APPLICATION NUMBER:

209445Orig1s000

OTHER REVIEW(S)
**FOOD AND DRUG ADMINISTRATION**
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

**Memorandum**

**Date:** October 8, 2019

**To:** Shabnam Naseer, M.D.
Division of Anti-Infective Products (DAIP)

J. Christopher Davi, Regulatory Project Manager, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

**From:** David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Jim Dvorsky, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for FETROJA (cefiderocol) for injection, for intravenous use

**NDA:** 209445

In response to DAIP’s consult request dated January 10, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Fetroja.

**PI:** OPDP’s comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on September 30, 2019, and are provided below.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 21, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

27 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID F FOSS
10/08/2019 11:19:55 AM
1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on August 21, 2019 for Fetroja. Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Fetroja (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions were made to revise to “single-dose” on the proposed container label and carton labeling.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.
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/s/

DEBORAH E MYERS  
08/23/2019 12:50:54 PM

OTTO L TOWNSEND  
08/23/2019 01:34:18 PM
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: August 16, 2019
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 209445
Product Name and Strength: Fetroja (cefiderocol) for injection, 1 gram per vial
Applicant/Sponsor Name: Shionogi, Inc. (Shionogi)
OSE RCM #: 2018-2681-1
DMEPA Safety Evaluator: Deborah Myers, RPh, MBA
DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM
The Applicant submitted revised container label and carton labeling received on August 14, 2019 for Fetroja. Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Fetroja (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION
The Applicant implemented all of our recommendations and we have no additional recommendations at this time. Additionally, we defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate package type term, to be used on the container label and carton labeling.

¹ Myers, D. Label and Labeling Review for Fetroja (NDA 209445). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 04. RCM No.: 2018-2681.
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/s/

DEBORAH E MYERS  
08/16/2019 11:16:58 AM

OTTO L TOWNSEND  
08/16/2019 12:09:26 PM
I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two studies were submitted as the primary efficacy and safety studies in support of this 505(b)(1) NDA for cefiderocol (S-649266). Four study sites were selected for clinical inspection as part of PDUFA pre-approval clinical investigation and data validation. The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the proposed indication.

II. BACKGROUND

The proposed product is an injectable siderophore cephalosporin antibiotic that exerts its antibacterial activity against Gram-negative bacteria by inhibiting cell wall synthesis. Cefiderocol is a new molecular entity (NME). The proposed indication for cefiderocol is the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, in adults.
Study 2121 was the primary Phase 2 efficacy and safety study submitted in support of NDA 209445. The population in this trial was the proposed population for cefiderocol labeling - patients with complicated UTIs and pyelonephritis. Supplemental efficacy information in Study 2131 was also submitted in support of NDA 209445. The population of Study 2131 is pathogen-based. For Study 2131, patients with gram-negative infections including hospital-acquired/ventilator-associated pneumonia (HAP/VAP), sepsis, and complicated UTI were included. Protocol 2131 is an ongoing, open-label study. The preliminary results of Study 2131 included data for 70 subjects. Review of the data from Study 2131 revealed an imbalance in mortality in the cefiderocol arm (27 vs. 6). Therefore, sites from both Studies 2121 and 2131 were chosen for clinical inspection as part of the NDA review process for cefiderocol.

**Study 2121 (APEKS-cUTI Study)**

A Multicenter, Double-blind, Randomized, Clinical Study to Assess the Efficacy and Safety of Intravenous S-649266 in Complicated Urinary Tract Infections with or without Pyelonephritis or Acute Uncomplicated Pyelonephritis Caused by Gram-Negative Pathogens in Hospitalized Adults in Comparison with Intravenous Imipenem/Cilastatin

The primary objective of this study was to compare the composite outcome of clinical cure and microbiologic eradication of S-649266 with those of imipenem/cilastatin (IPM/CS) in a patient population at risk for multidrug resistant (MDR) Gram-negative pathogens originating from complicated urinary tract infection (cUTI) with or without pyelonephritis. Patients were randomized in a 2:1 ratio to receive the following:

- S-649266 2000 mg IV every 8 hours (for patients with normal renal function)
- Imipenem/cilastin (IPM/CS) 1000 mg IV every 8 hours (for patients with normal renal function)

The primary efficacy endpoint was the composite of microbiological eradication and clinical response outcomes at the test of cure (TOC) in the Micro-ITT population.

A total of 452 subjects were enrolled and randomized (2:1) to receive cefiderocol (303 subjects) or IPM/CS (149 subjects). Of these, 448 subjects were treated and 421 subjects completed the study.

In this multicenter study, 67 sites enrolled subjects: 4 in the Czech Republic, 4 in Poland, 4 in Italy, 4 in Hungary, 9 in Russia, 1 in Spain, 2 in the United States, 4 in German, 7 in Poland, 4 in Croatia, 7 in Romania, 4 in Bulgaria, 6 in Japan, 3 in Georgia, and 4 in Latvia.

The first subject was enrolled in the study on 05 February 2015. The last subject completed the study on 16 August 2016.
The primary objectives of the study were:

- To assess, at test of cure (TOC), the clinical outcome of treatment with S-649266 or best available therapy (BAT) in adult patients with either hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)/healthcare-associated pneumonia (HCAP) or bloodstream infections/sepsis (BSI/sepsis) caused by carbapenem-resistant Gram-negative pathogens
- To assess, at TOC, the microbiologic outcome of treatment with S-649266 or BAT in adult patients with complicated urinary tract infection (cUTI) caused by carbapenem-resistant Gram-negative pathogens

The primary endpoint is clinical response at TOC with patients diagnosed with HAP/VAP/HCAP or BSI/sepsis and microbiological response at TOC in patients with cUTI; each response rate was provided with the 95% confidence interval (CI) by treatment group.

Patients were randomized (2:1) to receive either cefiderocol (S-649266) 2 g administered intravenously over 3 hours, every 8 hours (q8h) or best available therapy (BAT). The BAT was determined by the investigator for each infection diagnosis and involved up to three antibiotic agents specifically for the carbapenem-resistant Gram-negative pathogen

The cut-off date for the Study 2131 data submitted with the initial NDA was 03 March 2018. The data included information for 70 subjects—47 subjects in the cefiderocol group and 23 subjects in the BAT group. Among these first 70 subjects, 18 subjects died. To have the most up-to-date information on the number of subjects who died during the study, an additional cut-off of 15 Aug 2018 was set (for mortality only); this cut-off included 9 additional deaths. Of these subjects, 21 received cefiderocol and 6 subjects received BAT.

**Rationale for Site Selection**

The Office of Scientific Investigations (OSI) Risk-Based Site Selection Tool (RBSST) was utilized to select sites for Protocol 2121 (the pivotal study submitted for NDA 209445). Site #314 (Study 2121) was chosen for inspection because it was the site with the highest enrollment. The site enrolled 33 subjects. The mean study enrollment was 7 subjects per site. Site #213 (Study 2121) was also chosen for inspection due to its relatively high enrollment rate (12 subjects).

Supplemental efficacy information was submitted from the Phase 3 Study CREDIBLE-CR (Protocol 2131). Sites in Israel and Korea were chosen for inspection for Protocol 2131 due to the imbalance in the number of deaths in the cefiderocol arm (briefly described above).
III. RESULTS (by site):

1. Dr. Gabriel Bako/ Site #314/ Protocol 2121/Romania

This inspection was the first FDA inspection of this clinical investigator. At this site, 35 subjects were screened, and 33 subjects were enrolled. Among 33 enrolled subjects, 32 subjects completed the study and one subject (Subject [b] [b]) was lost to follow-up. An audit was conducted for 27 of 33 enrolled subjects. The inspection was conducted 22 April 2019 to 25 April 2019.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability, source data evaluation, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary and secondary endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

A single item was discussed during the inspection close-out meeting—incorrect dosing (based on weight and creatinine level) of investigational medicinal product (IMP) in four study subjects:

- Subject [b] [b], based on subject weight and creatinine clearance level, should have received 1.5 g of IMP every 8 hours. However, this subject was given 2.0 g of IMP every 8 hours for the duration of the study.
- Subject [b] [b] should have received 0.5 g IMP every 8 hours (three times daily, a total of 1.5 g/day); instead the subject was given 0.5 g IMP every 6 hours (four times daily, a total of 2.0 g/day)
- Subject [b] [b] should have received 1.0 g IMP every 6 hours (four times daily, a total of 4.0 g/day); instead the subject was given 1.0 g IMP every 8 hours (three times daily, a total of 3 g/day)
- Subject [b] [b] should have received 0.5 g IMP every 6 hours (four times daily, a total of 2.0 g); instead the subject was given 0.75 g IMP every 8 hours (three times daily, a total of 2.25 g).

These instances of incorrect dosing were reported appropriately during the study and acknowledged by Dr. Bako during the close-out meeting.

Other than described above, the inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.
2. Dr. Czeslaw Marcisz/ Site # 213/ Protocol 2121/Poland

At this site, there were 25 subjects screened, 19 subjects enrolled, and 18 subjects completed study visits. Subject withdrew due to an adverse event. There were no deaths reported during the study. The data audit included source records for all 19 enrolled subjects and two screen failures (Subjects ). The inspection was conducted 14 May 2019 to 17 May 2019.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability, source data evaluation, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary and secondary endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

Two items were discussed with the principal investigator during the close-out meeting:

1. Unreported concomitant medications for three subjects:
   a. Subject – Biseptol/cotrimoxazole after the subject was discontinued from study treatment due to rash, but continued with follow-up visits;
   b. Subject – Biseptol/cotrimoxazole on , prescribed at an outside ER visit; and,
   c. Subject – OTC furagen, self-initiated, taken .

2. Emergence of new pathogen(s) not reported as adverse events. Subjects had microbiological eradication of their originally presenting pathogen and had emergence of new pathogen(s) prior to study completion. All new pathogens were reported and included in the line listings. The PI stated that the new pathogens were not assessed as AEs because they were not treated given lack of symptomatology.

3. Dr. Galia Rahav / Site 3HJ/ Protocol 2131/ Israel

At this site, there were nine subjects screened and enrolled. All nine subjects experienced SAEs. Eight of the nine subjects were unconscious at enrollment and the informed consent forms were signed by either a legal guardian or family member and the independent physician. There were four deaths and two additional discontinuations due to serious adverse events (Subject due to septic shock and Subject due to deterioration of Acinetobacter pneumonia).

Three subjects died during the study and one subject died after the end of the study:
- (BAT)- died 10 days after last treatment dose, due to general physical deterioration secondary to sepsis and status epilepticus
- (cefiderocol)- died on last day of study treatment, deterioration due to Acinetobacter pneumonia
The records of all nine enrolled subjects were reviewed during the inspection. The inspection was conducted 12 May 2019 to 15 May 2019.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability, source data evaluation, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan except the items described as above. A Form FDA 483 (Inspectional Observations) was not issued.

4. Dr. Young Keun Kim/ Site 4CB/ Protocol 2131/ South Korea

At this site, there were nine subjects screened and six subjects enrolled (one screen failure). Five subjects completed the study. Study enrollment was temporarily suspended (September 20 to October 31, 2017) at this site by the Sponsor due to the unexpected number of deaths in the cefiderocol treatment group. The site was reopened after an investigation. An audit was conducted for all six enrolled subjects. The inspection was conducted 7 May 2019 to 10 May 2019.

Three subjects died during the study:
- (cefiderocol)- died 23 days after last treatment dose due to pneumonia
- (BAT)- died 12 days after last treatment dose due to acute cardiorespiratory arrest
- (cefiderocol)- died on last day of study treatment due to acute renal failure

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability, ethics committee approvals, financial disclosures, informed consent forms, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary and secondary endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

An FDA 483, Inspectional Observations was issued at the end of this inspection for the following deficiencies:
1. An investigation was not done in accordance with the investigational plan.

Specifically,

a. Subject (b)(6) was treated with the prohibited antibiotic Citopin, (b)(6) (Subject's IP dosing period was (b)(6)).

b. Subject (b)(6) was treated with the prohibited antibiotic Colis, (b)(6) (Subject's IP dosing period was (b)(6)).

2. Failure to prepare and maintain adequate case histories with respect to observations and data pertinent to the investigation and informed consent.

Specifically, informed consent documents were not entered into the EMR (source data) contemporaneously for Subjects (b)(6). There was also no statement indicating that no study-related procedures were performed before consent was obtained.

3. Inadequate investigational drug disposition records with respect to dates, quantity, and use by subjects.

Specifically, the original source (IV bag labels) were not maintained for documentation of dosing of subjects with the investigational product. The study coordinator wrote the start time on each bag and instructed nurses regarding duration and frequency of infusions and created an IP infusion worksheet. The morning following infusion, the IV bag labels were discarded at the site.

The deviations noted above were not reported in the study summary.

In a letter dated May 31, 2019, Dr. Kim responded to the issues outlined in the FDA Form 483.

OSI Reviewer comment:

While numerous, none of the protocol deviations noted in the FDA Form 483 had the potential to result in significant harm to study subjects. Allowing prohibited concomitant antibiotics has the potential to affect the overall efficacy conclusions of the study data derived from this site. No further regulatory action is justified, and corrective action is left to Dr. Kim. His written response is adequate.
CONCURRENCE:

Min Lu, M.D.
Acting Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/Sumathi Nambiar
Review Division /Medical Team Leader/ Edward Weinstein
Review Division /Project Manager/L. Christopher Davi
Review Division/MO/ Shabnam Naseer
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Min Lu
OSI/DCCE/GCP Reviewer/ Aisha Johnson
OSI/ GCP Program Analysts/ Yolanda Patague/ Joseph Peacock
OSI/Database PM/Dana Walters
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/s/

AISHA P JOHNSON
07/08/2019 08:29:18 AM

MIN LU
07/08/2019 08:32:29 AM

SUSAN D THOMPSON
07/08/2019 10:12:58 AM
LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
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<td>Date of This Review</td>
<td>April 4, 2019</td>
</tr>
<tr>
<td>Requesting Office or Division</td>
<td>Division of Anti-Infective Products (DAIP)</td>
</tr>
<tr>
<td>Application Type and Number</td>
<td>NDA 209445</td>
</tr>
<tr>
<td>Product Name and Strength</td>
<td>Fetroja (cefiderocol) for injection, 1 gram per vial</td>
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<tr>
<td>Product Type</td>
<td>Single-Ingredient Product</td>
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<tr>
<td>Rx or OTC</td>
<td>Rx</td>
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<tr>
<td>Applicant/Sponsor Name</td>
<td>Shionogi, Inc. (Shionogi)</td>
</tr>
<tr>
<td>FDA Received Date</td>
<td>December 14, 2018</td>
</tr>
<tr>
<td>OSE RCM #</td>
<td>2018-2681</td>
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<tr>
<td>DMEPA Safety Evaluator</td>
<td>Deborah Myers, RPh, MBA</td>
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<tr>
<td>DMEPA Team Leader</td>
<td>Otto L. Townsend, PharmD</td>
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</table>
1 REASON FOR REVIEW

As part of the approval process for Fetroja (cefiderocol) for injection, 1 gram per vial, the Division of Anti-Infective Products (DAIP) requested that we review the proposed container label, carton labeling, and prescribing information (PI) for areas that may lead to medication errors.

2 MATERIALS REVIEWED

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section for Methods and Results</th>
</tr>
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<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>C – N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>D – N/A</td>
</tr>
<tr>
<td>Other</td>
<td>E – N/A</td>
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<tr>
<td>Labels and Labeling</td>
<td>F</td>
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</table>

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted container label, carton labeling, and PI, DMEPA’s rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)

<table>
<thead>
<tr>
<th>Prescribing Information</th>
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<tbody>
<tr>
<td>IDENTIFIED ISSUE</td>
</tr>
</tbody>
</table>

General Issues

<p>| 1. As currently presented the package type term, | is not considered an appropriate package | We defer to the Office of Pharmaceutical Quality (OPQ) |</p>
<table>
<thead>
<tr>
<th>(b)(4) is used throughout the prescribing information (PI), as well as on the container label and carton labeling. Additionally, we acknowledge Shionogi’s justification of the use of the phrase “single-dose” to determine the appropriate package type term. Additionally, we acknowledge Shionogi’s justification of the use of the phrase “single-dose” to determine the appropriate package type term, “single-dose” to be used in the PI labeling. If OPQ determines that the package type term “single-dose” is correct and recommends its use in the PI labeling, this recommendation to use the package type term, “single-dose” should also be made for the container label and carton labeling.</th>
</tr>
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<tbody>
<tr>
<td>2. As currently presented, the abbreviation “g” is used throughout the PI.</td>
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</tbody>
</table>

### Highlights of Prescribing Information – Dosage and Administration

| 1. As currently presented, there is no space included between the Arabic numeral and the unit of measurement (i.e., “2g”). Additionally, the unit of measurement is abbreviated. | Presenting a dose, strength, or volume without a space between the numeral and unit of measurement can negatively impact readability. As stated above, abbreviations can be misinterpreted. | Add a space between the Arabic numeral “2” and the unit of measurement. In addition, replace the abbreviation “g” with its intended meaning “grams”. For example, “Administer 2 grams...” |

**Full Prescribing Information (FPI), Section 2.1, Recommended Dosage**
1. As currently presented, in Table 1 the “Dose” (in the second column) is presented as “2 g.”

Abbreviations can be misinterpreted and result in confusion, as well as medication errors.

To provide clarity and minimize the potential for misinterpretation, we recommend replacing the abbreviation “g” with its intended meaning “gram.” For example, “2 grams.”

2. As currently presented, in Table 1 a hyphen is present vs. the word “to” between the numbers “7” and “14.”

Prescribers may misread or become confused about the appropriate duration of treatment.

To provide consistency and clarity, consider replacing the hyphen with its intended meaning “to.” For example, “7 to 14 days.”

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**FPI, Section 2.2, Dosage Adjustments in Patients with Altered Renal Function**

1. As currently presented, in Tables 2 and 3 we note the use of the symbols “<” and “≥” respectively. Additionally, as currently presented in Table 2 the first numerals of the range (CrCL 60, CrCL 30, and CrCL 15) do not include the unit of measurement (mL/min).

The symbols ‘<’, ‘≤’, ‘>’, and ‘≥’ are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended. Use of these symbols in the Dosage and Administration sections of the Highlights.

To provide clarity we recommend replacing the “<” symbol with the intended meaning “less than” and the “≥” symbol with the intended meaning “greater than or equal to.” Additionally, to provide clarity and minimize the risk for misinterpretation, add the unit of measurement,

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and FPI, could lead to medication errors.

Additionally, the lower measurements (CrCL 60, CrCL 30, and CrCL 15) in the ranges could be missed or misinterpreted because it is not followed by the appropriate unit of measurement (mL/min).

“mL/min” following “CrCL 60”, “CrCL 30”, and “CrCL 15.”

For example, “(CrCL 60 mL/min to less than 90 mL/min)” “(CrCL 30 mL/min to less than 60 mL/min)” (CrCL 15 mL/min to less than 30 mL/min), “CrCL less than 15 mL/min), and “(CrCL greater than or equal to 120 mL/min).

2. As currently presented, in Tables the “Dose(s)” are presented using the abbreviation “g.”

Abbreviations can be misinterpreted and result in confusion, as well as medication errors.

To provide clarity and minimize the potential for misinterpretation, we recommend replacing the abbreviations “g” with its intended meaning “gram” or “grams”, as appropriate.

For example, “1.5 grams”, “1 gram”, etc.

3.

FPI, Section 2.3, Preparation of FETROJA Solution for Administration

1. As currently presented, the final sentence of the first paragraph, under the sub-header “Preparation of Doses” is, statements have the potential to result in the opposite of its intended effect.

To provide clarity we recommend revising
<table>
<thead>
<tr>
<th>2.</th>
<th>As currently presented, the abbreviation “g” is used throughout.</th>
<th>Abbreviations can be misinterpreted and result in confusion, as well as medication errors.</th>
<th>To provide clarity and minimize the potential for misinterpretation, we recommend replacing the abbreviation “g” with its intended meaning “gram” or “grams”, as appropriate.</th>
</tr>
</thead>
</table>
| **FPI, Section 2.5, Storage of Reconstituted Solutions** | **1.**  
As currently presented, the final sentence of the first paragraph is,  
statements such as have the potential to result in the opposite of its intended effect. | To provide clarity we recommend revising the statement.  
Additionally, we defer to OPQ to determine if it is appropriate to remove “at room temperature” since there is no storage data provided for reconstituted vials at other temperatures. | **FPI, Section 3, Dosage Forms and Strengths** |
| **1.**  
As currently presented, the abbreviation “g” is used throughout the Section 3. | Abbreviations can be misinterpreted and result in confusion, as well as medication errors. | To provide clarity and minimize the potential for misinterpretation, we recommend replacing the abbreviation “g” with its intended meaning “gram” or “grams”, as appropriate. |
<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. As currently presented, the strength statement (1 gram per vial) lacks prominence.</td>
<td>The proprietary and established names should be the most prominent information on container label and carton labeling. Additionally, the product strength is considered to be “critical information.” To avoid strength confusion, the product strength statement (1 gram per vial) should be prominently displayed on the principal display panel (PDP). As currently presented, the strength statement (1 gram per vial) is in small light font that could be easily missed, which could lead to confusion, as well as wrong strength or wrong dose medication errors.</td>
<td>We recommend that you increase the prominence of the strength statement (1 gram per vial) on the PDP.</td>
</tr>
</tbody>
</table>

1. As currently presented, the format for the expiration date is not defined. The use of abbreviations within the expiration date can result in confusion regarding the actual expiration date leading to deteriorated drug medication errors. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. As currently presented, the storage statement, “Store 2°C to 8°C [36°F to 46°F].” lacks the statement “Must be refrigerated.” Improperly storing this product (i.e., not refrigerating the product prior to reconstitution) could lead to deteriorated drug medication errors. Revise and bold the statement to includes “Must be refrigerated.” For example, “Must be refrigerated. Store at 2°C to 8°C (36°F to 46°F).”

Carton Labeling

1. As currently presented, there is no space notated for the product lot The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the Include the space notation for the lot number statement and expiration date. When determining this placement,
number and expiration date. The product expiration date is also required on the carton labeling per 21 CFR 201.17. Please ensure that there are no other numbers located in close proximity to the lot number/expiration date that can be mistaken as the lot number/expiration date.

Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

As currently presented, the side panel reads “Each vial contains 1 g cefiderocol (equivalent to 1.6 g of cefiderocol sulfate tosylate), sucrose...” Abbreviations, such as “g” can be misinterpreted and result in confusion, as well as medication errors. To minimize the potential for misinterpretation, we recommend replacing all instances of the abbreviation “g” with the intended...
(0.9 g) and sodium chloride (0.2 g).” and “...concentration is 0.1 g/mL.”

meaning “gram” or “grams” as appropriate
For example, “Each vial contains 1 gram cefiderocol (equivalent to 1.6 grams of cefiderocol sulfate tosylate), sucrose (0.9 gram) and sodium chloride (0.2 gram).” and “...concentration is 0.1 gram/mL.”

4 CONCLUSION
Our evaluation of the proposed container label, carton labeling, and PI identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Shionogi so that recommendations are implemented prior to approval of this NDA.
Table 4 presents relevant product information for Fetroja that Shionogi submitted on December 14, 2018.

<table>
<thead>
<tr>
<th>Table 4. Relevant Product Information for Fetroja</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
</tbody>
</table>
| **Dose and Frequency** | 2 grams every 8 hours  
Maximum Daily Dose: 6 grams (for normal renal function)  
Dosing in Specific Populations: Dose adjustment required for renal impairment and augmented renal function |
| **How Supplied** | In clear glass vials sealed with a rubber stopper and an aluminum seal with flip-off cap. Each vial is supplied in carton containing 10 vials. |
| **Storage** | Vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Store in the carton until time of use. |
| Container Closure | The primary container closure components comprise a clear glass vial, stopper, and aluminum seal with a plastic flip-off cap. |
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 21, 2019, we searched the L:drive and AIMS using the terms, Fetroja and cefiderocol to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews\(^d\),\(^e\), that we reviewed and determined were not applicable to this review.

\(^d\) Myers, D. Proprietary Name Review for Fetroja (IND 116787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 APR 21. RCM No.: 2016-2908602.

\(^e\) Myers, D. Proprietary Name Review for Fetroja (NDA 209445). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 08. RCM No.: 2018-27985888.
APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Fetroja labels and labeling submitted by Shionogi on December 14, 2018.

- Container label
- Carton labeling
- Prescribing Information available at the following link: `\cdsesub\evsprod\nda209445\0000\m1\us\proposed.docx`

F.2 Label and Labeling Images

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS  
04/04/2019 10:57:02 AM

OTTO L TOWNSEND  
04/04/2019 11:56:00 AM
1 SUMMARY

No significant QT prolongation effect of cefiderocol (S-649266 2 g, S-649266 4 g) was detected in this TQT study.

The effect of cefiderocol was evaluated in clinical study # 1603R2116. The highest dose evaluated was 4 g (administered as an intravenous infusion over 3 h), and it covers the worst-case exposure scenario (renal impairment, section 3.1). The data from Study #1603R2116 was analyzed using central tendency as the primary analysis, which did not suggest that cefiderocol is associated with significant QTc prolonging effect (refer to section 4.3 and 4.5) – overall results are summarized Table 1. The largest upper bounds of the 2-sided 90% CI on the mean difference between cefiderocol and placebo ($\Delta\Delta\text{QTcF}$) was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI on $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 1, indicating that assay sensitivity was established.

The findings of this analysis are further supported by the available exposure-response analysis (section 4.5) and categorical analysis (section 4.4).
Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

<table>
<thead>
<tr>
<th>ECG parameter</th>
<th>Treatment</th>
<th>Time</th>
<th>ΔΔQTcF (ms)</th>
<th>90% CI (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>S-649266 2 g</td>
<td>10</td>
<td>4.8</td>
<td>(2.5, 7.2)</td>
</tr>
<tr>
<td>QTc</td>
<td>S-649266 4 g</td>
<td>10</td>
<td>4.0</td>
<td>(1.6, 6.4)</td>
</tr>
<tr>
<td>QTc</td>
<td>Moxifloxacin 400 mg*</td>
<td>4</td>
<td>12.5</td>
<td>(10.1, 14.9)</td>
</tr>
</tbody>
</table>

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 9.2 ms.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR
Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION
Not applicable

2 PROPOSED LABEL

Reviewer’s comments: The study is only powered for QTcF assessment not for secondary endpoints. Thus, claims regarding secondary endpoints have been removed from the label.

Our changes are highlighted (addition, deletion). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

FETROJA does not prolong the QT interval to any clinically relevant extent at a dose 2 times the maximum approved recommended dose.

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW
Shionogi Inc. is developing Cefiderocol (S-649266; IND-116787) for the treatment of complicated urinary tract infections, including pyelonephritis. Cefiderocol is an injectable
siderophore cephalosporin antibiotic with bactericidal activity against Gram-negative aerobic bacteria. Similar to other β-lactam antibiotics, the bactericidal action of cefiderocol is primarily attributed to inhibition of cell wall biosynthesis to penicillin binding proteins. The proposed dose is 2 g every 8 h to be administered as intravenous infusion over 3 h (CrCL ≥ 60 mL/min). The product is formulated as a sterile injection with lyophilized powder containing 1 g of cefiderocol free base (~1.6 g of sulfate tosylate salt; sodium ~176 mg/vial) per vial. Cefiderocol sulfate tosylate possesses 2 chiral centers.

The clinical development program for cefiderocol included 6 clinical pharmacology studies. Following a single 2000-mg dose infusion over 3 hours, the maximum plasma concentration of 89.7 μg/mL (20.5%) is observed at ~3 h (end of infusion). Cefiderocol exhibits linear pharmacokinetics (Study 1203R2111; 1603R2116), has a relatively short half-life (~2.5 h) and low protein binding 40.8% to 60.4% (Study R-649266-PF-037-L). Cefiderocol is primarily excreted unchanged in the urine (>90%; Study 1516R2114) and the steady state levels are attained within 1 day following multiple doses (every 8 h) with minimal accumulation at steady-state (<10% for Cmax; Study 1203R2111). It has a low pharmacokinetic drug interaction (CYP-mediated as well as transported-mediated) liability. The exposures are increased in subjects with impaired renal function (CrCL <60 mL/min; 1222R2113). Hepatic impairment is not expected to affect the pharmacokinetics of cefiderocol.

Previously, the QT-IRT reviewed the study protocol under IND-116787 (Dt: 04/11/2016). During the QT-IRT review, PK assessment time (Pre-dose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dose) appeared is reasonable. However, ECG assessment time (Pre-dose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4, 4.5, 5, 6 and 7 hours post-dose) was not considered adequate. The same ECG extraction time for all treatments (including moxifloxacin which was planned only at pre-dose and 2, 3 and 4 hours post-dose) was recommended to minimize the potential bias. To evaluate the potential of delayed effects over 24 hours, additional ECG extraction at 8, 10, 12, 16, and 24 hours post-dose was recommended. In general, the QT-IRT agreed with the sample size, doses (3 and 4 g) and overall crossover design. Subsequently, considering the sponsor’s non-clinical safety findings, the QT-IRT agreed (Dt: 04/13/2016) with the sponsor’s proposed change to extend the infusion duration to 3 h.

Considering that the highest dose evaluated in previous studies was a 2 g, the sponsor conducted a 2-part study (Study 1603R2116) in healthy subjects. Part-1 evaluated safety and tolerability of 2 higher doses (Group A: 3 g and Group B: 4 g) using a randomized, double-blind, placebo-controlled study (n=6+2/group). Part-2 assessed the potential of QT/QTc prolongation of cefiderocol using a randomized, double-blind (without moxifloxacin), placebo- and positive-controlled, 4-period (Williams square design), 4-sequence, crossover study (n=48; 12/sequence). Treatments included - A) a single 2 g dose; therapeutic, B) a single 4 g dose; supratherapeutic, C) a matching placebo, and D) a single 400 mg dose of oral moxifloxacin. Cefiderocol and its matching placebo were administered intravenously over 3 hours. The ECG extraction time points were time-matched with the PK sampling time points. The primary endpoint for the thorough QT/QTc assessment was the time-matched placebo- and baseline adjusted QTcF (ΔΔQTcF) interval calculated using a mixed-effects model.
Supratherapeutic dose (4 g intravenous infusion over 3 h) covers 2-fold higher Cmax at the therapeutic dose (2 g intravenous infusion over 3 h) and also covers Cmax at therapeutic dose with higher infusion rate (2 g intravenous infusion over 1 h). The peak concentrations of 89.7 (CV% 20.5; n=43) µg/mL and 183 (CV% 17.3; n=44) µg/mL were observed following single therapeutic (2 g) dose and single supratherapeutic (4 g) dose, respectively. The effects of the cefiderocol (0, 0.15, 0.5, or 1.5 mg/mL) on hERG channels (stably expressed HEK-293 cells) was assessed using the whole-cell patch clamp technique (Report R-649266-SF-031-L). The IC50 of potassium tail peak current was estimated to be more than 1.5 mg/mL (11.58% inhibition). The peak concentrations of ~90 µg/mL (free: 54 µg/mL; PPB: 41%) at therapeutic dose (2 g intravenous infusion over 3 h) offers >27-fold margin.

3.2 SPONSOR’S RESULTS

3.2.1 Central tendency analysis

Cefiderocol excluded the 10 ms threshold at both supratherapeutic and therapeutic dose levels. The results of the reviewer’s analysis are similar to the sponsor’s results. Please see Section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm. Both FDA’s analysis and sponsor’s analysis confirm that the assay sensitivity was established. FDA analysis is presented in Section 4.3.1.1.

Exposure-response relationship of moxifloxacin group also supported the assay sensitivity. Please see section 4.5 for additional details.

3.2.1.1.1 QT bias assessment

The sponsor’s analysis report did not describe QT bias assessment and the assay sensitivity was established with the moxifloxacin treatment.

3.2.2 Categorical Analysis

None of the subjects had absolute QTcF > 480 ms or a change from baseline QTcF >60 ms. The results of the reviewer’s analysis are similar to the sponsor’s results. Sponsor did not provide exact numbers for each of the categories for PR, QRS and HR. Please see Section 4.4 for additional details.

3.2.3 Safety Analysis

For Parts 1 and 2, there were no deaths or serious TEAEs reported. For Part 1, there were no TEAEs leading to study discontinuation reported. For Part 2, one subject (Subject 0) had a TEAE of increased hepatic enzymes that led to study drug discontinuation.

No clinically significant abnormalities in vital sign measurements or ECG parameters, except for 1 subject (Subject 0) with a TEAE of possible second-degree AV block with 400 mg dose of moxifloxacin.
Reviewer’s comment: None of the events identified to be of clinical importance per the ICH E14 guidelines, i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, occurred in this study.

3.2.4 Exposure-Response Analysis
The sponsor performed PK-PD analyses to explore the relationship between the time-matched placebo- and baseline-adjusted QTcF interval (ΔΔQTcF) and plasma concentrations of cefiderocol (S-649266) using a linear mixed-effects modeling approach. The sponsor’s PK/PD model indicated a slightly negative slope which is not statistically significant. The model predicted ΔΔQTcF (90% two-sided upper confidence interval) values of 2.37 (4.3) ms and 1.94 (4.6) ms at the mean peak parent plasma levels for the therapeutic dose 2 g (geomean Cmax 89.69 µg/mL) and the supratherapeutic dose of 4 g (geomean Cmax 183 µg/mL), respectively, following administration as a single intravenous infusion over 3 h. This indicated that there is no positive association between the peak concentrations of cefiderocol and ΔΔQTcF interval. The sponsor conducted same linear mixed-effects model with a random intercept was performed with replacement subjects excluded, as a secondary analysis, with very similar results.

The results of the reviewer’s analysis are similar to the sponsor’s results. Please see section 4.5 for additional details.

4 REVIEWERS’ ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD
The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e. |mean| > 10 bpm) were observed (see Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall
Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment
N/A

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc
The statistical reviewer used mixed effect model to analyze the ΔQTcF values. The model includes treatment, time, sequence, time and treatment interaction as fixed effects and subject (sequence) as a random effect. Baseline values are also included in the model as a covariate. For ΔQTcF effect, the analysis results are listed in Table 4. The largest upper bounds of the 2-sided 90% CI for the mean difference between S-649266 2 g and placebo, between S-649266 4 g and placebo are 7.2 ms and 6.4 ms, respectively.
Table 2: Analysis Results of ΔQTcF and ΔΔQTcF for S-649266

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>S-649266 2 g</th>
<th>S-649266 4 g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔQTcF</td>
<td>Placebo</td>
</tr>
<tr>
<td>0.5</td>
<td>-1.5</td>
<td>-3.5</td>
</tr>
<tr>
<td>1</td>
<td>-1.5</td>
<td>-1.9</td>
</tr>
<tr>
<td>2</td>
<td>-1.8</td>
<td>-2.2</td>
</tr>
<tr>
<td>3</td>
<td>-2.2</td>
<td>-4.3</td>
</tr>
<tr>
<td>3.5</td>
<td>-2.2</td>
<td>-4.5</td>
</tr>
<tr>
<td>4</td>
<td>-1.2</td>
<td>-4.5</td>
</tr>
<tr>
<td>4.5</td>
<td>-1.8</td>
<td>-4.9</td>
</tr>
<tr>
<td>5</td>
<td>-3.0</td>
<td>-3.5</td>
</tr>
<tr>
<td>6</td>
<td>-4.4</td>
<td>-7.5</td>
</tr>
<tr>
<td>8</td>
<td>-7.3</td>
<td>-10.0</td>
</tr>
<tr>
<td>10</td>
<td>-4.4</td>
<td>-9.3</td>
</tr>
<tr>
<td>12</td>
<td>-4.9</td>
<td>-8.0</td>
</tr>
<tr>
<td>16</td>
<td>-1.7</td>
<td>-2.2</td>
</tr>
<tr>
<td>24</td>
<td>-3.4</td>
<td>-5.0</td>
</tr>
</tbody>
</table>

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups.
4.3.1.1 Assay sensitivity

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 3. In QTcF correction method, the largest lower bound of the unadjusted 90% confidence interval is 10.1 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower bound is 9.2 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study. The time profile of moxifloxacin is consistent with ascending, peak, and descending phase of historical moxifloxacin profile. Overall, assay sensitivity was demonstrated in this study.

Table 3: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>ΔQTcF</th>
<th>Placebo</th>
<th>Diff LS Mean (ms)</th>
<th>ΔΔQTcF</th>
<th>90% CI (ms)</th>
<th>97.5% CI (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>2.7</td>
<td>-3.5</td>
<td>6.2</td>
<td>(3.8, 8.6)</td>
<td>(2.9, 9.4)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.3</td>
<td>-1.9</td>
<td>10.2</td>
<td>(7.8, 12.6)</td>
<td>(6.9, 13.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7.3</td>
<td>-2.2</td>
<td>9.4</td>
<td>(7.0, 11.8)</td>
<td>(6.2, 12.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6.1</td>
<td>-4.3</td>
<td>10.5</td>
<td>(8.1, 12.9)</td>
<td>(7.2, 13.7)</td>
<td></td>
</tr>
<tr>
<td>3.5</td>
<td>7.3</td>
<td>-4.5</td>
<td>11.8</td>
<td>(9.4, 14.2)</td>
<td>(8.5, 15.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8.0</td>
<td>-4.5</td>
<td>12.5</td>
<td>(10.1, 14.9)</td>
<td>(9.2, 15.7)</td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td>7.3</td>
<td>-4.9</td>
<td>12.3</td>
<td>(9.9, 14.7)</td>
<td>(9.0, 15.5)</td>
<td></td>
</tr>
</tbody>
</table>
### Treatment Group

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>ΔQTcF Moxifloxacin 400mg</th>
<th>ΔQTcF Placebo</th>
<th>ΔΔQTcF</th>
<th>90% CI (ms)</th>
<th>97.5% CI (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6.9</td>
<td>-3.5</td>
<td>10.4</td>
<td>(8.0, 12.8)</td>
<td>(7.1, 13.6)</td>
</tr>
<tr>
<td>6</td>
<td>1.7</td>
<td>-7.5</td>
<td>9.3</td>
<td>(6.9, 11.6)</td>
<td>(6.0, 12.5)</td>
</tr>
<tr>
<td>8</td>
<td>-1.0</td>
<td>-10.0</td>
<td>8.9</td>
<td>(6.5, 11.3)</td>
<td>(5.7, 12.2)</td>
</tr>
<tr>
<td>10</td>
<td>-0.0</td>
<td>-9.3</td>
<td>9.3</td>
<td>(6.9, 11.7)</td>
<td>(6.0, 12.5)</td>
</tr>
<tr>
<td>12</td>
<td>-1.3</td>
<td>-8.0</td>
<td>6.7</td>
<td>(4.3, 9.1)</td>
<td>(3.4, 9.9)</td>
</tr>
<tr>
<td>16</td>
<td>4.3</td>
<td>-2.2</td>
<td>6.5</td>
<td>(4.1, 8.9)</td>
<td>(3.2, 9.8)</td>
</tr>
<tr>
<td>24</td>
<td>0.8</td>
<td>-5.0</td>
<td>5.8</td>
<td>(3.4, 8.2)</td>
<td>(2.6, 9.1)</td>
</tr>
</tbody>
</table>

#### 4.3.2 HR

The same statistical analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the HR mean differences between S-649266 2 g and placebo, between S-649266 4 g and placebo are 1.9 bpm and 2.7 bpm, respectively.

**Figure 2: Mean and 90% CI ΔΔHR Timecourse**
4.3.3 PR
The same statistical analysis was performed based on PR interval (Figure 3). The largest upper limits of 90% CI for the HR mean differences between S-649266 2 g and placebo, and between S-649266 4 g and placebo are 3.5 ms and 2.3 ms, respectively.

Figure 3: Mean and 90% CI ΔΔPR Timecourse

4.3.4 QRS
The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between S-649266 2 g and placebo, between S-649266 4 g and placebo are 2.4 ms and 2.0 ms, respectively.

Figure 4: Mean and 90% CI ΔΔQRS Timecourse
4.4 CATEGORICAL ANALYSIS

4.4.1 QTc and ΔQTc

Table 4 lists the number of subjects as well as the number of observations whose QTcF values are \( \leq 450 \) ms, between 450 ms and 480 ms. No subject’s QTcF was above 480 ms.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total (N)</th>
<th>Value ( \leq 450 ) ms</th>
<th>450 ms &lt; Value ( \leq 480 ) ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subj.</td>
<td># Obs.</td>
<td># Subj.</td>
</tr>
<tr>
<td>S-649266 2 g</td>
<td>43</td>
<td>602</td>
<td>41 (95.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (4.7%)</td>
</tr>
<tr>
<td>S-649266 4 g</td>
<td>44</td>
<td>616</td>
<td>43 (97.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>47</td>
<td>653</td>
<td>46 (97.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Moxifloxacin 400mg</td>
<td>42</td>
<td>588</td>
<td>41 (97.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (2.4%)</td>
</tr>
</tbody>
</table>

Table 5 lists the categorical analysis results for ΔQTcF. No subject’s change from baseline was above 60 ms.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>Value ( \leq 30 ) ms</th>
<th>30 ms &lt; Value ( \leq 60 ) ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subj.</td>
<td># Obs.</td>
<td># Subj.</td>
</tr>
<tr>
<td>S-649266 2 g</td>
<td>43</td>
<td>602</td>
<td>42 (97.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>S-649266 4 g</td>
<td>44</td>
<td>616</td>
<td>44 (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>47</td>
<td>653</td>
<td>47 (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Moxifloxacin 400mg</td>
<td>42</td>
<td>588</td>
<td>42 (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

4.4.2 PR

The outlier analysis results for PR are presented in Table 6. There are 7 subjects who experienced PR interval greater than 200 ms in both S-649266 2 g and S-649266 4 g groups.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total</th>
<th>Value ( \leq 200 ) ms</th>
<th>200 ms &lt; Value ( \leq 220 ) ms</th>
<th>Value &gt; 220 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subj.</td>
<td># Obs.</td>
<td># Subj.</td>
<td># Obs.</td>
</tr>
<tr>
<td>S-649266 2 g</td>
<td>43</td>
<td>602</td>
<td>40 (93.0%)</td>
<td>591 (98.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 (7.0%)</td>
<td>11 (1.8%)</td>
</tr>
<tr>
<td>S-649266 4 g</td>
<td>44</td>
<td>616</td>
<td>40 (90.9%)</td>
<td>595 (96.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 (6.8%)</td>
<td>20 (3.2%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>47</td>
<td>653</td>
<td>42 (89.4%)</td>
<td>630 (96.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 (8.5%)</td>
<td>22 (3.4%)</td>
</tr>
<tr>
<td>Moxifloxacin 400mg</td>
<td>42</td>
<td>588</td>
<td>38 (90.5%)</td>
<td>578 (98.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (4.8%)</td>
<td>8 (1.4%)</td>
</tr>
</tbody>
</table>

Reference ID: 4411019
4.4.3 QRS
The outlier analysis results for QRS are presented in Table 7. There are 5 subjects who experienced QRS interval greater than 110 ms in both S-649266 2 g and S-649266 4 g groups.

Table 7: Categorical Analysis for QRS

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>T Value&lt;=100 ms</th>
<th>Value&lt;=110 ms</th>
<th>Value&gt;110 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td># Subj.</td>
<td># Obs.</td>
<td># Subj.</td>
<td># Obs.</td>
</tr>
<tr>
<td>S-649266 2 g</td>
<td>43</td>
<td>602</td>
<td>20 (46.5%)</td>
</tr>
<tr>
<td>S-649266 4 g</td>
<td>44</td>
<td>616</td>
<td>21 (47.7%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>47</td>
<td>653</td>
<td>20 (42.6%)</td>
</tr>
<tr>
<td>Moxifloxacin 400mg</td>
<td>42</td>
<td>588</td>
<td>18 (42.9%)</td>
</tr>
</tbody>
</table>

4.4.4 HR
The outlier analysis results for HR are presented in Table 8. There is one subject who experienced HR greater than 100 bpm in S-649266 4 g group.

Table 8: Categorical Analysis for HR

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total (N)</th>
<th>Value&lt;=100 bpm</th>
<th>Value&gt;100 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td># Subj.</td>
<td># Obs.</td>
<td># Subj.</td>
<td># Obs.</td>
</tr>
<tr>
<td>S-649266 2 g</td>
<td>43</td>
<td>602</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>S-649266 4 g</td>
<td>44</td>
<td>616</td>
<td>43 (97.7%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>47</td>
<td>653</td>
<td>47 (100%)</td>
</tr>
<tr>
<td>Moxifloxacin 400mg</td>
<td>42</td>
<td>588</td>
<td>42 (100%)</td>
</tr>
</tbody>
</table>

4.5 EXPOSURE-RESPONSE ANALYSIS
The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and concentration of cefiderocol (S-649266).

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF; and 3) presence of non-linear relationship.

An evaluation of the time-course of drug concentration and changes in ΔΔHR and ΔΔQTcF is shown in Figure 5, which shows an absence of significant changes in HR. There is an approximately dose-proportional increase in cefiderocol concentrations between two dose levels (2 g and 4 g). Considering the low magnitude of effect, there is no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of cefiderocol indicating no significant hysteresis Figure 6.
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and $\Delta$QTcF was evaluated to determine if a linear model would be appropriate. Figure 7 shows the relationship between drug concentration and $\Delta$QTcF and supports the use of a linear model.

**Figure 6: Assessment of hysteresis cefiderocol (S-649266; 2 g and 4 g doses)**
Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 8.

Figure 7: Assessment of linearity of concentration-QTc relationship

Figure 8: Goodness-of-fit plot for QTc
4.5.1 Assay sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control for detecting small increases from baseline for QTcF in the part-II of the study (Figure 9).

![Figure 9: Time course of heart rate and QTcF for moxifloxacin group](image)

Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin (Figure 10). The sponsor determined concentrations in moxifloxacin group only at 1 and 2 h post-dose. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms (Figure 9). Therefore, assay sensitivity is established. Please see section 4.3.1.1 for additional details.

![Figure 10: Assessment of linearity of concentration-QTc relationship (Left) and goodness-of-fit plot for QTc (Right) of moxifloxacin](image)

4.6 SAFETY ASSESSMENTS

See section 3.2.3. No additional safety analyses were performed.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FERDOUSE BEGUM
03/28/2019 12:29:29 PM

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