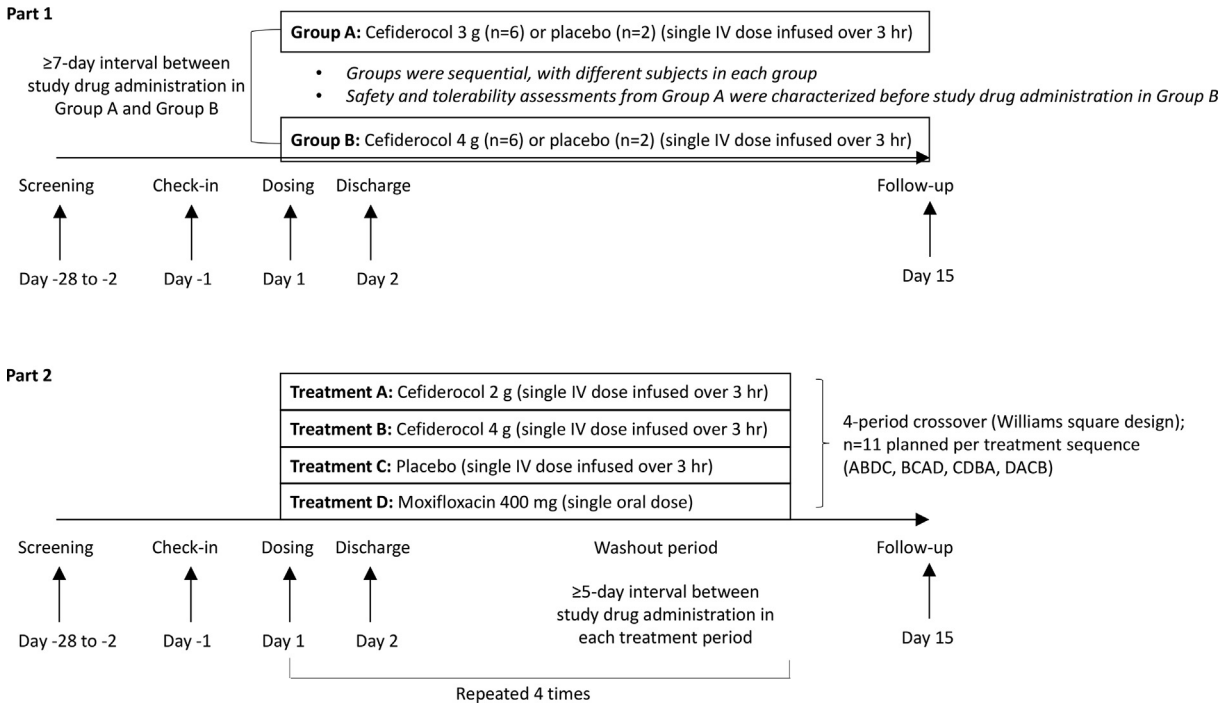


Figure 1. Study design.

study. The study was conducted at Spaulding Clinical Research (West Bend, Wisconsin), in accordance with all appropriate regulatory requirements and using the protocol approved by Chesapeake Institutional Review Board (Columbia, Maryland). The study was conducted in accordance with current International Conference on Harmonisation (ICH) Good Clinical Practices guideline, all appropriate subject-privacy requirements, and the ethics-related principles outlined in the Declaration of Helsinki. All subjects provided written informed consent.

Continuous 12-lead ECG (Part 2)

In each treatment period of Part 2 of the study, continuous 12-lead ECGs were recorded digitally using the Montara Surveyor system (Welch Allyn, Skaneateles Falls, NY). Subjects were monitored for ~25 hours, beginning at ~1 hour before until 24 hours after the initiation of the cefiderocol or saline (placebo) infusion, or postdose in the moxifloxacin group. Triplicate 10-s ECG recordings were extracted, each 1 minute apart, from the Surveyor recordings at predose (0.5 hours before study drug administration) and at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours after the initiation of the cefiderocol or placebo infusions or after oral dosing of moxifloxacin. A window of 5 minutes around the nominal timepoint was utilized to capture ECGs of adequate quality. If targeted ECG timepoints were of poor quality, the central ECG laboratory extracted analyzable 10-s ECGs as close as possible to the targeted timepoints. Subjects refrained from talking and were instructed to lie in a supine position in a quiet room, with no external stimuli, for ~10 minutes prior to and 5 minutes after the nominal ECG-extraction timepoints. The ECG-extraction timepoints were time-matched with the PK-sampling timepoints, but ECG extractions were performed before the PK sample was obtained, to avoid changes in autonomic tone associated with the psychological aspects of blood collection as well as the reduction in blood volume subsequent to blood collection.

The recorded ECG data were stored on-site in the Spaulding ECG core laboratory. The ECGs were read using a high-resolution manual on-screen caliper method in accordance with the ICH E14 guidance.

The ECG core laboratory cardiology staff was blinded to subject, treatment, time, and study-day identifiers. ECGs from each subject were reviewed by a single cardiologist. Lead II was the lead of choice for the over-reads. Baseline and on-treatment ECGs were based on the same lead. If lead II was not analyzable, ECG measurements were conducted in lead V5. If lead V5 was not analyzable, the most appropriate lead (eg, lead V2) was used.

Pharmacodynamics (Part 2)

In each treatment period, continuous cardiac monitoring was implemented to assess the potential effects of cefiderocol on ECG parameters, including heart rate (HR), RR interval, PR interval, QRS interval, QT interval, and QTcF interval. The QT interval, expressed in units of ms and corrected using the Fridericia formula, was the primary ECG parameter used for the assessment of the potential effect of cefiderocol on QTc interval prolongation. The primary parameter used for the assessment of the potential effect of cefiderocol on QTc interval prolongation at each timepoint after the initiation of infusion of the 2- and 4-g doses of cefiderocol was the *baseline-adjusted QTcF interval* (dQTcF), defined as the difference between the mean triplicate QTcF interval values at each timepoint after the initiation of infusion and the mean predose (baseline) triplicate QTcF interval value. The primary study end point was the time-matched placebo- and baseline-adjusted QTcF interval (ddQTcF) at each timepoint after the initiation of infusion of the 2- and 4-g doses of cefiderocol and was defined as the dQTcF interval value at each postdose timepoint minus the dQTcF interval value of placebo at the corresponding postdose timepoint in each subject: ddQTcF = (dQTcF [2- or 4-g dose of cefiderocol] − dQTcF[placebo]).

The above definitions were also applied to the sensitivity analyses for the 400-mg moxifloxacin treatment. For the secondary end points (HR and RR, PR, and QRS intervals), corresponding derived variables were also calculated.

Pharmacokinetics (Parts 1 and 2)

The plasma PK parameters of cefiderocol were calculated based on the concentration−time profiles in all evaluable subjects in each dose group (part 1) or with each dose (2 or 4 g in part 2). Blood samples for the determination of plasma cefiderocol concentrations (parts 1 and 2) were collected at predose and at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours after the initiation of infusion on day 1 in part 1 of the study or in each cefiderocol or placebo treatment period in part 2 of the study. Blood samples for the determination of plasma moxifloxacin concentrations (part 2 only) were collected at predose and at 1 and 2 hours postdose on day 1. Plasma concentrations of cefiderocol, as described in detail previously (QPS Holdings LLC, Newark, Delaware),[19] and of moxifloxacin were determined using a validated LC-MS/MS method (QPS Holdings). For measurements of moxifloxacin, plasma samples were spiked with internal standard, processed using liquid−liquid extraction, and analyzed using reversed-phase HPLC with TurboIonSpray MS/MS detection (Sciex, Framingham, Massachusetts). Positive $(M + H)^+$ ions for moxifloxacin and moxifloxacin-d_4 were monitored in MRM mode. The lower limit of quantification of moxifloxacin was 25 ng/mL using 50 μL of plasma sample. The assay was linear from 25 to 5000 ng/mL. The intraday precision and accuracy were 1.5% to 6.3% and –3.5% to 5.6%, respectively. The interday precision and accuracy were 3.3% to 6.3% and –2.5% to 2.5%, respectively. The following plasma PK parameters of cefiderocol were calculated using noncompartmental analyses: C_{max}, T_{max}, AUC_{0-last}, AUC_{0-inf}, percentage of the AUC extrapolated from time zero to infinity (AUC_{extr}); terminal elimination rate constant (λ_z); terminal elimination half-life ($t_{1/2,z}$); total clearance (CL); and volume of distribution in the terminal elimination phase (V_z). All PK analyses were performed using Phoenix WinNonlin version 6.3 (Certara, Princeton, NJ).

Tolerability (Parts 1 and 2)

Tolerability was monitored using repeated assessments of tolerability parameters, including physical examinations with vital sign measurements, 12-lead ECG for tolerability, clinical laboratory tests (hematology, blood chemistry, and urinalysis; see Supplemental Table I in the online version at https://doi.org/10.1016/j.clinthera.2019.07.006), and spontaneous reporting of adverse events (AEs).

Statistical Analysis

The ddQTcF interval was the primary end point used for investigating potential QTc interval prolongation associated with cefiderocol. A mixed-

effects model was used for evaluating the primary end point. The model included terms for treatment, period, timepoint, treatment-by-post initiation of the infusion−timepoint interaction, and sequence as fixed effects and subjects nested within sequence as a random effect, and baseline QTcF interval and sex 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.

Continuous variables were summarized using descriptive statistics (number of subjects, mean [SD], 2-sided CI [90% CI] for the QTcF interval or 95% CI of HR, and PR and QRS intervals], median [interquartile range], and range). The means and 90% CIs of the dQTcF and ddQTcF intervals were calculated in all subjects by treatment and timepoint. For the secondary end points (HR, and PR and QRS intervals), the means and 95% CIs were calculated in all subjects by treatment and timepoint. Of note, the results at each timepoint after the initiation of infusion are presented as the *predicted ddQTcF*, with 2-sided 90% CIs, where the upper bound of the 90% CI equals the upper bound of the 1-sided 95% CI. The mean and upper bound of the 95% 1-sided CI of the ddQTcF interval at each timepoint after the initiation of infusion was used for the primary statistical comparison. The relationship between the ddQTcF and plasma cefiderocol concentration, and ECG parameters were investigated using the mixed-effects model.

Plasma cefiderocol and moxifloxacin concentrations were summarized using descriptive statistics (mean [SD], %CV, geometric mean, %CV of the for geometric mean, median, and range) by timepoint and treatment. Mean plasma concentration−time profiles were plotted by treatment on linear and semilogarithmic scales using nominal timepoints. Individual concentration−time profiles and spaghetti plots were created with subject concentration−time profiles overlaid, using linear and semilogarithmic scales, with respective treatments. Dose-dependency and -independency of PK parameters were assessed using an ANOVA model. All statistical and ECG data analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Study Subjects

The study included 64 subjects. A total of 16 subjects (8 in each dose group) completed part 1 of the study. A total of 48 subjects were enrolled in part 2 of the study. Due to a higher-than-expected dropout rate, an additional 4 subjects were randomized in part 2 as replacement subjects and received the same treatment sequence as did the subjects whom they replaced. A total of 40 subjects completed part 2 of the study and 8 subjects prematurely discontinued due to AEs (n = 1), protocol deviation (n = 3), and withdrawal of consent (n = 4). Subjects' demographic and clinical characteristics at baseline are summarized in Table I.

QTcF Interval and Other Pharmacodynamic Results

No clinically significant prolongation of the QTcF interval after the administration of either the 2-g dose (therapeutic dose) or 4-g dose (supratherapeutic dose) of cefiderocol was observed. The changes in the mean ddQTcF interval associated with the 2- or 4-g dose of cefiderocol were variably positive and negative, small, and clinically insignificant. The 2-sided 90% CI of the ddQTcF interval was in the positive range and excluded zero at 6 timepoints after the initiation of infusion of the 2-g dose of cefiderocol (4, 4.5, 6, 8, 10, and 12 hours after the initiation of infusion) and at a single timepoint after the initiation of the infusion of the 4-g dose of cefiderocol (10 hours) (Figure 2 and Table II). However, all point estimates of the ddQTcF interval were <5 ms, and the upper bounds of the 90% CIs at each timepoint after the initiation of infusion were well below 10 ms. Thus, the single 2- and 4-g doses of cefiderocol did not prolong the ddQTcF interval to a level of regulatory concern.

Adequate assay sensitivity was demonstrated in the mixed-effects model for the ddQTcF interval with moxifloxacin treatment, as the lower bounds of the 90% CIs of the mean ddQTcF interval exceeded 5 ms at all prespecified postdose timepoints (1 and 2 hours) after the application of the Hochberg procedure (Hochberg lower bounds of the 90% CI were 7.1, 7.6, and 9.4 ms, respectively). The changes from baseline in HR were similar between the

Table I. Subjects' demographic and clinical characteristics at baseline.

Parameter	Part 1			Part 2 (Overall) (n = 48)
	Cefiderocol 3 g (n = 6)	Cefiderocol 4 g (n = 6)	Placebo (n = 4)	
Age, mean (SD), y	36.7 (12.06)	32.7 (8.36)	29.3 (13.89)	33.3 (8.83)
Weight, mean (SD), kg	78.07 (14.671)	77.73 (10.974)	71.00 (18.750)	75.84 (10.800)
Height, mean (SD), cm	169.7 (11.09)	177.8 (7.75)	173.9 (14.99)	169.1 (9.06)
BMI, mean (SD), kg/m^2	26.92 (2.613)	24.53 (2.533)	23.10 (2.376)	26.43 (2.430)
Sex, no. (%)				
Female	3 (50.0)	0	2 (50.0)	21 (43.8)
Male	3 (50.0)	6 (100.0)	2 (50.0)	27 (56.3)
Race, no. (%)				
White	4 (66.7)	5 (83.3)	2 (50.0)	19 (39.6)
Black or African American	2 (33.3)	1 (16.7)	2 (50.0)	25 (52.1)
Other	0	0	0	4 (8.3)
Ethnicity, no. (%)				
Not Hispanic or Latino	6 (100.0)	4 (66.7)	3 (75.0)	40 (83.3)
Hispanic or Latino	0	2 (33.3)	1 (25.0)	8 (16.7)

BMI = body mass index.

cefiderocol treatments and placebo and were not clinically significant; HR was increased modestly with the moxifloxacin treatment (see Supplemental Figure 1A in the online version at https://doi.org/10.1016/j.clinthera.2019.07.006). The relatively minor changes from baseline in PR and QRS intervals were similar between the placebo, cefiderocol, and moxifloxacin treatments and were not clinically

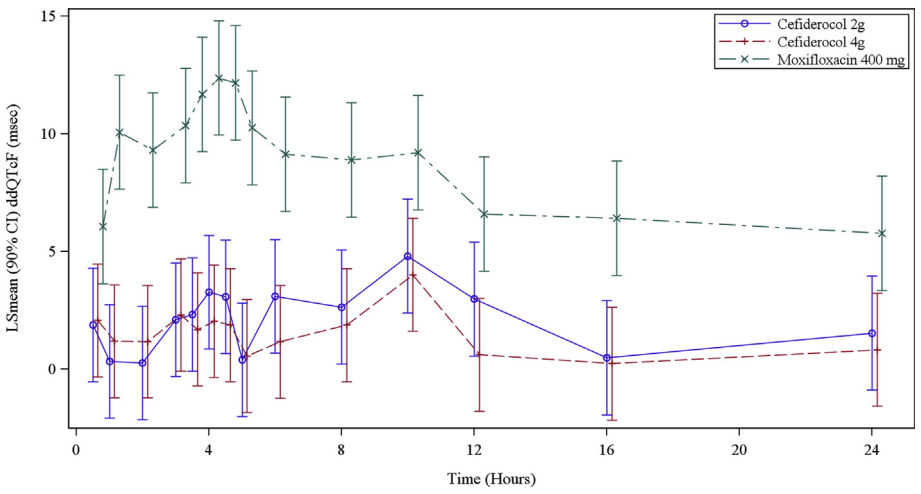


Figure 2. Mean (90% CI) ddQTcF interval versus time by treatment, mixed effects model. ddQTcF = time-matched placebo- and baseline-adjusted QT time-matched placebo- and baseline-adjusted QT corrected using the Fridericia formula; LS = least squares.

significant (see Supplemental Figures 1B and 1C in the online version at https://doi.org/10.1016/j.clinthera.2019.07.006). There were no apparent trends suggestive of a treatment effect in the frequency of abnormal electrocardiographic statements before and during treatment.

Influence of Sex on QTc Prolongation

In the overall analysis of the current study, sex was found to be a statistically significant covariate ($P = 0.0014$), with an apparent effect on dQTcF in the moxifloxacin arm. However, there was very little influence of sex on change in QTcF in the cefiderocol arms (see Supplemental Figure 2 in the online version at https://doi.org/10.1016/j.clinthera.2019.07.006 for dQTcF changes at T_{max} of cefiderocol [~3 hours] and moxifloxacin [2−5 hours after oral administration]). The next largest effect was seen in the placebo group, with a minimal influence of sex on the change in QTcF observed in the cefiderocol arms; this effect had no apparent correlation with the dose of cefiderocol.

Pharmacokinetic/Pharmacodynamic Analysis

In part 2, plasma cefiderocol concentrations were quantifiable from 0.5 hour through the 16-hour timepoint after the initiation of infusion in all subjects who received a 2-g dose and through the 24-hour timepoint after the initiation of infusion in all subjects who received a 4-g dose (Figure 3). After the administration of a 2- or 4-g dose, the plasma C_{max}, AUC_{0-last}, and AUC_{0-inf} values of cefiderocol were increased in a dose-proportional manner (Table III). The cefiderocol geometric mean $t_{1/2,z}$, CL, and V_z were comparable (ie, independent of the cefiderocol dose). Similar cefiderocol PK results were seen with the 3- and 4-g doses in part 1 of the study (see Supplemental Figure 3 and Supplemental Table II in the online version at https://doi.org/10.1016/j.clinthera.2019.07.006). Concentration-effect modeling showed a slightly negative slope (–0.0046) and predicted modestly negative values for the ddQTcF interval at the C_{max} of cefiderocol (Figure 4).

Table II. ddQTcF interval per timepoint. Data are given in milliseconds.

Timepoint	Cefiderocol 2 g (n = 42)		Cefiderocol 4 g (n = 44)		Moxifloxacin 400 mg (n = 41)	
	Mean	90% CI	Mean	90% CI	Mean	90% CI
0.5 h	1.9	−0.5 to 4.3	2.1	−0.3 to 4.5	6.1	3.6 to 8.5*
1 h	0.3	−2.1 to 2.7	1.2	−1.2 to 3.6	10.1	7.6 to 12.5*
2 h	0.3	−2.2 to 2.7	1.2	−1.2 to 3.6	9.3	6.9 to 11.7*
3 h	2.1	−0.3 to 4.5	2.3	−0.1 to 4.7	10.4	7.9 to 12.8*
3.5 h	2.3	−0.1 to 4.7	1.7	−0.7 to 4.1	11.7	9.2 to 14.1*
4 h	3.3	0.8 to 5.7*	2.0	−0.4 to 4.4	12.4	9.9 to 14.8*
4.5 h	3.1	0.7 to 5.5*	1.9	−0.5 to 4.3	12.2	9.7 to 14.6*
5 h	0.4	−2.0 to 2.8	0.6	−1.8 to 2.9	10.3	7.8 to 12.7*
6 h	3.1	0.7 to 5.5*	1.2	−1.2 to 3.6	9.1	6.7 to 11.6*
8 h	2.6	0.2 to 5.1*	1.9	−0.5 to 4.3	8.9	6.4 to 11.3*
10 h	4.8	2.4 to 7.2*	4.0	1.6 to 6.4*	9.2	6.8 to 11.6*
12 h	3.0	0.5 to 5.4*	0.6	−1.8 to 3.0	6.6	4.1 to 9.0*
16 h	0.5	−1.9 to 2.9	0.2	−2.2 to 2.6	6.4	4.0 to 8.9*
24 h	1.5	−0.9 to 4.0	0.8	−1.6 to 3.2	5.8	3.3 to 8.2*

ddQTcF = time-matched placebo- and baseline-adjusted QT corrected using the Fridericia formula.
* CI excludes zero.

Tolerability

A total of 4 treatment-emergent (TE)-AEs were reported in 4 subjects in part 1 of the study; 2 TEAEs (headache and phlebotomy pain) were reported after the administration of the 3-g dose of cefiderocol; 2 TEAEs (phlebotomy pain and right wrist numbness) were reported after the administration of placebo. All AEs were mild in severity and resolved without intervention by the end of the study. There were no deaths, serious AEs, or AEs leading to study discontinuation reported in part 1. There were no apparent clinically significant abnormal findings observed with regard to ECG parameters, vital sign measurements, or clinical laboratory test results.

A total of 45 TEAEs in 19 subjects were reported in part 2 of the study (Table IV). All were mild in severity and resolved without intervention by the end of the study, except for ongoing anemia in 1 subject, who was prescribed ferrous sulfate and ascorbic acid (vitamin C) and instructed to follow up with her primary care physician. One subject had elevated aspartate and alanine aminotransferase (AST and ALT) levels of 87 and 152 U/L (normal ranges, 13–39 and 7–52 U/L, respectively) on day 15 of treatment period 4 after receiving a 4-g dose of cefiderocol; the patient was followed up until his values returned to nearly within normal limits. There were no apparent clinically significant abnormalities in vital sign measurements or ECG parameters, except second-degree atrioventricular block (Mobitz I) in 1 subject; on day 1 of treatment period 1, after the administration of a 400-mg dose of moxifloxacin, the subject had an ECG finding at the 2-hour timepoint that was considered clinically significant and was reported as a TEAE of second-degree atrioventricular

Table III. Plasma pharmacokinetic parameters for cefiderocol (Part 2). Data are given as geometric mean (%CV) unless otherwise noted.

Parameter	Cefiderocol 2 g (n = 43)	Cefiderocol 4 g (n = 44)
C_{max}, µg/mL	89.7 (20.5)	183 (17.3)
T_{max}, h*	2.90 (2.08–4.58)	2.90 (2.08–2.97)
AUC_{0-last}, µg·h/mL	384.8 (17.3)	790.5 (17.1)
AUC_{0-inf}, µg·h/mL	386.1 (17.2)	791.6 (17.1)
$t_{1/2}z$, h	2.41 (14.0)	2.57 (7.5)
CL, L/h	5.18 (17.2)	5.05 (17.1)
Vz, L	18.0 (18.1)	18.8 (18.5)

CL = total clearance; $t_{1/2}z$ = terminal elimination half-life; Vz, volume of distribution in the terminal elimination phase.
* Median (range).

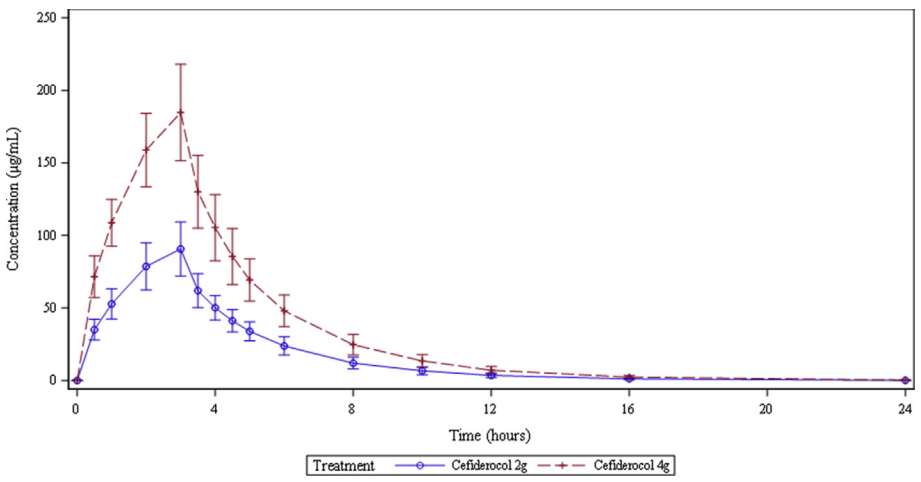


Figure 3. Mean (SD) plasma cefiderocol concentration–time profile, linear scale (Part 2).

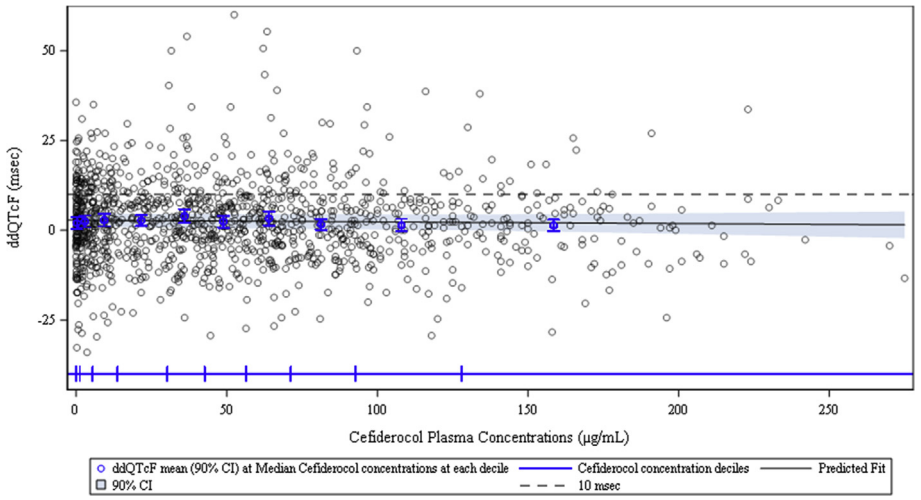


Figure 4. Observed median-decile cefiderocol concentrations and associated mean (90% CI) ddQTcF interval together with the mean (90% CI) predicted ddQTcF interval. The observed mean ddQTcF interval values at the median point of each plasma concentration decile are plotted with their 90% CI and the decile lower and upper boundaries. ddQTcF = time-matched placebo- and baseline-adjusted QT corrected using the Fridericia formula.

block (Mobitz I). It was an asymptomatic event, considered mild in severity and related to the study drug, did not require treatment, and was documented as "recovered/resolved" within ~1 hour of onset. The subject did not report any relevant medical history and completed the study without recurrence. One subject was discontinued from the study for noncompliance with the study restrictions. The subject had elevated AST, ALT, and lactate dehydrogenase (LDH) levels of 282, 90, and 403 U/L (LDH normal range, 100–192 U/L), respectively, on day 1 of treatment period 4 after receiving a 2-g dose of cefiderocol in the previous treatment period. The subject subsequently confirmed that she had consumed 3 units of alcohol (12 oz of alcohol per unit) during the interval between treatment periods, 6 days before the sampling. Clinical laboratory values in this subject at screening and at days –1 and 2 of treatment periods 1, 2, and 3 were all within the respective reference ranges. At the early-termination visit, the subject's AST, ALT, and LDH values were all within the respective reference ranges. The increased hepatic enzymes were considered as not related to the study drug. There were no deaths or serious AEs reported in part 2 of the study.

DISCUSSION

Cefiderocol, a novel parenteral siderophore cephalosporin, has activity against multidrug-resistant gram-negative bacteria, including Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.[11–13] Since cefiderocol is excreted primarily via the kidneys, a previous study was conducted to develop a population PK model to determine dose adjustment based on renal function.[22] The study demonstrated that the optimal therapeutic dose of cefiderocol was 2 g infused over 3 hours, every 8 hours, with adjustments based on renal function.[22]

An extensive preclinical tolerability investigation in monkeys showed that high doses of cefiderocol of 1000 and 600 mg/kg/d, with corresponding drug concentrations (C_0) of 2300–2600 and 1530–1610 µg/mL, respectively, resulted in a QTc prolongation in the range of 10% to 34% versus predose baseline. The no-observed-effect level of QTc interval prolongation in monkeys was found to be at the 300-mg/kg/d dose of cefiderocol, with corresponding C_0 values at the no-observed-effect level of 770 to 876 µg/mL. Based on the results of

Table IV. Treatment-emergent adverse events (Part 2).

MedDRA System Organ Class Preferred Term	Cefiderocol 2 g (n = 43)	Cefiderocol 4 g (n = 44)	Moxifloxacin 400 mg (n = 42)	Placebo (n = 47)	All Subjects (n = 48)
Number of subjects with at least 1 TEAE, no. (%)	10 (23.3)	11 (25.0)	3 (7.1)	6 (12.8)	19 (39.6)
No. of TEAEs	15	16	5	9	45
Blood and lymphatic system disorders	0	0	1 (2.4)	1 (2.1)	1 (2.1)
Anemia	0	0	1 (2.4)	1 (2.1)	1 (2.1)
Cardiac disorders	0	0	1 (2.4)	0	1 (2.1)
Atrioventricular block second degree	0	0	1 (2.4)	0	1 (2.1)
Eye disorders	0	0	0	1 (2.1)	1 (2.1)
Dry eye	0	0	0	1 (2.1)	1 (2.1)
Gastrointestinal disorders	0	4 (9.1)	0	2 (4.3)	6 (12.5)
Abdominal pain upper	0	1 (2.3)	0	0	1 (2.1)
Constipation	0	0	0	1 (2.1)	1 (2.1)
Diarrhea	0	2 (4.5)	0	0	2 (4.2)
Dyspepsia	0	1 (2.3)	0	0	1 (2.1)
Nausea	0	0	0	1 (2.1)	1 (2.1)
Vomiting	0	0	0	1 (2.1)	1 (2.1)
General disorders and administration site conditions	7 (16.3)	3 (6.8)	0	2 (4.3)	9 (18.8)
Chest discomfort	1 (2.3)	0	0	0	1 (2.1)
Discomfort	0	0	0	1 (2.1)	1 (2.1)
Infusion site irritation	0	1 (2.3)	0	0	1 (2.1)
Infusion site pain	0	2 (4.5)	0	0	2 (4.2)
Infusion site swelling	1 (2.3)	0	0	0	1 (2.1)
Pain	1 (2.3)	0	0	0	1 (2.1)
Vessel puncture site bruise	1 (2.3)	0	0	0	1 (2.1)
Vessel puncture site pain	4 (9.3)	0	0	1 (2.1)	4 (8.3)
Vessel puncture site swelling	0	1 (2.3)	0	0	1 (2.1)
Infections and infestations	0	1 (2.3)	0	0	1 (2.1)
Upper respiratory tract infection	0	1 (2.3)	0	0	1 (2.1)
Investigations	1 (2.3)	1 (2.3)	0	0	2 (4.2)
Hepatic enzyme increased	1 (2.3)	0	0	0	1 (2.1)
Laboratory test abnormal	0	1 (2.3)	0	0	1 (2.1)
Musculoskeletal and connective tissue disorders	1 (2.3)	0	0	0	1 (2.1)
Pain in extremity	1 (2.3)	0	0	0	1 (2.1)
Nervous system disorders	4 (9.3)	3 (6.8)	1 (2.4)	2 (4.3)	8 (16.7)
Dizziness	1 (2.3)	1 (2.3)	1 (2.4)	2 (4.3)	5 (10.4)
Headache	3 (7.0)	2 (4.5)	1 (2.4)	0	5 (10.4)
Psychiatric disorders	1 (2.3)	0	0	0	1 (2.1)
Anxiety	1 (2.3)	0	0	0	1 (2.1)

(*continued on next page*)

Table IV. (*Continued*)

MedDRA System Organ Class Preferred Term	Cefiderocol 2 g (n = 43)	Cefiderocol 4 g (n = 44)	Moxifloxacin 400 mg (n = 42)	Placebo (n = 47)	All Subjects (n = 48)
Respiratory, thoracic and mediastinal disorders	0	1 (2.3)	0	0	1 (2.1)
Dyspnea	0	1 (2.3)	0	0	1 (2.1)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

the present study, this level of exposure to cefiderocol is 9- to 10-fold higher than that achieved at the proposed clinical dose of 2 g infused over 3 hours, every 8 hours. Of note, such high exposure was not achieved with the highest supratherapeutic dose tested, infused over 3 hours, in the present study. As certain nonantiarrhythmic drugs, such as fluoroquinolones and macrolides, are associated with an increased risk for life-threatening cardiac arrhythmias such as torsades de pointes,[2] a comprehensive evaluation of cardiac tolerability is a part of the regulatory requirements of product registration in the United States and other countries that follow the ICH E14 Guidance for Industry.[20]

In order to be aligned with the regulatory requirement,[20] the current study was conducted to evaluate the tolerability of single doses (3 and 4 g) that are higher than a therapeutic dose (2 g) of cefiderocol (part 1), and to evaluate the effect of single therapeutic (2 g) and supratherapeutic (4 g) doses of cefiderocol on the QTcF (part 2) in healthy adult subjects. Single 3- and 4-g doses of cefiderocol, each administered by infusion over 3 hours, were well tolerated. In addition, the PK properties of single 3- and 4-g doses of cefiderocol were consistent with a linear PK profile. Overall, the assessment of ECG parameters, vital signs, clinical laboratory test results, and AEs after each dose in part 1 of the study indicated that a 4-g dose (2-fold the therapeutic dose) was appropriate for inclusion as the supratherapeutic dose in part 2 of the study.

After the administration of the single 2- and 4-g doses, cefiderocol was not associated with a prolonged ddQTcF interval in part 2 of the study. While the 90% CI of the ddQTcF interval was in the positive range and excluded zero at 6 timepoints after the initiation of infusion of the 2-g dose of cefiderocol and at a single timepoint after the initiation of infusion of the 4-g dose of cefiderocol, all point estimates of the ddQTcF interval were <5 ms, and the upper bound of the 2-sided 90% CI equivalent to the upper bound of the 1-sided 95% CI was well <10 ms at all timepoints after the initiation of infusion. Thus, single therapeutic and supratherapeutic doses of cefiderocol were not associated with prolonged ddQTcF interval to a level of regulatory concern, and this study met the criteria for a negative thorough QT/QTc study stipulated in the ICH E14 Guidance for Industry.[20] Assay sensitivity was confirmed by the moxifloxacin treatment ddQTcF response. There were no apparent clinically significant changes in other ECG parameters, including HR and the duration of PR and QRS intervals. Concentration-effect modeling indicated no apparent positive association between the C_{max} of cefiderocol and the ddQTcF interval. Furthermore, there were no apparent differences in dQTcF values between female and male subjects receiving either the 2- or 4-g dose of cefiderocol, while dQTcF values were significantly prolonged with the moxifloxacin 40-mg dose in the female versus the male subjects. After the administration of single 2- and 4-g doses, the PK properties of cefiderocol were consistent with a linear PK profile. All AEs were mild in severity and resolved by the end of part 2 of the study.

CONCLUSIONS

Single doses (3 and 4 g) of cefiderocol that are higher than a therapeutic dose (2 g) were well tolerated in these healthy subjects. Furthermore, therapeutic (2-g) and supratherapeutic (4-g) doses of cefiderocol administered by IV infusion over 3 hours were also well tolerated in these healthy adult subjects, with no

clinically significant effect on the QT/QTc interval or other ECG parameters.

ACKNOWLEDGMENTS

We thank the subjects and families who participated in the study. We also thank the investigators who conducted the study. Medical writing and editorial support were provided by Erik Sakowski, PhD, Phase Five Communications Inc.

C. Sanabria contributed to conceptualization of the study; methodology (protocol development); investigation (conduct of the study); data curation (acquisition, interpretation); writing, reviewing, and revising the manuscript; and approving the final version for submission. E. Migoya contributed to methodology (protocol development); investigation (conduct of the study); data curation (acquisition, interpretation); project administration; writing, reviewing, and revising the manuscript; and approving the final version for submission. J.W. Mason contributed to investigation (conduct of the study); data curation (acquisition, analysis, interpretation); writing, reviewing, and revising the manuscript; and approving the final version for submission. S.H. Stanworth contributed to data curation (analysis, interpretation); writing, reviewing, and revising the manuscript; and approving the final version for submission. T. Katsube contributed to conceptualization of the study; methodology (protocol development); investigation (conduct of the study); data curation (analysis, interpretation); writing, reviewing, and revising the manuscript; and approving the final version for submission. M. Machida contributed to conceptualization of the study; methodology (protocol development); investigation (conduct of the study); data curation (analysis, interpretation); writing, reviewing, and revising the manuscript; and approving the final version for submission. Y. Narukawa contributed to conceptualization of the study; methodology (protocol development); investigation (conduct of the study); data curation (analysis, interpretation); writing, reviewing, and revising the manuscript; and approving the final version for submission. T.D. Nagata contributed to conceptualization of the study; methodology (protocol development); data curation (interpretation); writing, reviewing, and revising the manuscript; and approving the final version for submission.

CONFLICTS OF INTEREST

This study was funded and conducted by Shionogi & Co Ltd (Osaka, Japan) and its subsidiary Shionogi Inc (Florham Park, New Jersey). Medical writing and editorial support were funded by Shionogi Inc.

T. Katsube, M. Machida, Y. Narukawa, and T.D. Nagata are employees of Shionogi & Co Ltd. E. Migoya was an employee of Shionogi Inc. at the time of the study and during the initial preparation of the manuscript. The institutes of C. Sanabria and J.W. Mason received study-related research grants. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

REFERENCES

1. Schwartz PJ, Woosley RL. Predicting the unpredictable: drug-induced QT prolongation and torsades de pointes. *J Am Coll Cardiol*. 2016;67:1639–1650.
2. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart*. 2003;89:1363–1372.
3. Owens Jr RC. An overview of harms associated with β-lactam antimicrobials: where do the carbapenems fit in? *Crit Care*. 2008;12(Suppl 4):S3.
4. Ball P. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. *J Antimicrob Chemother*. 2000;45:557–559.
5. Teppler H, Gesser RM, Friedland IR, et al. Safety and tolerability of ertapenem. *J Antimicrob Chemother*. 2004;53(Suppl 2):ii75–ii81.
6. Riccobene TA, Rekeda L, Rank D, et al. Evaluation of the effect of a supratherapeutic dose of intravenous ceftaroline fosamil on the corrected QT interval. *Antimicrob Agents Chemother*. 2013;57:1777–1783.
7. Das S, Armstrong J, Mathews D, et al. Randomized, placebo-controlled study to assess the impact on QT/QTc interval of supratherapeutic doses of ceftazidime-avibactam or ceftaroline fosamil-avibactam. *J Clin Pharmacol*. 2014;54:331–340.
8. *Doribax (Doripenem for Injection) [prescribing Information]*. Florham Park, NJ: Shionogi Inc; 2015.
9. Ito A, Nishikawa T, Matsumoto S, et al. Siderophore cephalosporin cefiderocol utilizes ferric iron transporter systems for antibacterial activity against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2016;60:7396–7401.
10. Ito-Horiyama T, Ishii Y, Ito A, et al. Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases. *Antimicrob Agents Chemother*. 2016;60:4384–4386.

11. Hackel MA, Tsuji M, Yamano Y, et al. In vitro activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant Gram-negative bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 Study). *Antimicrob Agents Chemother*. 2017;61. e00093-17.
12. Falagas ME, Skalidis T, Vardakas KZ, et al. Activity of cefiderocol (S-649266) against carbapenem-resistant gram-negative bacteria collected from inpatients in Greek hospitals. *J Antimicrob Chemother*. 2017;72:1704–1708.
13. Dobias J, Denervaud-Tendon V, Poirel L, et al. Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens. *Eur J Clin Microbiol Infect Dis*. 2017;36: 2319–2327.
14. Diene SM, Rolain JM. Carbapenemase genes and genetic platforms in Gram-negative bacilli: Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* species. *Clin Microbiol Infect*. 2014;20:831–838.
15. Livermore DM. Current epidemiology and growing resistance of Gram-negative pathogens. *Korean J Intern Med*. 2012;27:128–142.
16. World Health Organization. *Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics*; February 27, 2017. http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en. Accessed July 27, 2017.
17. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2018;18:1319–1328.
18. Saisho Y, Katsube T, White S, et al. Pharmacokinetics, safety, and tolerability of cefiderocol, a novel siderophore cephalosporin for Gram-negative bacteria, in healthy subjects. *Antimicrob Agents Chemother*. 2018;62. e02163-17.
19. Katsube T, Echols R, Arjona Ferreira JC, et al. Cefiderocol, a siderophore cephalosporin for Gram-negative bacterial infections: pharmacokinetics and safety in subjects with renal impairment. *J Clin Pharmacol*. 2017;57:584–591.
20. US Food and Drug Administration. *Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs*; October 2005. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf. Accessed July 27, 2017.
21. Darpo B. The thorough QT/QTc study 4 years after the implementation of the ICH E14 guidance. *Br J Pharmacol*. 2010;159: 49–57.
22. Katsube T, Wajima T, Ishibashi T, et al. Pharmacokinetic/pharmacodynamic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, for dose adjustment based on renal function. *Antimicrob Agents Chemother*. 2017;61. e01381-16.

Address correspondence to: Carlos Sanabria, MD, Spaulding Clinical, 525 South Silverbrook Drive, West Bend, WI 53095, USA. E-mail: carlos.sanabria@spauldingclinical.com

APPENDIX

Supplementary Table I. Clinical laboratory tests

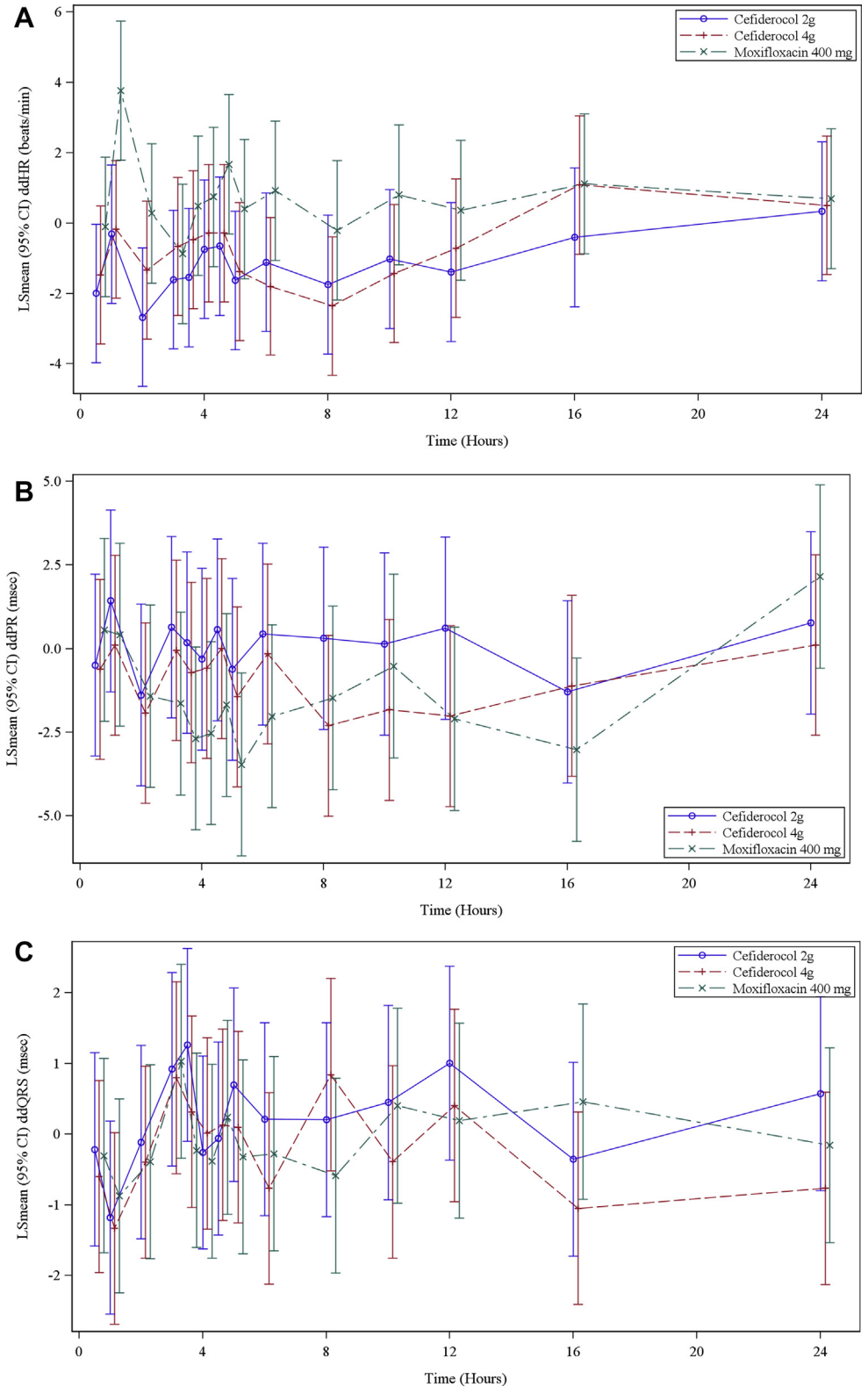
Category	Tests
Routine laboratory tests	
Hematology	Hematocrit
	Hemoglobin
	Total and differential leukocytes count
	Red blood cell count
	Platelet count
	Morphologic indices
Blood chemistry[a]	Aspartate aminotransferase
	Alanine aminotransferase
	Lactate dehydrogenase
	Gamma glutamyltransferase
	Alkaline phosphatase
	Direct and total bilirubin
	Indirect bilirubinTotal protein
	Total cholesterolAlbuminBlood urea nitrogen
	Electrolytes (sodium, potassium, chloride, calcium, and magnesium)
	Glucose (fasting)
	Uric acid
	Creatinine[b]
Urinalysis	Specific gravity
	Protein[c]
	Glucose
	Bilirubin[c]
	Urobilinogen[c]
	Leukocyte esterase[c]
	Ketone[c]pH
	Nitrite[c]
	Occult blood[c]
Other laboratory tests	Blood coagulation tests for prothrombin time/international normalized ratio and activated partial thromboplastin time
	Serum tests for hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antigen/antibody
	Urine screening test for alcohol, phencyclidines, benzodiazepines, amphetamines, cocaine-based narcotics, cannabis, opiate-based narcotics, barbiturates, and tricyclic antidepressants
	Urine cotinine test
	Serum pregnancy test, for female subjects of child-bearing potential only
	Serum test for FSH level to confirm postmenopausal status if documentation of FSH level was otherwise unavailable

Abbreviation: FSH, follicle-stimulating hormone.
[a] Blood chemistry tests were performed after at least an 8-hour fast; however, in the case of dropouts or rechecks, subjects may not have fasted for 8 hours before the chemistry sample was taken.
[b] At the screening visit, creatinine clearance was calculated using the Cockcroft-Gault formula.
[c] If urinalysis was positive for protein, occult blood, nitrite, leukocyte esterase, bilirubin, urobilinogen, and/or ketone, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) was performed.

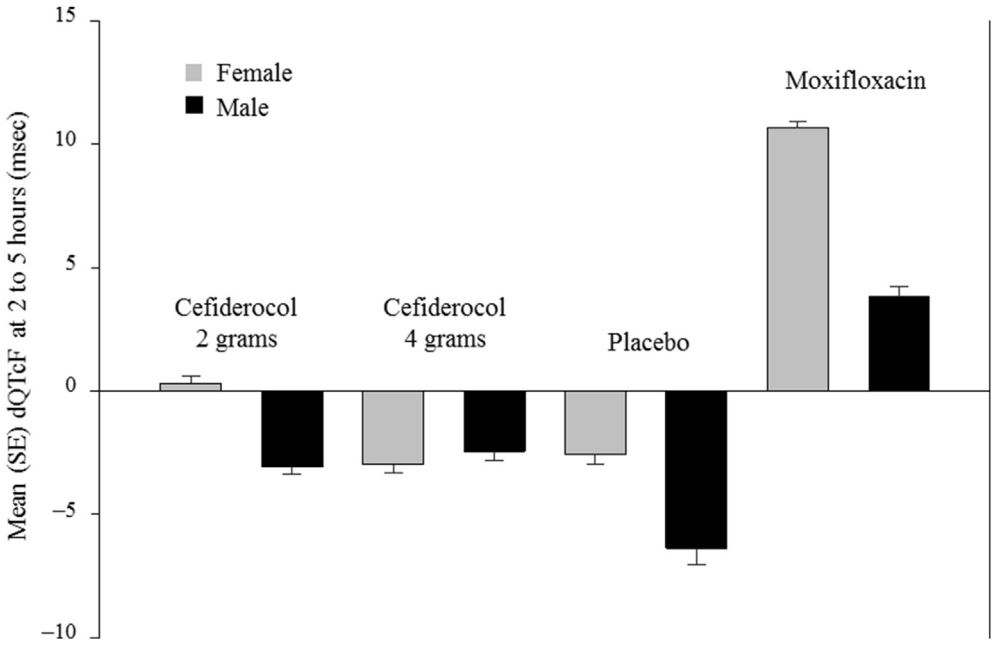
Supplementary Table II. Plasma pharmacokinetic parameters for cefiderocol (Part 1)

Parameter (units)	Cefiderocol 3 g (n=6)	Cefiderocol 4 g (n=6)
C_{max} (μg/mL)	132 (25.5)	186 (28.4)
T_{max} (hr)	2.86 (2.00–2.90)	2.90 (2.90–2.93)
$AUC_{0\text{-last}}$ (μg·hr/mL)	524.9 (28.5)	722.2 (13.3)
$AUC_{0\text{-inf}}$ (μg·hr/mL)	525.9 (28.4)	723.3 (13.2)
$t_{1/2,z}$ (hr)	2.29 (19.3)	2.71 (9.8)
CL (L/hr)	5.70 (28.3)	5.53 (13.2)
V_z (L)	18.9 (21.7)	21.6 (20.6)

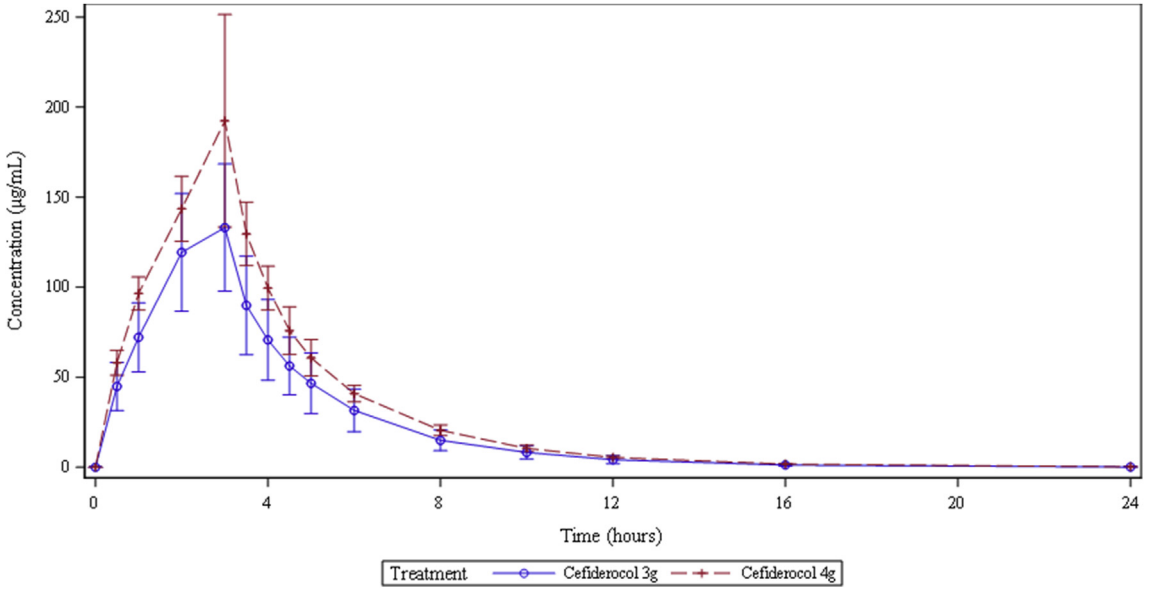
Values are geometric mean (CV % geometric mean) except for T_{max}, which was reported as median (minimum–maximum).
Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration–time curve extrapolated from time zero to infinity; $AUC_{0\text{-last}}$, area under the concentration–time curve from time zero to the time of the last quantifiable concentration after dosing; CL, total clearance; C_{max}, maximum observed plasma concentration; CV%, percent coefficient of variation; $t_{1/2,z}$, terminal elimination half-life; T_{max}, time of maximum observed plasma concentration; V_z, volume of distribution in the terminal elimination phase.



Supplementary Figure 1. Mean placebo-subtracted change from baseline for HR (panel A), PR (Panel B) and QRS (Panel C).



Supplementary Figure 2. Comparison between females and males of change from baseline of QTcF at hours 2 to 5 in the four treatment groups.



Supplementary Figure 3. Mean plasma concentration of cefiderocol over time at the 3-g and 4-g doses in Part 1.