CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200327

OTHER REVIEW(S)

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 29, 2010

TO: Caremen DeBellas, PharmD, Regulatory Project Manager
Ariel Porcalla, MD, MPH, Medical Officer, DAIOP
Janice Pohlman, MD, MPH, Medical Team Leader, DAIOP
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

RE: NDA 200327

SPONSOR: Cerexa, Inc.
Bruce Lu, RPh RAC, Senior Director Regulatory Affairs
2100 Franklin St, Suite 900
Oakland CA, 94612

DRUG: (b) (4) ceftaroline fosamil for injection

NEW MOLECULAR ENTITY (NME): Yes

REVIEW PRIORITY (STANDARD OR PRIORITY): Standard

PROPOSED INDICATION: Complicated skin and skin structure infections (cSSSI), Community acquired bacterial pneumonia (CABP)

SUBJECTS < 18 YEARS: Yes

CONSULTATION REQUEST DATE: March 11, 2010

DIVISION ACTION GOAL DATE: October 29, 2010

PDUFA: October 29, 2010

I. BACKGROUND:

Cerexa, Inc. a wholly-owned subsidiary of Forest Laboratories, Inc, submitted an original New Drug Application (NDA) in the eCTD format for (b) (4), ceftaroline fosamil for injection, 400mg and 600mg, dated on December 30, 2009, to support a labeling claim for the treatment of complicated skin and skin structure infection (cSSSI) and community acquired bacterial pneumonia (CABP) caused by designated susceptible bacteria. Complicated skin and skin structure infections can be life-threatening or serious conditions requiring systemic antibiotic therapy, surgical management, and hospitalization . Community-acquired bacterial pneumonia is a commonly occurring serious infection requiring systemic antibiotic therapy that often requires hospitalization and is often associated with significant morbidity, mortality, and considerable costs of care.

The applicant has provided efficacy and safety studies consisting two Phase 3 cSSSI studies (P903-06, 2009 and P903-07, 2009) and two Phase 3 CABP studies (P903-08, 2009 and P903-09, 2009), with supportive evidence for the cSSSI indication from two Phase 2 studies (P903-03, 2007 and P903-19, 2009). The overall duration of subject participation in the protocols targeted for inspection, P903-06, P903-07, P903-08 and P903-09, was between 26 and 56 days.

(b) (4) is being developed by Cerexa, Inc and Forest Laboratories. In December 2004, Peninsula Pharmaceuticals, Inc. (PPI, Alameda, California) submitted an Investigational New Drug (IND) application to develop ceftaroline fosamil for the treatment of cSSSI and CABP; in June 2005, the sponsorship of IND 71,371 was transferred to Cerexa, Inc. In February 2006, FDA granted Cerexa Inc. fast track designation to ceftaroline fosamil for the treatment of cSSSI. Ceftaroline is a new molecular entity (NME) cephalosporin antibiotic with broad-spectrum activity against gram-positive bacteria and gram-negative bacteria. Cerexa, Inc., which initiated and conducted the study, became a wholly owned subsidiary of Forest Laboratories, Inc. on January 11, 2007. As the Sponsor of record and holder of the Investigational New Drug (IND) application, Cerexa, Inc. is understood to be the Sponsor.

The most common reported adverse reactions occurring in ≥4% of patients are diarrhea, nausea, and headache. The proposed recommended dosing regimen for ceftaroline fosamil is 600 mg administered as a 1-hour intravenous (IV) infusion every 12 hours (q12h) for 5 to 14 days for cSSSI and 5 to 7 days for CABP.

The studies inspected were Study # P903-06, Study # P903-07, Study #P903-08, Study #P903-09. Brief descriptions of the studies inspected are provided below:

Study P903-06: A Phase 3, Multicenter, Randomized, Double-blind, Comparative Study to Evaluate the Safety and Efficacy of Ceftaroline Versus Vancomycin plus Aztreonam in Adult Subjects With Complicated Skin and Skin Structure Infection: This was to be a Phase 3, multicenter, randomized, double-blind, comparative safety and efficacy study of IV ceftaroline fosamil versus IV vancomycin plus IV aztreonam for 5 to 14 days in adults with cSSSI. Additional days of treatment (Study Days 15 to 21) could be allowed after discussion with the Medical Monitor. This study was to be performed at 55 study centers located in ten countries. In Eastern Europe, there were three study centers in Romania, seven in Russia, and four in Ukraine. In Latin America, there were six study centers in Argentina, four in Chile, one in Mexico, and four in Peru. In the United States, there were 12 study centers. In Western Europe, there were seven study centers in Germany and seven in Poland. The primary objectives of the study was to determine the noninferiority in clinical cure rate of ceftaroline treatment compared with that of vancomycin plus aztreonam treatment at the Test-of-Cure (TOC) Visit in Clinically Evaluable (CE) and Modified Intent-to-Treat (MITT) Populations of adult subjects with a complicated skin and skin structure infection (cSSSI).

Study # P903-08: A Phase 3, Multicenter, Randomized, Double-blind, Comparative Study to Evaluate the Safety and Efficacy of Ceftaroline versus Ceftriaxone, with Adjunctive Clarithromycin, in the Treatment of Adult Subjects with Community-acquired Pneumonia: This study was to be a Phase 3, multi-center, randomized, double-blind, comparative safety and efficacy study of intravenous (IV) ceftaroline versus IV ceftriaxone (defined as study drug therapy) for 5 to 7 days for treatment of adults with CAP.

Study # P903-09: A Phase 3, Multicenter, Randomized, Double-blind, Comparative Study to Evaluate the Safety and Efficacy of Ceftaroline versus Ceftriaxone in the Treatment of Adult Subjects with Community-acquired Pneumonia: This was to be a Phase 3, multicenter, randomized, double-blind, comparative safety and efficacy study of IV ceftaroline fosamil versus IV ceftriaxone administered for 5 to 7 days to adults with CABP. In Asia, there were 3 study centers in India. In Western Europe, there were 2 study centers in Austria, 7 in Germany, 3 in Hungary, and 15 in Poland. In Eastern Europe, there were 6 study centers in Bulgaria, 12 in Russia, 1 in Latvia, 5 in Romania, and 8 in Ukraine. In Latin America, there were 14 study centers in Argentina, 3 in Chile, 4 in Mexico, and 1 in Peru. Study # P903-09 was similar to Study # P903-08 in design and conduct.

Study # P903-07: A Phase 3, Multicenter, Randomized, Double-blind, Comparative Study to Evaluate the Safety and Efficacy of Ceftaroline Versus Vancomycin plus Aztreonam in Adult Subjects With Complicated Skin and Skin Structure Infection: The study was to be a Phase 3, multicenter, randomized, double-blind, comparative safety and efficacy study of IV ceftaroline fosamil versus IV vancomycin plus IV aztreonam for 5 to 14 days in adults with cSSSI. This study was identical in design with **Study P903-06.**

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	**Protocol #/site # and # of Subjects:**	**Inspection Date**	**Final Classification**
Sergey Goryunov, M.D. Filatov Municipal Hospital #15 23, Veshnyakovskaya str. Moscow, Russia 111539	P903-06/ Site #5007/ Screened: 56 Enrolled: 56	Between June 21 and 25, 2010	*Pending (Interim classification: NAI)
Alexander Konychev V, M.D. Municipal Hospital #14 19, Kosinova St. St. Petersburg, Russia	P903-07/Site #5014 Screened: 75 Enrolled: 75	Between June 15 and 18, 2010	NAI
Veronika B. Popova, M.D. Saint George Municipal Hospital, Therapy Department #1 1 Severny pr. St. Petersburg, Russia 194354	P903-09/ Site # 5011 Screen: 40 Enroll: 37	Between June 28 and July 2, 2010	*Pending (Interim classification: NAI)
Oleg Kraydashenko, M.D. Zaporizhzhya State Medical University, City Clinical Hospital #6 26 Mayakovskoho Pr. AND34, Stalevariv vul Zaporizhzhya, Ukraine, 69035	P903-09/ Site # 7004 Screen: 38 Enroll: 38	Between June 14 and 18, 2010	NAI
Lyudmyla Yashyna, , M.D. F H Yanovskyi Phthisiology and Pulmonology Institute 10 Amosova Vul Kyiz, Ukraine 03680	P903-08/ Site # 7030 Screened: 26 Enrolled: 25	Between June 14 and 18, 2010	NAI

Joseph Surber, M.D. Southeast Regional Research Group 5210 Armour Rd, Suite 400 Columbus, GA 31904	P903-07/ Site # 0037 Screened: 46 Enrolled: 46	July 16, 2010	*Pending (Interim classification: NAI)
Purvi Mahra, M.D. eStudy Site 752 Medical Center Ct #105 Chula Vista, CA 91911	P903-06/ Site #0002/ Screened: 137 Enrolled: 120	Between May 5 and 27, 2010 -	*Pending (Interim classification: VAI)
Revas Tabukashvili, M.D. 9 Tsinandall Str. Internal Medicine Clinic of Georgian Patriarchate Tbilisi, Georgia 0144	P903-08/Site # 5428 Screened: 24 Enrolled: 24	Between September 6 and 10, 2010	*Pending (Interim classification: NAI)
Cerexa, Inc. 2100 Franklin St., Ste 900 Oakland, CA 94612	P903-06/ Site #5007/ Screened: 56 Enrolled: 56 P903-07/Site #5014 Screened: 75 Enrolled: 75 P903-09/ Site # 5011 Screen: 40 Enroll: 37 P903-09/ Site # 7004 Screen: 38 Enroll: 38 P903-08/ Site # 7030 Screened: 26 Enrolled: 25 P903-07/ Site # 0037 Screened: 46 Enrolled: 46 P903-06/ Site #0002/ Screened: 137	Between July 21 and 29, 2010	NAI

	Enrolled: 120 P903-08/Site # 5428 Screened: 24 Enrolled: 24		

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary, letter has not yet issued to the CI.

1. **Sergey V. Goryunov, M.D.**
   Filatov Municipal Hospital #15
   Department of Surgery
   23 Veshnyakovskaya Street
   Moscow, Russia 111539

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between June 21 and 25, 2010.

   At this site, 56 subjects were screened and all were enrolled into the study. There were two SAEs, reported one resulting in death. It was determined by Dr. Sergey Goryunov that the two incidents were unrelated to the study drug.

   One hundred percent of informed consents, for all the subjects enrolled, were reviewed and verified to have been correctly completed. In addition, in depth audits of 10 subjects' records were conducted. Records reviewed included: study related procedures, patient histories, concomitant medications, blinding/ randomization, inclusion/exclusion criteria, test article administration, adverse events and SAEs. Twenty-nine of the fifty-six subjects were reviewed for primary efficacy data by comparing line listings submitted with the NDA against source documents and special instructions for data validation contained in the inspection assignment (i.e., Day 3-5 vital signs and Day 1-3 signs and symptoms of infection). While several minor errors in data entry to CRFs were identified and discussed with the CI during the closeout visit, the errors do not appear to significantly impact primary efficacy or safety data. No significant regulatory violations were noted and a Form FDA 483 was not issued.

b. **General observations/commentary**: In general, the study was conducted appropriately and no significant issues were identified. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

c. **Assessment of data integrity**: Based on the provided EIR for this site, data derived from Dr. Goryunov's site are considered acceptable.

2. Alexander V. Konychev, M.D.
Municipal Hospital #14
19, Kosinova St.
St. Petersburg, Russia 198099

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between June 15 and 18, 2010.

At this site, 77 subjects were screened and 75 enrolled into the study. Fifty subjects completed the study. There were two SAEs reported.

One hundred percent of informed consents, for all the subjects enrolled, were reviewed and verified to have been correctly completed. In addition, an in depth audit of 10 subjects' charts was conducted. Records reviewed included: study related procedures, patient histories, concomitant medications, blinding/ randomization, inclusion/exclusion criteria, test article administration, adverse events and SAEs. Records for 50 of the 75 subjects enrolled were reviewed for primary efficacy data and special instructions for data validation contained in the inspection assignment (i.e., Day 3-5 vital signs and Day 1-3 signs and symptoms of infection). Of the 50 subjects' records errors in line listings were identified for three subjects at the EOT visit. Temperatures had been recorded correctly between source data and case report forms, but line listings were incorrect. This error appears to have occurred because the third party data entry entity for this study misread "six" as "eight" in each case, which appeared likely due the penmanship style used in the CRFs. The following table summarizes data entry errors.

Subject #	EOT Temperature (source document)	EOT Temperature (CRF)	EOT Temperature (Line Listing)
7015	36.7°C	36.7°C	38.7°C
7020	36.6°C	36.6°C	38.6°C
7024	36.6°C	36.6°C	38.6°C

No significant regulatory violations were noted and a Form FDA 483 was not issued to the CI. The study appears to have been conducted adequately, and the data generated by this site (with the exception of EOT temperature line listing errors for the three subjects identified above) appear acceptable in support of the respective indication.

b. **General observations/commentary**: In general, the study was conducted appropriately and no significant issues were identified. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

c. **Assessment of data integrity**: Based on the provided EIR for this site, data derived from Dr. Konychev's site are considered acceptable.

3. Veronika B. Popova, M.D.
Hospital St. George the Martyr
1 Severniy Prospect
St. Petersburg, 194354
Russia

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between June 28 and July 2, 2010.

At this site, 40 subjects were screened and 37 enrolled into the study. There were four SAEs reported. Twenty-one (21) subjects completed the study.

A 100% of informed consent documents were reviewed during the inspection. In addition, an in depth audit of the study records for 16 subjects was conducted. Records reviewed included, but were not limited to, source documents, CRFs, protocol specified blinding/randomization procedures, inclusion/exclusion criteria, test pneumonia, adverse events, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

b. **General observations/commentary**: In general, the study was conducted appropriately and no significant issues were identified. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

c. **Assessment of data integrity**: Based on the provided EIR for this site, data derived from Dr. Popova,'s site are considered acceptable.

4. Oleg Kraydashenko, M.D.
Zaporizhzhya City Clinical Hospital #6
34 Stalevariv Street
Zaporizhzhya, 69035
Ukraine

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between June 14 and 18, 2010.

At this site, 38 subjects were screened and all enrolled into the study. Thirty-six (36) subjects completed the study.

The informed consents, for all the 38 subjects enrolled, were reviewed and verified to have been correctly completed. In addition, an in depth audit of the study records for the 36 subjects who completed the study was conducted. Records reviewed included, but were not limited to, source documents, CRFs, protocol specified blinding/randomization procedures, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. Day 3-5 vital signs and Day 1-3 signs and symptoms of infection (chest pain, dyspnea, tachypnea, cyanosis, and disorientation) as reported in line listings were also compared against source documents for a subset of subjects, and no significant discrepancies were identified. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

b. **General observations/commentary**: In general, the study was conducted appropriately and no significant issues were identified. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

c. **Assessment of data integrity**: Based on the provided EIR for this site, data derived from Dr. Kraydashenko's site are considered acceptable.

5. Lyudmyla Yashyna, F.H. M.D.
Yanovsky Physiology & Pulmonary Institute
10 Amosova Street
Kiev, 03680
Ukraine

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between June 14 and 18, 2010.

At this site, 26 subjects were screened and 25 enrolled into the study. Twenty-one (21) subjects completed the study.

The informed consents, for the 25 subjects enrolled, were reviewed and verified to have been correctly completed. In addition, an in depth audit of the study records for 21 subjects was conducted. Records reviewed included, but were not limited to, source documents, CRFs, protocol specified blinding/randomization procedures, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. Day 3-5 vital signs and Day 1-3 signs and symptoms of infection (chest pain, dyspnea, tachypnea, cyanosis, and disorientation) as reported in line listings were also compared against source documents for a subset of

subjects, and no significant discrepancies were identified. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

b. **General observations/commentary**: In general, the study was conducted appropriately and no significant issues were identified. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

c. **Assessment of data integrity**: Based on the provided EIR for this site, data derived from Dr. Yashyna's site are considered acceptable.

6. Joseph Surber, M.D.
Southeast Regional Research Group
5210 Armour Rd, Suite 400
Columbus, GA 31904

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 on July 16, 2010

At this site, 66 subjects were screened and 46 enrolled into the study. Thirty-nine (39) subjects completed the study. An in depth audit of the study records for 24 subjects were conducted. Records reviewed included, but were not limited to, source documents, CRFs, protocol specified blinding/randomization procedures, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability.

b. **General observations/commentary**: In general, the study was conducted appropriately and no significant issues were identified. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

c. **Assessment of data integrity**: Based on the provided EIR for this site, data derived from Dr. Surber's site are considered acceptable.

7. Purvi Mahra, M.D.
eStudy Site
752 Medical Center Ct #105
Chula Vista, CA 91911

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between May 5, 2010 and May 27, 2010.

At this site, 120 subjects were screened and all enrolled into the study. An in depth audit of the study records for the 40 subjects who completed the study was conducted. Records reviewed included, but were not limited to, source documents, informed consents, CRFs, protocol specified blinding/randomization procedures, primary efficacy endpoints, protocol deviations, concomitant therapies, and test

article accountability. Day 3-5 vital signs and Day 1-3 signs and symptoms of infection (chest pain, dyspnea, tachypnea, cyanosis, and disorientation) as reported in line listings were also compared against source documents for a subset of subjects, and no significant discrepancies were identified. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

b. **General observations/commentary:** The inspection of Dr. Mahra's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator because of the following regulatory violation observed during the inspection:

- Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. In one subject **(**Subject 02-06539) the CI failed to capture and investigate a laboratory adverse event (thrombocytopenia, PLT + 64 x 10^9/L) according to provisions outlined in the protocol in one subject. Additionally, the CI failed to document evidence to show severity and causality of the adverse event.

***DSI Reviewer Comments**: Although the clinical investigator failed to o capture and investigate the above laboratory adverse event, based on DSI's review of the EIR and the Applicant's response, the subsequent platelet counts for the subject were within normal range and the above adverse event was reported to the sponsor.*

c. **General observations/commentary:** Although several regulatory violations were noted above, it is unlikely based on the nature of the violations that they significantly affect overall reliability of safety and efficacy data from the site. Based on the provided EIR for this site and Dr. Mahra responses regarding Form FDA 483 observations made during the inspection, which were documented in the EIR, data derived from Dr. Mahra's site are considered reliable.

8. Revas Tabukashvili, M.D.
9 Tsinandall Str.
Internal Medicine Clinic of Georgian
Patriarchate
Tbilisi, Georgia 0144

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between September 6, 2010 and 10, 2010.

At this site 24 subjects were screened and enrolled. Twenty one (21) subjects completed the study and three withdrew. No serious adverse events were reported. The site audit included, but was not limited to, informed consents, CRFs, primary efficacy values, concomitant medications and drug dispensing records, adverse events, IRB/Ethics committee correspondence, sponsor correspondence, monitoring reports, and test article accountability.

b. **General observations/commentary:** The inspection of Dr. Tabukashvili's site revealed that the study was conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity:** There were no regulatory violations noted by the FDA inspector. In general, based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Tabukashvili's site are considered a reliable.

9. Cerexa, Inc.
2100 Franklin St., Ste 900
Oakland, CA 94612

a. **What was inspected**: This sponsor inspection was conducted in accordance with Compliance Program 7348.811 between between July 21 and 29, 2010. The purpose of the inspection, which was conducted in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program, was to review sponsor/CRO activities conducted in support of this application. The inspection audited and focused on clinical investigators, Joseph Surber, M.D. (Columbus GA), Sergey Goryunov, M.D. (Moscow, Russia), Aleander Konychev V, M.D. (St. Petersburg, Russia), Lyudmyla Yashyna, M.D. (Kyiz, Ukraine), Revaz Tabukashvili, M.D. (Tbilisi, Georgia), Oleg Kraydashenko, M.D. (Zaporizhzhya, Ukraine) , Purvi Mahra, M.D. (Chula Vista, CA), Veronika B. Popova, M.D. (St. Petersburg, Russia) and the sponor Cerexa, Inc.

b. General observations/commentary: No objectionable conditions were observed during the inspection. No refusals were encountered. No significant observations of noncompliance were noted. No FDA Form 483 was issued.

c. Assessment of data integrity: Based on the provided Establishment Inspection Report (EIR) for this site, data received from Cerexa, Inc.'s site are considered acceptable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Eight clinical investigators and one sponsor sites were inspected in support of the NDA. In general, the studies appear to have been conducted adequately and the data in support of the NDA 200327 appear reliable based on available information.

The preliminary classification of the inspections for the following clinical investigators and sponsor, Joseph Surber, M.D. (Columbus GA), Sergey Goryunov, M.D. (Moscow, Russia), Aleander Konychev V, M.D. (St. Petersburg, Russia), Lyudmyla Yashyna, M.D. (Kyiz, Ukraine), Revaz Tabukashvili, M.D. (Tbilisi, Georgia), Oleg Kraydashenko, M.D. (Zaporizhzhya, Ukraine) , Cerexa, Inc. are, No Action Indicated (NAI).

The preliminary classification of Clinical Investigator inspection of Dr. Purvi Mahra is Voluntary Action Indicated (VAI). Although a regulatory violation was noted at the site of Dr. Purvi Mahra, the violation is considered isolated and unlikely to significantly impact reliability of the data. The data generated by Dr. Mahra's site may be considered reliable in support of the application.

From the evaluation of the establishment inspection reports and the documents submitted with those reports, the studies at the inspected sites appear to have been conducted adequately, and the data generated from the above sites appear acceptable in support of the indications in the application.

Note: Final classification for Drs. Goryunov, Popova, Surber, Mahra and Tabukashvili, are pending and will be determined when the final EIR and associated exhibits are received and/or reviewed. Should the final classification for Clinical Investigators be different from the current preliminary classification, the Division will be notified and an inspection summary addendum will be generated.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KASSA AYALEW
10/29/2010

LAUREN C IACONO-CONNORS
10/29/2010

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A trial in pediatric patients evaluating single dose pharmacokinetic parameters and safety of Teflaro in all pediatric age groups (five age cohorts)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	11/2010
	Study/Trial Completion:	01/2014
	Final Report Submission:	07/2014
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Teflaro is ready for approval for treatment of Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

There is a need to evaluate pharmacokinetic parameters and safety of Teflaro in the pediatric population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A single dose pharmacokinetic trial in pediatric patients who are being treated concomitantly with antibacterial agents and given Teflaro intravenously.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Randomized comparison of Teflaro and comparator in treating pediatric patients under 17 years of age with Community-Acquired Bacterial Pneumonia (CABP)

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09/2011
Study/Trial Completion:	05/2014
Final Report Submission:	11/2014
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Teflaro is ready for approval for treatment of Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

There is a need to evaluate Teflaro as treatment for CABP in pediatric patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized prospective comparison of Teflaro and a comparator in the treatment of CABP in pediatric patients under 17 years of age using an enrichment strategy for enrollment of patients with methicillin-resistant *Staphylococcus aureus*.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Randomized comparison of Teflaro and comparator in treating pediatric patients under 17 years of age with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09/2011
Study/Trial Completion:	05/2014
Final Report Submission:	11/2014
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Teflaro is ready for approval for treatment of Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

There is a need to evaluate Teflaro as treatment for ABSSSI in pediatric patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized prospective comparison of Teflaro and a comparator in the treatment of ABSSSI in pediatric patients under 17 years of age, including patients with infection suspected or demonstrated to be caused by MRSA.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Cerebrospinal Fluid (CSF) Concentration Study in Infants < 2 months of age

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	05/2014
	Study/Trial Completion:	09/2016
	Final Report Submission:	03/2017
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Teflaro is ready for approval for treatment of Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

There is a need to determine whether Teflaro reaches adequate concentrations in the cerebrospinal fluid in infants < 2 months of age who can benefit from the use of Teflaro to treat (b) (4) late-onset neonatal sepsis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A pharmacokinetic trial in infants < 2 months of age to determine the CSF concentration profile of Teflaro in this age group.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Randomized prospective comparison of Teflaro and comparator as treatment for Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP) in infants < 2 months of age.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	05/2014
Study/Trial Completion:	09/2016
Final Report Submission:	03/2017
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Teflaro is ready for approval for treatment of Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Teflaro has the potential to be used as treatment for ABSSSI and CABP in infants < 2 months of age, including infants with infection suspected or demonstrated to be caused by MRSA.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized prospective comparison of Teflaro and a comparator to treat ABSSSI and CABP in infants < 2 months of age, including infants with infection or suspected to be caused by MRSA.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Prospective study over a five-year period after initial marketing of Teflaro to determine if decreased susceptibility to Teflaro is occurring in the target bacteria included in the Indications section of the approved Teflaro package insert.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	01/2011
	Study/Trial Completion:	04/2016
	Final Report Submission:	10/2016
	Other: Interim report	10/2011 and annually till 10/2015

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Long-term microbiologic surveillance data are needed to study development of bacterial resistance against Teflaro

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Development of bacterial resistance with use of Teflaro.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective study over a five-year period on the susceptibility of target bacteria to Teflaro.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMC Description: Randomized prospective trial to evaluate and compare the efficacy and safety of Teflaro to a comparator in the treatment of patients with CABP suspected or documented to have an infection caused by MRSA

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	10/2011
	Study/Trial Completion:	09/2016
	Final Report Submission:	04/2017
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   The Phase 3 clinical trials for CABP excluded patients with pneumonia caused by MRSA. Because Teflaro has activity against MRSA, its efficacy should be evaluated in patients with CABP caused by MRSA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   The goal of the trial is to determine the efficacy and safety of Teflaro in the treatment of patients with CABP caused by MRSA, since they were excluded from the Phase 3 clinical trials for CABP.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective randomized trial to evaluate the efficacy and safety of Teflaro versus comparator in the treatment of patients with CABP caused by MRSA.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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/s/

SUSMITA SAMANTA
10/29/2010

ARIEL R PORCALLA
10/29/2010

SUMATHI NAMBIAR
10/29/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

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

Memorandum

Date: October 12, 2010

To: Carmen DeBellas, Project Manager
Division of Anti-Infective and Ophthalmology Products

From: Nital Patel, Pharm.D., MBA
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: Teflaro (ceftaroline fosamil)

DDMAC has reviewed the proposed product labeling for Teflaro® (ceftaroline fosamil) and offer the following comments:

27 Pages of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

NITAL PATEL
10/12/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	September 14, 2010
Application Type/Number:	NDA 200327
To:	Wiley Chambers, Acting Division Director Division of Anti-infective and Ophthalmology Products
Through:	Melina Griffis, RPh, Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Lubna Najam, M.S., Pharm.D, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Teflaro (Ceftaroline Fosamil) for Injection, 400 mg per Vial and 600 mg per Vial
Applicant/sponsor:	Cerexa Inc.
OSE RCM #:	2010-65

CONTENTS

1. INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Teflaro (Ceftaroline Fosamil) Injection (NDA 200327) for areas of vulnerabilities that could lead to medication errors. The proposed proprietary name is evaluated under separate review (OSE # 2010-1546).

2. METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the container labels, carton and insert labeling. This review focuses on labels and labeling submitted as part of the July 14, 2010 original NDA submission. See Appendices A-C for images of the proposed container labels and carton labeling.

3. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations to the insert labeling in Section 3.1 Comments to the Division for discussion during the labeling meetings. Section 3.2 Comments to the Applicant contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Brantley Dorch at 301-796-0150

3.1 COMMENTS TO THE DIVISION:

A. General Comment

The abbreviation I.V is used by the Applicant through out the insert labeling. The abbreviation, I.V can be misinterpreted to mean I.U or I.N. As part of a national campaign[2] to decrease the use of dangerous abbreviations, FDA agreed to not use such abbreviations in the approved labeling of products. Therefore, we recommend that IV be replaced with the text "intravenous."

3.2 COMMENTS TO THE APPLICANT:

A. Container Label (400 mg and 600 mg vials)

1. As currently presented, the dosage form is not present on the vial label. The established name presentation should include the active ingredient followed by the dosage form. Include the dosage form immediately following the active ingredient presentation. Ensure the established name presentation and dosage form presentation shall have a prominence commensurate with the prominence with which such proprietary name or designation

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[2] ISMP and FDA Campaign to Eliminate Use of Error-Prone Abbreviations available at http://www.ismp.org/tools/abbreviations/

appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2). We request you revise the label as follows:

Teflaro
Ceftaroline Fosamil For Injection
XXX mg/vial

2. Replace the statement '*single–use vial'* with the statement '*Single use vial- Discard after use'* and relocate the statement away from the strength presentation.

3. The container label should provide the following directions for dilution in the event the drug vial is stored out of the carton.

   Reconstitute this vial with 20 mL of Sterile Water to obtain a concentration of X mg/mL. Further, dilute the entire contents before infusing. See package insert for instructions on reconstitution, dilution, and dosage.

   The directions should be prominently displayed on the vial.

4. Move the statement 'Each vial contains....' to the side panel to allow room on the PDP for the reconstitution directions.

5. Revise the route of administration to read "FOR INTRAVENOUS INFUSION ONLY"

B. Carton Labeling (400 mg and 600 mg vials)

1. The carton labeling uses the abbreviation I.V. on the PDP. Replace the abbreviation, I.V with the text "intravenous."

2. As currently presented, the 400 mg/vial carton labeling utilizes blue color in the proprietary name and is identical to the blue color utilized in strength differentiation of the 600 mg/vial carton labeling, which minimizes the strength differentiation. Revise the labeling of the 400 mg/vial to utilize a color in the proprietary name that is not similar to the blue incorporated in 600 mg/vial strength differentiation.

3. Revise the presentations of the strengths by adding a space between the number and the unit of measure and include per vial (i.e., 400 mg/vial).

4. The product strength and RX only statement are located next to each other on the principal display panel and are of equal prominence. The RX only statement should be decreased in size and relocated to a less prominent area of the label.

5. Revise the reconstitution statement on the side panel to read as follows:

   Following constitution with 20 mL Sterile Water for Injection, USP, the resultant solution will contain approximately X mg/mL. Further, dilute the entire contents before infusing. See package insert for.....'

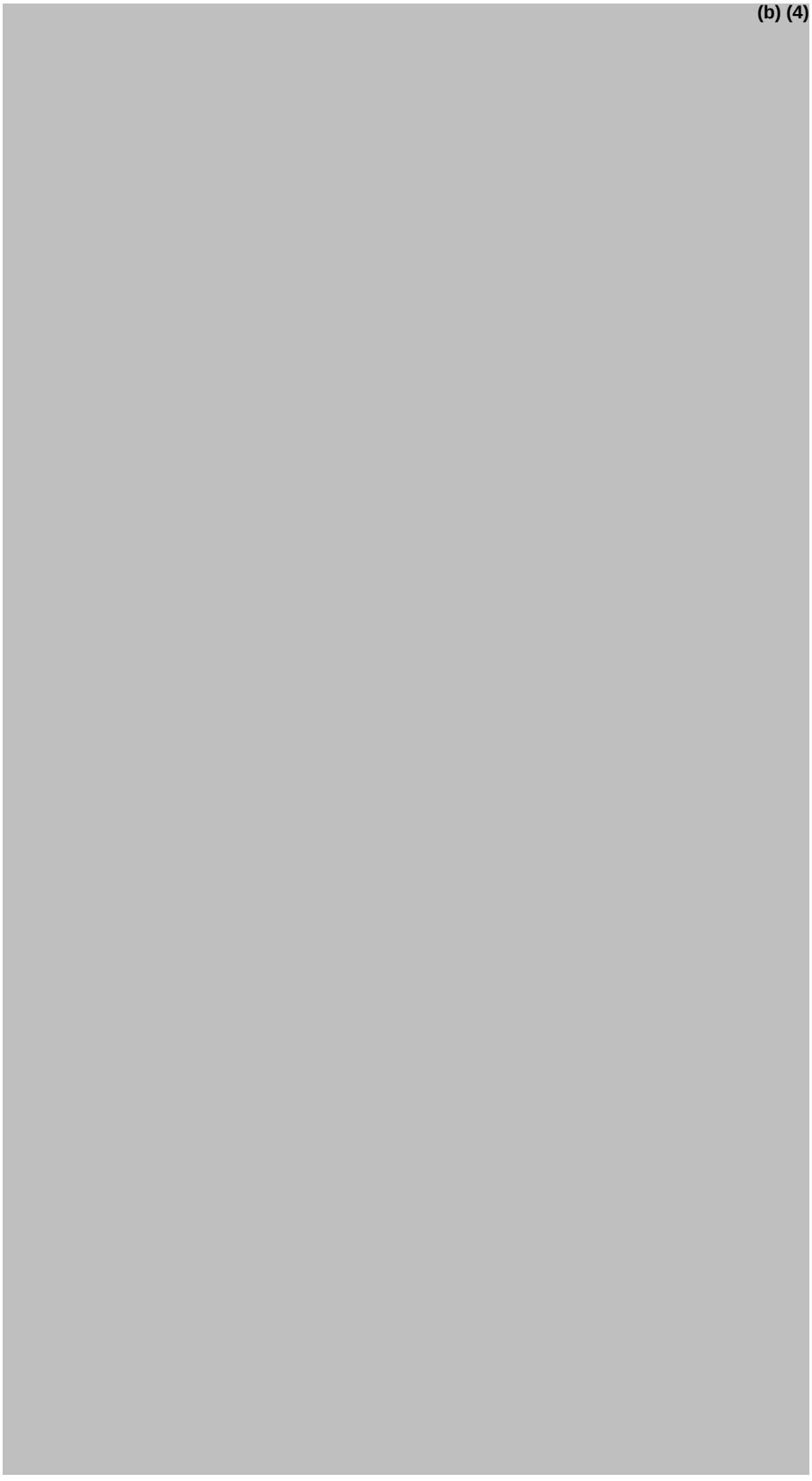
6. The proprietary and established names appear on the portion of the carton that is intended to be removed upon opening. Revise the presentation of the proprietary and established names in conjunction with the strength to provide this information on the carton before and after the carton is opened.

Appendices:

Appendix A: Container Label

Appendix B: Carton Labeling

(b) (4)



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

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/s/

LUBNA NAJAM
09/14/2010

MELINA N GRIFFIS
09/14/2010

CAROL A HOLQUIST
09/14/2010

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 200327
Brand Name	(b) (4)
Generic Name	Ceftaroline Fosamil
Sponsor	Cerexa Inc
Indication	For the treatment of the following infections caused by designated susceptible bacteria: • Complicated skin and skin structure infections (cSSSI) • Community-acquired bacterial pneumonia (CABP)
Dosage Form	Intravenous Injection
Drug Class	Cephalosporin (Antibacterial)
Therapeutic Dosing Regimen	600 mg every 12 hours by IV infusion administered over 1 hour in adults ≥ 18 years of age. • Dosage adjustment in patients with renal impairment Estimated Creatinine Clearance# / TRADE NAME Dosage Regimen > 50 / No dosage adjustment necessary (b) (4) # As calculated using the Cockcroft-Gault formula
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	No MTD was detected at the highest doses evaluated Highest dose tested: > 1000 mg (single) > 600 mg q12 hr daily for 14 days
Submission Number and Date	SDN 001, 31 Dec 2009
Review Division	DAIOP / HFD 520

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of ceftaroline1500 mg was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between ceftaroline 1500 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcIb (individual subject correction formula based on the baseline QT-RR slope) for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, double-blind, placebo-controlled, three-period crossover study, fifty-four subjects were received ceftaroline 1500 mg, moxifloxacin 400 mg, and placebo. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ceftaroline (37.5 mg and 75 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcIb (ms)	90% CI (ms)
Ceftaroline 1500 mg	1.5	1.6	(-0.8, 4.0)
Moxifloxacin 400 mg*	1	19.2	(16.8*, 21.5)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 16.0 ms.

The supratherapeutic dose (1500 mg in QT study) produces mean ceftaroline, ceftaroline M-1, ceftaroline fosamil C_{max} values 3.9, 1.4, 3.1-fold higher than those observed after therapeutic dose (600 mg from Study P903-01). These concentrations are above those for the predicted worst case scenario (severe renal impairment) and show that at these concentrations there are no detectable prolongations of the QT-interval. The mean ceftaroline, ceftaroline M-1, ceftaroline fosamil C_{max} after 1500-mg dose is approximately 4.6, 2.4, 4.5 times than those observed in subjects with severe renal impairment who received a single dose of 400 mg (Study P903-04).

2 SPONSOR'S PROPOSED LABEL

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled crossover thorough QTc study, 54 healthy subjects were administered a single 1500 mg dose of TRADE NAME by IV infusion over 1 hour, [redacted] (b) (4) Following administration of a 1500 mg dose of TRADE NAME, no effect on QTc interval was detected at peak plasma concentration or at any other time.

QT-IRT Recommendation

[redacted] (b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Ceftaroline fosamil is a sterile, semi-synthetic cephalosporin class of betalactams (ß-lactams), indicated for the treatment of complicated skin and skin structure infection (cSSSI) and community-acquired bacterial pneumonia (CABP) caused by designated susceptible bacteria.

3.2 MARKET APPROVAL STATUS

Ceftaroline is not approved for marketing in any country

3.3 PRECLINICAL INFORMATION

Source: Pharmacology Written Summary- eCTD 2.6.2

> "Human Ether-a-Go-Go–Related Gene Channel In Vitro
>
> The effect of ceftaroline fosamil (50, 200, 800, and 1200 µg/mL) on human ether-a-go-go–related gene ([hERG]/Kcnh2 gene) K+ currents was studied in vitro in human embryonic kidney-293 cells stably expressing the hERG channel using the whole-cell patch-clamp electrophysiological technique (Study P0903-T-014, 2007; Table 4-2, Section 2.6.3, Tabulated Summary/Pharmacology). The actual concentration of ceftaroline fosamil, based on formulation analyses, was 44.4, 177.7, 711.0, and 1070.3 µg/mL, respectively. Ceftaroline fosamil did not inhibit the hERG channel maximal tail current amplitude at any of the concentrations tested. The positive control, [N-[4-[[1-[2- (6-methyl-2-pyridinyl) ethyl)]-4-piperidinyl] carbonyl] phenyl] methane sulfonamide dihydrochloride] (E-4031, 500 nM), produced a 96% inhibition of the maximal tail current amplitude.
>
> "Intracellularly Recorded Action Potentials From Dog Purkinje Fibers In Vitro
>
> The effect of increasing concentrations of TAK-599 (ceftaroline fosamil 1, 10, and 100 µmol/L) or vehicle (physiological saline) on cardiac action potential physiology (action potential duration at 60% and 90% repolarization [APD60 and APD90], maximum rate of depolarization [MRD], upstroke amplitude [UA], and resting membrane potential [RMP]) was assessed in vitro in isolated canine ventricular cardiac Purkinje fiber preparations from 5 male Beagle dogs (Study DFEW1029, 2002; Table 4-2, Section 2.6.3, Tabulated Summary/Pharmacology). The effect of ceftaroline fosamil was assessed using both a normal stimulation rate (0.5 and 1 Hz for all concentrations) and a pacing frequency of 3 Hz (100 µmol/L). Ceftaroline fosamil did not produce a significant effect on APD60, APD90, MRD, UA, and RMP relative to vehicle controls at all concentrations and frequencies tested. The positive control, dl-sotalol (50 µmol/L), produced a significant prolongation of APD60 and APD90 ($p \leq .05$ and $p \leq .005$, respectively
>
> "Cardiovascular Studies in Conscious Monkeys

The effect of escalating doses of ceftaroline fosamil or vehicle (physiological saline) on cardiovascular function was assessed in conscious male cynomolgus monkeys (4/group) at doses providing estimated Cmax levels up to 25 times the MRHD (Study DFEW1026, 2002; Table 4-3, Section 2.6.3, Tabulated Summary/Pharmacology). Vehicle was administered on Day 1, and ceftaroline fosamil (40, 120, and 400 mg/kg) was administered via a 1-hour IV infusion on Days 4, 8, and 11, respectively. Cardiovascular function (systolic blood pressure, diastolic blood pressure, heart rate, and lead II electrocardiogram [ECG] variables [PR interval, QT interval, and QRS duration]) and mean arterial blood pressure were monitored by telemetry for 30 minutes predose, up to 1 hour after the start of dosing, and 1.5 to 4 hours postdose. There were no clinical observations at the 40-mg/kg dose. Vomiting was reported during and following administration of doses ≥ 120 mg/kg. These animals also had cloudy urine containing thick yellow precipitate at 90 to 100 minutes post-dose. Systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure were comparable to vehicle controls at all doses of ceftaroline fosamil, and there were no drug-induced changes in heart rate and PR interval, QT interval or QTcQ, and QRS duration. The ECG waveform was not affected by ceftaroline fosamil in 2 of 4 animals. In the other 2 monkeys, ventricular tachycardia developed 2 to 3 hours following administration of 400 mg/kg. Considering that no signs indicative of arrhythmia, such as ECG parameters, were observed in these animals and ceftaroline fosamil did not have any effects on action potential parameters in isolated dog Purkinje fibers, the relation of these events to treatment is questionable. In addition, both of these animals exhibited premature ventricular contractions following vehicle dosing."

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safet,y eCTD 2.7.4

The program consisted of a total of 3153 subjects, 1745 of whom were treated with ceftaroline fosamil (1608 adult subjects received IV ceftaroline fosamil, 98 adult subjects received IM ceftaroline fosamil in a Phase 2 study, 30 adult subjects received only IM ceftaroline fosamil in a Clinical Pharmacology study, and 9 adolescent subjects received IV ceftaroline fosamil) and 1462 of whom were treated with a comparator.

Across the pooled Clinical Pharmacology studies and all Phase 2 and Phase 3 clinical studies, 71 (4.2%) of the subjects who received ceftaroline fosamil and 67 (4.6%) of the subjects who received comparator or placebo had TEAEs in the Cardiac Disorders SOC. In the pooled Phase 3 cSSSI and CABP studies, the incidences of TEAEs in the Cardiac Disorders SOC were low, and were similar in the ceftaroline and comparator groups (5.1% vs 5.1%, respectively). SAEs within the Cardiac Disorders SOC that had outcomes of death occurred in three subjects in the ceftaroline group and in seven subjects in the comparator group and none was assessed by an Investigator as related to study drug. SAEs within the Cardiac Disorders SOC were uncommon in both the ceftaroline and comparator groups (0.8% vs 1.2%, respectively) and all were assessed as unrelated to study drug. TEAEs in the Cardiac Disorders SOC that resulted in premature discontinuation of study drug or withdrawal from study were also infrequent and similar

in the ceftaroline and comparator groups (0.2% vs 0.7%, respectively) and all were assessed as unrelated to study drug.

Table 4.1.2.3.1
Incidence of Treatment Emergent Adverse Events
Phase 3 Studies for cSSSI and CAP
Safety Population

System Organ Class/ Preferred Term	cSSSI (06, 07) Ceftaroline (N=692) n(%)	cSSSI (06, 07) Vancomycin plus Aztreonam (N=686) n(%)	CAP (08, 09) Ceftaroline (N=613) n(%)	CAP (08, 09) Ceftriaxone (N=615) n(%)	Pooled Phase 3 Studies (06, 07, 08, 09) Ceftaroline (N=1305) n(%)	Pooled Phase 3 Studies (06, 07, 08, 09) Pooled Comparators (N=1301) n(%)
Cardiac disorders	28 (4.0)	26 (3.8)	39 (6.4)	40 (6.5)	67 (5.1)	66 (5.1)
Atrial fibrillation	2 (0.3)	0	7 (1.1)	4 (0.7)	9 (0.7)	4 (0.3)
Bradycardia	6 (0.9)	3 (0.4)	3 (0.5)	1 (0.2)	9 (0.7)	4 (0.3)
Tachycardia	4 (0.6)	8 (1.2)	3 (0.5)	2 (0.3)	7 (0.5)	10 (0.8)
Cardiac failure	1 (0.1)	3 (0.4)	5 (0.8)	4 (0.7)	6 (0.5)	7 (0.5)
Palpitations	5 (0.7)	1 (0.1)	1 (0.2)	0	6 (0.5)	1 (0.1)
Sinus bradycardia	1 (0.1)	0	4 (0.7)	3 (0.5)	5 (0.4)	3 (0.2)
Cardiac disorders (Cont)						
Atrioventricular block second degree	0	0	0	1 (0.2)	0	1 (0.1)
Cardiac failure acute	0	0	0	1 (0.2)	0	1 (0.1)
Cardiac valve disease	0	1 (0.1)	0	1 (0.2)	0	2 (0.2)
Cardio-respiratory arrest	0	0	0	2 (0.3)	0	2 (0.2)
Cardiovascular disorder	0	0	0	1 (0.2)	0	1 (0.1)
Cyanosis	0	0	0	2 (0.3)	0	2 (0.2)
Hypertrophic cardiomyopathy	0	0	0	1 (0.2)	0	1 (0.1)
Mitral valve incompetence	0	1 (0.1)	0	1 (0.2)	0	2 (0.2)
Pericarditis	0	0	0	1 (0.2)	0	1 (0.1)
Postinfarction angina	0	0	0	1 (0.2)	0	1 (0.1)
Right atrial dilatation	0	0	0	1 (0.2)	0	1 (0.1)
Sinoatrial block	0	1 (0.1)	0	0	0	1 (0.1)
Sinus tachycardia	0	0	0	1 (0.2)	0	1 (0.1)
Supraventricular tachycardia	0	1 (0.1)	0	1 (0.2)	0	2 (0.2)
Tricuspid valve incompetence	0	1 (0.1)	0	0	0	1 (0.1)
Ventricular dyskinesia	0	0	0	1 (0.2)	0	1 (0.1)
Ventricular extrasystoles	0	0	0	1 (0.2)	0	1 (0.1)

Source: ISS

Sponsor's Table 4.2–2 provides summaries of the post-baseline average and maximum QTcF changes for the pooled Phase 3 cSSSI and CABP studies. The mean postbaseline QTcF or QTcB average changes for the ceftaroline and comparator groups and mean post-baseline maximum changes were similar. The percentage of subjects with QTcF values greater than 500 mse and changes from baseline of 60 ms or more were low and similar in the ceftaroline group (0.3%) and the comparator group (0.2%). Seven subjects, four in the ceftaroline group and three in the comparator group, had QTcF values greater than 500 ms and changed from baseline by 60 ms or more.

Table 4.2–2. Summary of QTcF Phase 3 Studies for Complicated Skin and Skin Structure Infections and Community-acquired Bacterial Pneumonia—Safety Population

ECG Parameter	*cSSSI (06, 07)*		*CABP (08, 09)*		*Pooled Phase 3 Studies (06, 07, 08, 09)*	
	Ceftaroline (N = 692)	*Vancomycin plus Aztreonam (N = 686)*	*Ceftaroline (N = 613)*	*Ceftriaxone (N = 615)*	*Ceftaroline (N = 1305)*	*Pooled Comparators (N = 1301)*
QTcF						
Post-Baseline Average Change (msec)						
n	665	657	600	592	1265	1249
Mean	2.9	2.8	5.8	3.6	4.3	3.2
SD	16.37	15.62	20.74	19.03	18.62	17.32
Median	3.3	2.3	4.7	3.3	4.0	3.0
Min, Max	-94, 75	-55, 68	-81, 97	-67, 121	-94, 97	-67, 121
Post-Baseline Maximum Change (msec)						
n	665	657	600	592	1265	1249
Mean	13.8	13.7	18.8	16.9	16.2	15.2
SD	18.15	17.75	23.20	21.73	20.84	19.79
Median	13.3	12.7	17.7	14.0	15.0	13.3
Min, Max	-71, 88	-43, 75	-78, 128	-49, 149	-78, 128	-49, 149
QTcF						
Maximum Post-Baseline Value (msec), n/N1 (%)						
≤ 450	613/665 (92.2)	605/657 (92.1)	516/600 (86.0)	502/592 (84.8)	1129/1265 (89.2)	1107/1249 (88.6)
> 450 to ≤ 480	42/665 (6.3)	43/657 (6.5)	54/600 (9.0)	64/592 (10.8)	96/1265 (7.6)	107/1249 (8.6)
> 480 to ≤ 500	4/665 (0.6)	9/657 (1.4)	15/600 (2.5)	15/592 (2.5)	19/1265 (1.5)	24/1249 (1.9)
> 500	6/665 (0.9)	0/657	15/600 (2.5)	11/592 (1.9)	21/1265 (1.7)	11/1249 (0.9)
Total	665/665 (100.0)	657/657 (100.0)	600/600 (100.0)	592/592 (100.0)	1265/1265 (100.0)	1249/1249 (100.0)

Table 4.2–2. Summary of QTcF Phase 3 Studies for Complicated Skin and Skin Structure Infections and Community-acquired Bacterial Pneumonia—Safety Population

ECG Parameter	*cSSSI (06, 07)*		*CABP (08, 09)*		*Pooled Phase 3 Studies (06, 07, 08, 09)*	
	Ceftaroline (N = 692)	*Vancomycin plus Aztreonam (N = 686)*	*Ceftaroline (N = 613)*	*Ceftriaxone (N = 615)*	*Ceftaroline (N = 1305)*	*Pooled Comparators (N = 1301)*
Maximum Post-Baseline Change (msec), n/N1 (%)						
≤ 30	554/665 (83.3)	555/657 (84.5)	445/600 (74.2)	450/592 (76.0)	999/1265 (79.0)	1005/1249 (80.5)
> 30 to ≤ 60	106/665 (15.9)	97/657 (14.8)	128/600 (21.3)	126/592 (21.3)	234/1265 (18.5)	223/1249 (17.9)
> 60	5/665 (0.8)	5/657 (0.8)	27/600 (4.5)	16/592 (2.7)	32/1265 (2.5)	21/1249 (1.7)
Total	665/665 (100.0)	657/657 (100.0)	600/600 (100.0)	592/592 (100.0)	1265/1265 (100.0)	1249/1249 (100.0)
Potentially Clinically Significant						
> 500 msec and CFB ≥ 60 msec, n/N1 (%)	0/ 665	0/ 657	4/ 600 (0.7)	3/ 592 (0.5)	4/1265 (0.3)	3/1249 (0.2)

Notes: N1 = number of subjects with a baseline and at least one postbaseline value, CFB = change from baseline.
Baseline is defined as the average of the last set of three replicate assessments prior to administration of the first dose of study drug.
Source: Integrated Summary of Safety (2009) Supporting Table 7.3.3.1.

Reviewer's Comment: Except for cardiac arrest which was reported as unrelated to study drug there are no reports of sudden death or significant ventricular arrhythmias. QTcF outliers seem to be a little higher in the treatment group compared to comparator but the reason is unclear.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of ceftaroline, ceftaroline M-1 clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol (conducted under IND 71371) prior to conducting this study. The sponsor submitted the study report DFC-001 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Safety, Pharmacokinetics, and Effect on the Electrocardiogram of a Supratherapeutic Dose of Ceftaroline in Healthy Subjects

4.2.2 Protocol Number

P903-05

4.2.3 Study Dates

First Subject Enrollment: 13 June 2008
Last Subject Enrollment: 01 August 2008

4.2.4 Objectives

Primary Objectives:
Assess the effects of a single supratherapeutic dose of intravenous (IV) ceftaroline versus placebo on the QT interval corrected for heart rate (QTc) using an individual subject correction formula based on the baseline QT-RR slope (QTcIb) in healthy adult subjects.

Secondary Objectives:

- Determine the difference, if any, in the effect between IV ceftaroline at a supratherapeutic dose and placebo on the QTcIb interval between male and female subjects.
- Evaluate differences in the effects of IV ceftaroline at a supratherapeutic dose and placebo on the proportion of subjects with QTc interval data exceeding specified values and on changes in electrocardiogram (ECG) diagnostics (QRS complex, ST segment, T wave, or U wave morphologies).
- Evaluate the pharmacokinetic (PK) profile of ceftaroline at a supratherapeutic dose.
- Assess the safety and tolerability of an IV infusion of ceftaroline at a supratherapeutic dose in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, double-blind, placebo-controlled, three-period crossover study, fifty-four subjects were received ceftaroline 1500 mg, moxifloxacin 400 mg, and placebo.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was blinded.

4.2.5.4 Treatment Arms

Subjects received a single dose of three study drugs: one supratherapeutic dose (1500 mg) of IV ceftaroline fosamil (Study drug A), one dose of IV saline placebo (Study drug B) as the negative control, and one dose (400 mg) of IV moxifloxacin (Study drug C) as the positive control. Subjects were randomized (1:1:1:1:1:1) to one of six study drug administration sequences in a three-period crossover. A single dose of each subsequent study drug was administered 5 days after the previous dose, but at approximately the same time of day.

4.2.5.5 Sponsor's Justification for Doses

The supratherapeutic dose of 1500 mg IV ceftaroline fosamil used in this study was chosen to evaluate ECG effects since this dose has been previously shown to be safe and well tolerated in healthy subjects and is well above the therapeutic range. Since ceftaroline and its metabolites are eliminated mainly by the kidneys, the largest increases in ceftaroline systemic exposure are expected to be observed in the clinic in subjects with renal impairment. Subjects with severe renal impairment (Study P903-04) and subjects with ESRD given ceftaroline fosamil 1 hour after the end of hemodialysis (Study P903-18) had an increase in ceftaroline AUC and C_{max} relative to subjects with normal renal function. The 1500-mg supratherapeutic dose used in this study should adequately cover the exposure in these patients if they were given a 600-mg dose of ceftaroline fosamil. A 5-day washout period between study drug doses was established to ensure an adequate washout period for ceftaroline (T½ approximately 2.1 hours for a 600-mg dosage), ceftaroline M-1 (T½ approximately 4-5 hours for a 600-mg dosage), and moxifloxacin (T½ approximately 12 hours).

Reviewer's Comment: The AUC of ceftaroline increases less than 2-fold in patients with severe renal impairment. The dose of 1500 mg is acceptable since it covers the exposure in these patients if they were given the proposed lower dose (b) (4). (b) (4)

4.2.5.6 Instructions with Regard to Meals

Subjects fasted from midnight on the night (Study Day -1) before study drug was administered (Study Day 1). Once the subjects were admitted to the CRU, standardized meals, snacks, and beverages were provided. Consumption of alcohol-, caffeine- (eg tea, coffee, cocoa, chocolate, Coca-Cola™), or xanthine-, apple- or grapefruit-containing

products and the use of nicotine patches and nicotine gum within 48 hours before the first study drug administration until at least 48 hours after completion of the last study drug administration was prohibited.
Reviewer's Comment: Acceptable. Ceftaroline was administered as I.V. infusion.

4.2.5.7 ECG and PK Assessments

Table 2: ECG and PK Sampling Schedule

Measurement	Baseline (Study Day -1)	Treatment Day (Periods 1 to 3)
QT	-15min, 1, 1.25, 1.5, 2, 4, 8, 12 h.	-15min, 1, 1.25, 1.5, 2, 4, 8, 12, 24 h.
PK		-15min, 60min, 65min, 75min, 1.25h, 1.5h, 2h, 4h, 8h, 12h, 18h, 24h.

Reviewer's Comment: Acceptable.

4.2.5.8 Baseline

The sponsor used same day pre-dose as QTc baseline values.

4.2.6 ECG Collection

Continuous digital ECG recording began 24 hours and 30 minutes before study drug administration on Study Day 1 and continued until 24 hours and 30 minutes after infusion. Continuous digital ECG recording began up to 1 hour before study drug administration on Study Days 6 and 11 and continued until 24 hours and 30 minutes after infusion. Three ECG extractions were obtained from the Holter monitor at the time points specified above.

Electrocardiograms were analyzed centrally by eRT.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

Fifty-four healthy subjects in the MITT Population (27 male subjects and 27 female subjects) were assigned by block randomization (1:1:1:1:1:1), stratified by gender, to one of six treatment sequences in a three-period crossover design and one subject discontinued study drug due to an adverse event.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was the change from the baseline-adjusted mean differences between ceftaroline 1500 mg and placebo in QTcIb (QT interval corrected for

heart rate using an individual subject correction formula based on the contemporaneous linear QT-RR slope). The sponsor used mixed effects repeated measures model including treatment, sequence, and period as fixed effect, and subject as a random effect. Table 3 and Table 4 presented the time point means differences of ΔΔQTcIb for ceftaroline 1500 mg and moxifloxacin 400 mg, respectively.

The sponsor summarized that the largest mean difference of ΔΔQTcIb for ceftaroline versus placebo was 0.66 ms with 90% CI limits of -2.1 to 3.4 ms. The upper 90% CI limit was below 10 ms, indicating that the supratherapeutic dose of ceftaroline did not cause a clinically meaningful increase in QTc interval. The largest mean difference of ΔΔQTcIb for moxifloxacin versus placebo was 15.70 ms, with 90% CI limits of 12.8 ms to 18.5 ms. The largest lower 90% CI limit was greater than 5 ms which demonstrated assay sensitivity.

Table 3: Sponsor's Analysis Results of Change in QTcIb for Ceftaroline 1500 mg and Placebo, and Difference from Placebo for Ceftaroline 1500 mg

Time Point[a]	***Placebo (N = 54)***	***Ceftaroline (N = 54)***	***Ceftaroline - Placebo (ΔΔQTcIb)***	
	QTcIb Change From Baseline (ΔQTcIb) Mean (SD) msec	*QTcIb Change From Baseline (ΔQTcIb) Mean (SD) msec*	*Least-squares Mean Difference, msec*[b]	*90% CI, msec*[b]
1 hour	10.3 (8.50)	8.3 (9.89)	-2.01	-4.8, 0.8
1.25 hours	7.7 (8.93)	6.9 (8.39)	-0.77	-3.4, 1.9
1.5 hours	7.4 (9.14)	8.0 (9.21)	0.66	-2.1, 3.4
2 hours	6.9 (9.17)	4.5 (11.18)	-2.45	-5.4, 0.5
4 hours	6.8 (9.17)	5.3 (9.07)	-1.43	-4.0, 1.1
8 hours	-2.1 (9.98)	-3.4 (10.19)	-1.31	-4.2, 1.5
12 hours	-0.4 (10.13)	-1.6 (9.34)	-1.18	-3.7, 1.4
24.5 hours	-8.4 (14.17)	-8.9 (13.38)	-0.47	-3.8, 2.9

Abbreviations: ΔQTcIb = change in QTcIb from baseline; ΔΔQTcIb = between-treatment difference in ΔQTcIb; CI = confidence interval; ECG = electrocardiogram; QTcIb = QT interval corrected for heart rate using an individual subject correction formula based on the baseline QT-RR slope; SD = standard deviation.

a Time from the start of infusion of study drug. Study drug was infused over 1 hour.

b The least-squares mean estimates and CI were based on QTcIb as an independent variable in a repeated measures linear model with treatment regimen, sequence, and period as fixed effects and subject as a random effect.

Source: Sponsor's CSR Table 14.3.3.1.1A on Page 202/3808.

Table 4: Sponsor's Analysis Results of Change in QTcIb from Baseline for Moxifloxacin and placebo and Difference from Placebo and Moxifloxacin 400 mg

Time Point[a] (h)	***Placebo (N = 54)***	***Moxifloxacin (N = 53)***	***Moxifloxacin - Placebo (ΔΔQTcIb)***	
	QTcIb Change From Baseline (ΔQTcIb) Mean (SD) msec	*QTcIb Change From Baseline (ΔQTcIb) Mean (SD) msec*	*Least-squares Mean Difference, msec[b]*	*90% CI, msec[b]*
1 hour	10.3 (8.50)	26.0 (9.75)	15.70	12.8, 18.5
1.25 hour	7.7 (8.93)	21.7 (10.37)	14.03	11.3, 16.7
1.5 hour	7.4 (9.14)	21.4 (10.99)	13.99	11.2, 16.8
2 hour	6.9 (9.17)	18.5 (10.09)	11.60	8.7, 14.5
4 hour	6.8 (9.17)	17.0 (10.25)	10.23	7.7, 12.8
8 hours	-2.1 (9.98)	4.6 (11.64)	6.82	3.9, 9.7
12 hours	-0.4 (10.13)	5.7 (10.73)	5.95	3.4, 8.5
24.5 hours	-8.4 (14.17)	-4.3 (13.03)	4.10	0.7, 7.5

Abbreviations: ΔQTcIb = change in QTcIb from baseline; ΔΔQTcIb = between-treatment difference in ΔQTcIb; CI = confidence interval; ECG = electrocardiogram; h = hours; QTcIb = QT interval corrected for heart rate using an individual subject correction formula based on the baseline QT-RR slope; SD = standard deviation.

a Time from the start of infusion of study drug. Study drug was infused over 1 hour.

b The least-squares mean estimates and CI were based on QTcIb as an independent variable in a repeated measures linear model with treatment regimen, sequence, and period as fixed effects and subject as a random effect.

Source: Sponsor's CSR Table 14.3.3.1.1A on Page 202/3808.

Reviewer's Comments: We will provide our independent analysis results in section 5.2.

4.2.7.2.2 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc>450 ms, >480 ms, and >500 ms, and changes from baseline QTc >30 ms and >60 ms. No subject's absolute QTc > 480 ms and ΔQTc > 60 ms.

4.2.7.3 Safety Analysis

There were no deaths or SAEs in this study.

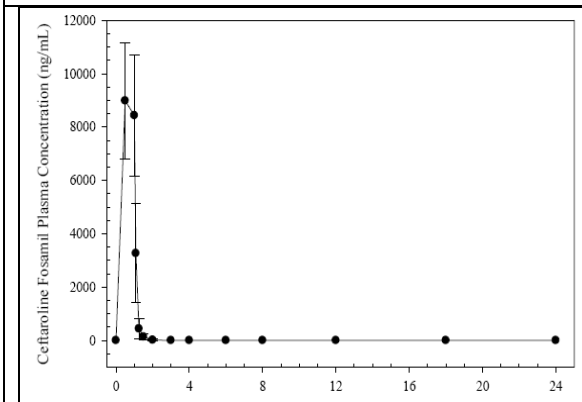
One subject was prematurely discontinued from study drug by the Investigator following administration of placebo due to a TEAE. Following dosing with placebo, Subject 0001-05208 had a TEAE of mild neutropenia on Study Day 7 that was assessed by the Investigator as possibly related to study drug. The subject was prematurely discontinued from study drug on Study Day 7.

4.2.7.4 Clinical Pharmacology

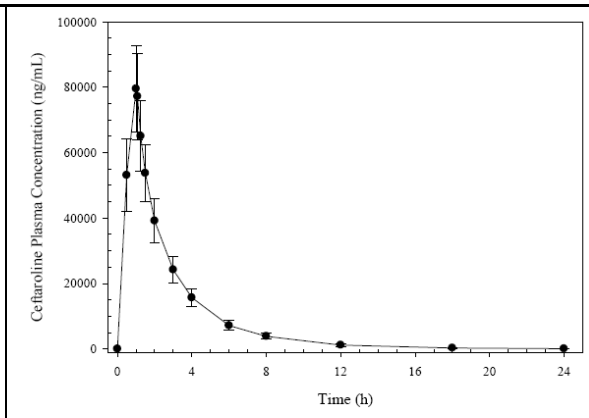
4.2.7.4.1 Pharmacokinetic Analysis

Figure 1 shows the mean (± sd) (A) ceftaroline fosamil (B) ceftaroline (C) ceftaroline M-1 plasma concentrations following intravenous infusion of 1500 mg ceftaroline fosamil.

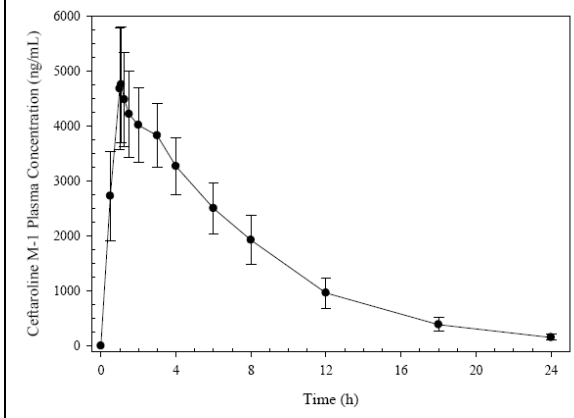
Figure 1: Mean (± SD) (A) Ceftaroline Fosamil (B) Ceftaroline (C) Ceftaroline M-1 Plasma Concentrations Following Intravenous Infusion (60 minutes) Of 1500 mg Ceftaroline Fosamil



(A)



(B)



(C)

The summary of pharmacokinetic parameters for ceftaroline, ceftaroline M-1, ceftaroline fosamil are presented in **Table 5**.

Table 5: Pharmacokinetic Parameters (Mean ± SD) for Ceftaroline, Ceftaroline M-1, and Ceftaroline Fosamil Following Intravenous Infusion (60 minutes) Of Ceftaroline Fosamil

PK Parameter	*Ceftaroline (N = 53)[a]*	*Ceftaroline M-1 (N = 53)[a]*	*Ceftaroline Fosamil (N = 53)[a]*
AUC_{0-t}, ng•hr/mL	204197.14 ± 28240.79	35990.35 ± 5609.47	7392.53 ± 1684.60
$AUC_{0-\infty}$, ng•hr/mL	204639.60 ± 28233.12	37006.76 ± 5840.56	7512.29 ± 1666.66[c]
C_{max}, ng/mL	81391.17 ± 12456.89	5071.21 ± 1034.14	9581.81 ± 2116.39
T_{max}, hour[b]	0.98 (0.98-1.30)	1.05 (0.98-3.00)	0.50 (0.50-1.05)
$T_{½}$, hour	2.59 ± 0.31	4.48 ± 0.38	0.13 ± 0.06[c]
CL, mL/hour	6592.88 ± 908.15	37676.64 ± 5514.48	209174.40 ± 45453.58[c]
V_z, mL	24698.56 ± 5175.53	243412.28 ± 41330.69	38612.88 ± 19662.20[c]
V_{ss}, mL	16443.84 ± 3434.62	245067.94 ± 42138.53	44636.42 ± 11859.01[c]

Abbreviations: AUC_{0-t} = area under the plasma concentration-time curve up to the time corresponding to the last measurable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; CL = plasma clearance; C_{max} = maximum (peak) drug concentration in plasma; PK = pharmacokinetic; SD = standard deviation; T_{max} = time of maximum plasma concentration; T½ = elimination half-life; Vss = volume of distribution at steady-state; Vz = volume of distribution based on the terminal phase.

a Subject 0001-05112 had an aberrant plasma concentration profile suggesting extravascular administration of ceftaroline fosamil. This subject was therefore not included in the mean calculation. PK parameters for Subject 0001-05112 are provided in Table 14.2-5, Table 14.2-6, and Table 14.2-7 for ceftaroline, ceftaroline M-1, and ceftaroline fosamil, respectively

b T_{max} results are expressed as median (minimum-maximum)

c N = 46

- The mean C_{max} (± SD) and AUC $_{0-\infty}$ (± SD) of ceftaroline were 81 ± 12 µg/mL and 204 ± 28 µg•h/mL, respectively, following a single 1500-mg dose of ceftaroline fosamil. The $T_{½}$ for ceftaroline was 2.6 ± 0.3 hours, and was consistent with previous studies with ceftaroline in subjects with normal renal function. T $_{max}$ occurred around the time of the end of study drug infusion.
- The supratherapeutic dose of ceftaroline fosamil used in this study resulted in substantially greater systemic exposure to ceftaroline than observed in subjects with normal renal function at the standard therapeutic dose (600 mg). The mean C_{max} and AUC values for ceftaroline in this study were 3.9-times and 3.7-times greater, respectively, than values observed in subjects with normal renal function receiving a 600-mg dose of ceftaroline fosamil. In addition, the C_{max} for ceftaroline following dosing with 1500 mg ceftaroline fosamil was approximately 4.6 times the C_{max} observed in subjects with severe renal impairment who received a single dose of 400 mg ceftaroline fosamil, and $AUC_{0-\infty}$ was 1.8 times the $AUC_{0-\infty}$ in subjects with severe renal impairment dosed with 400 mg ceftaroline fosamil.
- The mean C_{max} for ceftaroline M-1 following a single 1500-mg dose of ceftaroline fosamil was approximately 6% of the C_{max} for ceftaroline, and the mean $AUC_{0-\infty}$ for ceftaroline M-1 was approximately 18% of the $AUC_{0-\infty}$ for ceftaroline. The $T_{½}$ for

ceftaroline M-1 was 4.5 ± 0.4 hours, and was consistent with previous studies in subjects with normal renal function. The mean C_{max} and AUC values for ceftaroline M-1 in this study were 1.4-times and 2-times values observed in subjects with normal renal function receiving a 600-mg dose of ceftaroline fosamil.

- Ceftaroline fosamil appeared to be rapidly converted to ceftaroline and was generally only measurable in plasma for 0.5 to 1 hour after the end of study drug infusion. The mean C_{max} for ceftaroline fosamil was approximately 9.5% of the C_{max} for ceftaroline, and the mean $AUC_{0-\infty}$ for ceftaroline fosamil was approximately 3.7% of the $AUC_{0-\infty}$ for ceftaroline. The T½ for ceftaroline fosamil was 0.13 ± 0.06 hours, which is consistent with previous studies in subjects with normal renal function, and the median T_{max} was 0.50 hours. The mean C_{max} and AUC values for ceftaroline fosamil in this study were both about 3.1-times greater than values observed in subjects with normal renal function receiving a 600-mg dose of ceftaroline fosamil.
- PK parameters for ceftaroline, ceftaroline M-1, and ceftaroline fosamil were generally similar between male and female subjects, though there was a trend for a slightly higher ceftaroline AUC (~ 14%) and C_{max} (~ 22%) in female subjects.

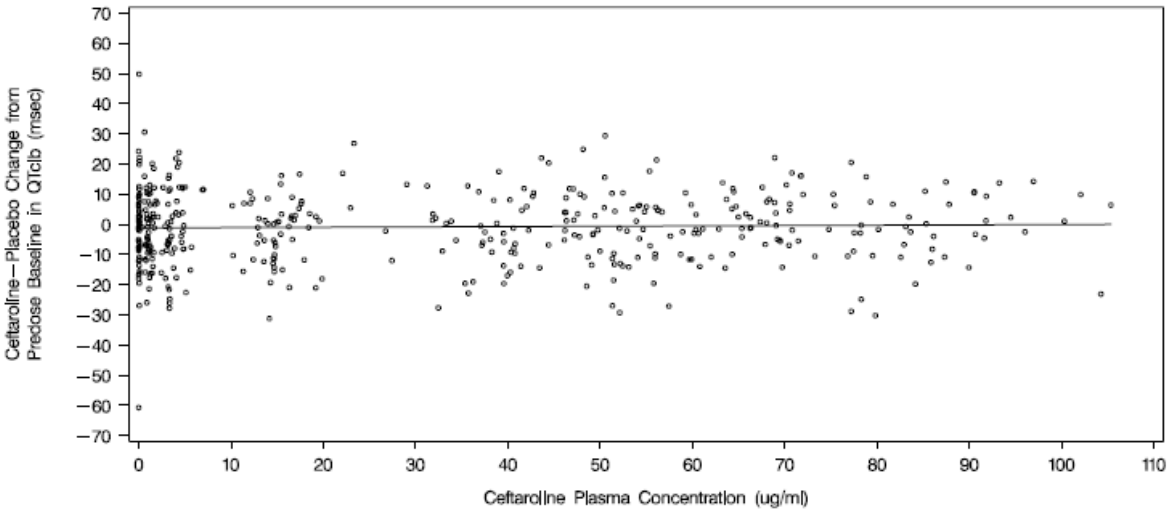
4.2.7.4.2 Exposure-Response Analysis

Figure 2 presents the scatter plot of the time-matched differences between ceftaroline and placebo from baseline in QTcIb intervals (ΔΔQTcIb) versus ceftaroline plasma concentrations. Values below the limit of quantitation are included as zeros. A linear mixed effects repeated measures model with an unstructured variance covariance for within-subject changes was used to estimate the relationship between ceftaroline concentration and ΔΔQTcIb.

ΔΔQTcIb=-1.2305+0.0044*ceftaroline concentration,

ΔΔQTcIb is time-matched ceftaroline-placebo difference in baseline adjusted QTcIb. Based on the slope of estimated regression line, with slope 0.0044, there was no concentration effect for ceftaroline on the changes in QTcIb interval from baseline.

Figure 2: ΔΔQTcIb vs. Ceftaroline Concentration



Source : Figure 14.5.3.8, Page 358 of 3808

Reviewer's Comments: Based on the sponsor's analysis, there is no relationship between ΔΔQTcIb and ceftaroline concentration. Please refer to section 5.3 for clinical pharmacology assessments.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcIb). Baseline values were excluded in the validation. We used the mixed model of the pooled post-dose data of QTcF and QTcIb distinguished by an indicator of correction method to

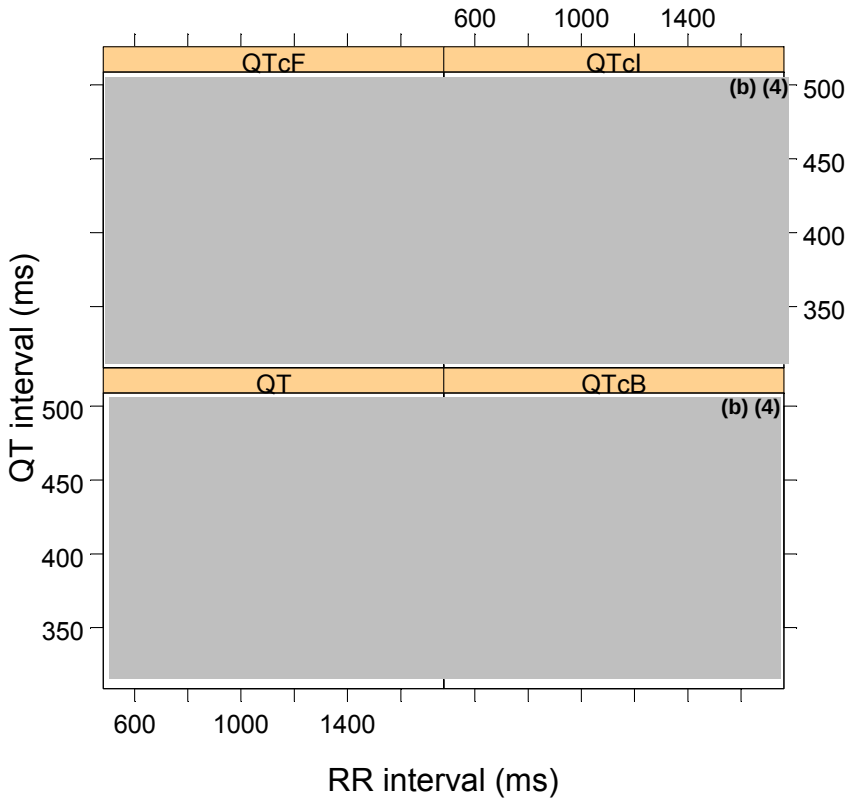
evaluate the linear relationships between different correction methods and RR. The model included gender, baseline, RR, correction type (QTcF or QTcIb), and the interaction term of RR and correction type. The slopes of QTcF and QTcIb versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 6, it appears that QTcIb had smaller absolute slopes than QTcF. Therefore, QTcIb is a better correction method for the study data. This is consistent with the primary endpoint selected by the sponsor.

Table 6: Comparison of QTcIc and QTcF Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcIb	Diff_p_value
Ceftaroline 1500 mg	0.0399	0.0312	0.0708
Moxifloxacin 400 mg	0.0642	0.0421	0.0003
Placebo	0.0385	0.0256	0.0023
All	0.0420	0.0312	0.0000

The relationship between different correction methods and RR is graphically presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcIb effect. The model included TIME, SEQUENCE, and PERIOD as fixed effects and SUBJECT as a random effect. The model also included the baseline and gender as covariates. The analysis results are presented in Table 7. The largest upper bound of the two-sided 90% CI for the mean difference between ceftaroline 1500 mg and placebo is 4.0 ms.

Table 7: **Analysis Results of ΔQTcIb and ΔΔQTcIb for ceftaroline 1500 mg and Moxifloxacin 400 mg**

		Treatment Group						
		Ceftaroline 1500 mg			Moxifloxacin 400 mg			
	Placebo	ΔQTc	ΔΔQTc		ΔQTc	ΔΔQTc		
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	Adj. 90% CI
1	9.1	9.0	-0.1	(-2.4, 2.3)	28.3	19.2	(16.8, 21.5)	(16.0, 22.4)
1.25	7.5	8.2	0.8	(-1.8, 3.3)	23.7	16.3	(13.7, 18.8)	(12.8, 19.8)
1.5	6.7	8.3	1.6	(-0.8, 4.0)	22.5	15.8	(13.4, 18.2)	(12.5, 19.1)
2	6.2	5.1	-1.1	(-3.5, 1.3)	19.1	12.8	(10.4, 15.3)	(9.6, 16.1)
4	5.6	5.8	0.2	(-1.8, 2.3)	18.4	12.7	(10.7, 14.8)	(9.9, 15.6)
8	-1.4	-1.7	-0.3	(-2.5, 1.9)	6.9	8.3	(6.0, 10.5)	(5.2, 11.3)
12	1.5	0.6	-0.9	(-2.9, 1.2)	9.3	7.8	(5.7, 9.9)	(5.0, 10.6)
24.5	-2.3	-3.2	-0.9	(-3.2, 1.4)	1.9	4.2	(1.9, 6.6)	(1.0, 7.4)

*The lower bound of the 90% CI is 16.0 ms after Bonferroni adjustment for 4 time points.

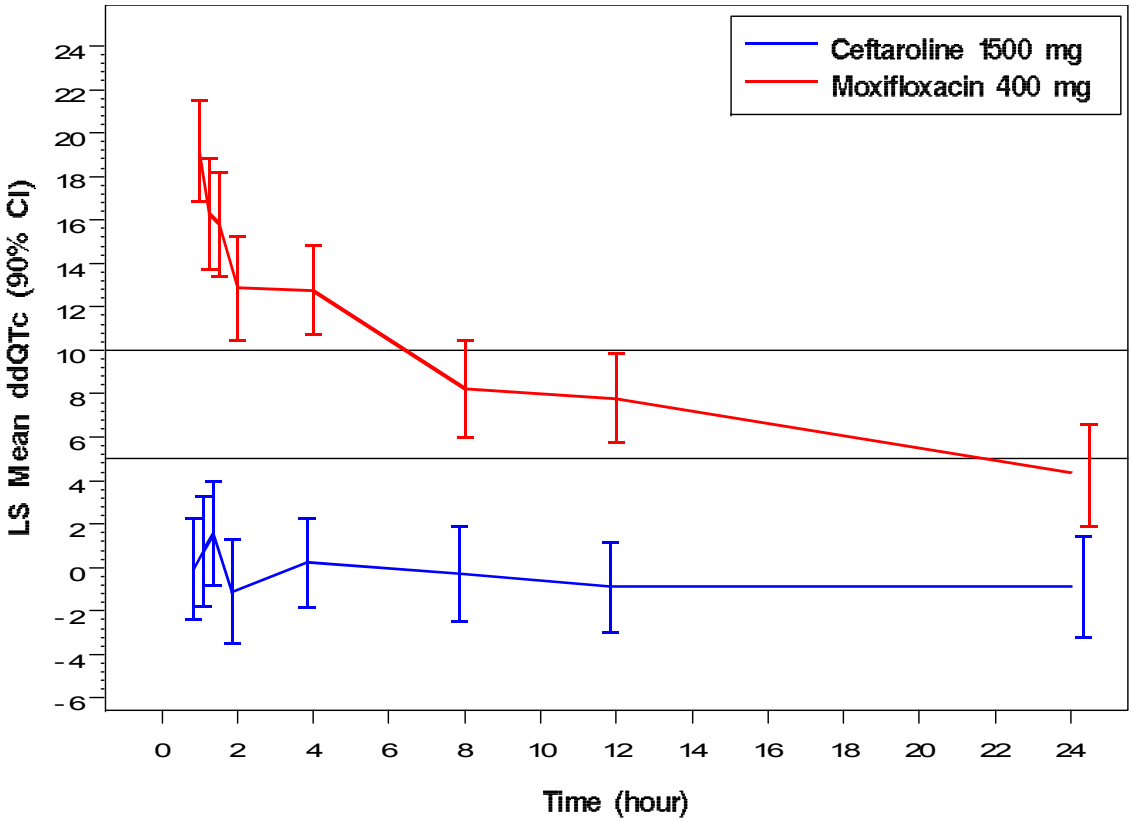
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7. The largest unadjusted 90% lower confidence interval is 16.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 16.0 ms, which indicates that an at least 5 ms QTcIb effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcIb Over Time

The following figure displays the time profile of ΔΔQTcIb for different treatment groups.

Figure 4: Mean and 90% CI ΔΔQTcIb Time Course



(Note: CIs are all unadjusted including moxifloxacin treatment group.)

Reviewer's comments: this reviewer also used the same statistical model to analyze the QTcF effect. The results are similar to those produced by ΔΔQTcIb. The maximum mean change from placebo for QTcF is 1.5 ms. The largest upper bound of the two-sided 90% CI for the mean difference between ceftaroline 1500 mg and placebo is 4.3 ms. For moxifloxacin 400 mg, the largest unadjusted 90% lower confidence interval is 16.2 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 15.1 ms.

5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcIb values are ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcIc is above 480 ms.

Table 8: Categorical Analysis for QTcIb

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
Ceftaroline 1500 mg	54	54 (100%)	0 (0.0%)
Moxifloxacin 400 mg	53	46 (86.8%)	7 (13.2%)
Placebo	54	54 (100%)	0 (0.0%)

Table 9 lists the categorical analysis results for ΔQTcIb. No subject's change from baseline is above 60 ms.

Table 9: Categorical Analysis of ΔQTcIb

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
Ceftaroline 1500 mg	54	53 (98.1%)	1 (1.9%)
Moxifloxacin 400 mg	53	32 (60.4%)	21 (39.6%)
Placebo	54	53 (98.1%)	1 (1.9%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper bounds of 2-sided 90% CI for the PR mean differences between ceftaroline 1500 mg and placebo is 3.3 mg. There is no subject who experienced absolute PR interval greater than 200 ms in ceftaroline treatment group.

Table 10: Analysis Results of ΔPR and ΔΔPR for Ceftaroline 1500 mg and Moxifloxacin 400 mg

		Treatment Group					
		Ceftaroline 1500 mg			Moxifloxacin 400 mg		
	Placebo	ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
1	2.2	3.0	0.8	(-1.6, 3.3)	5.0	2.9	(0.4, 5.3)
1.25	3.4	3.5	0.1	(-2.2, 2.5)	2.7	-0.7	(-3.0, 1.6)
1.5	2.0	1.5	-0.5	(-2.9, 1.8)	0.4	-1.7	(-4.0, 0.7)
2	1.7	1.0	-0.7	(-3.0, 1.6)	2.0	0.3	(-2.0, 2.6)
4	-0.1	-0.9	-0.8	(-3.3, 1.7)	-2.3	-2.2	(-4.8, 0.3)
8	-4.5	-6.7	-2.2	(-5.1, 0.6)	-7.0	-2.6	(-5.5, 0.3)
12	-0.6	-2.8	-2.2	(-5.1, 0.7)	-4.2	-3.6	(-6.5, -0.7)
24.5	-7.8	-8.1	-0.3	(-3.3, 2.7)	-7.3	0.5	(-2.6, 3.5)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper bounds of 2-sided 90% CI for the QRS mean differences between ceftaroline 1500 mg and placebo is 0.7 ms. There is no subject who experienced absolute QRS interval greater than 110 ms in ceftaroline treatment group.

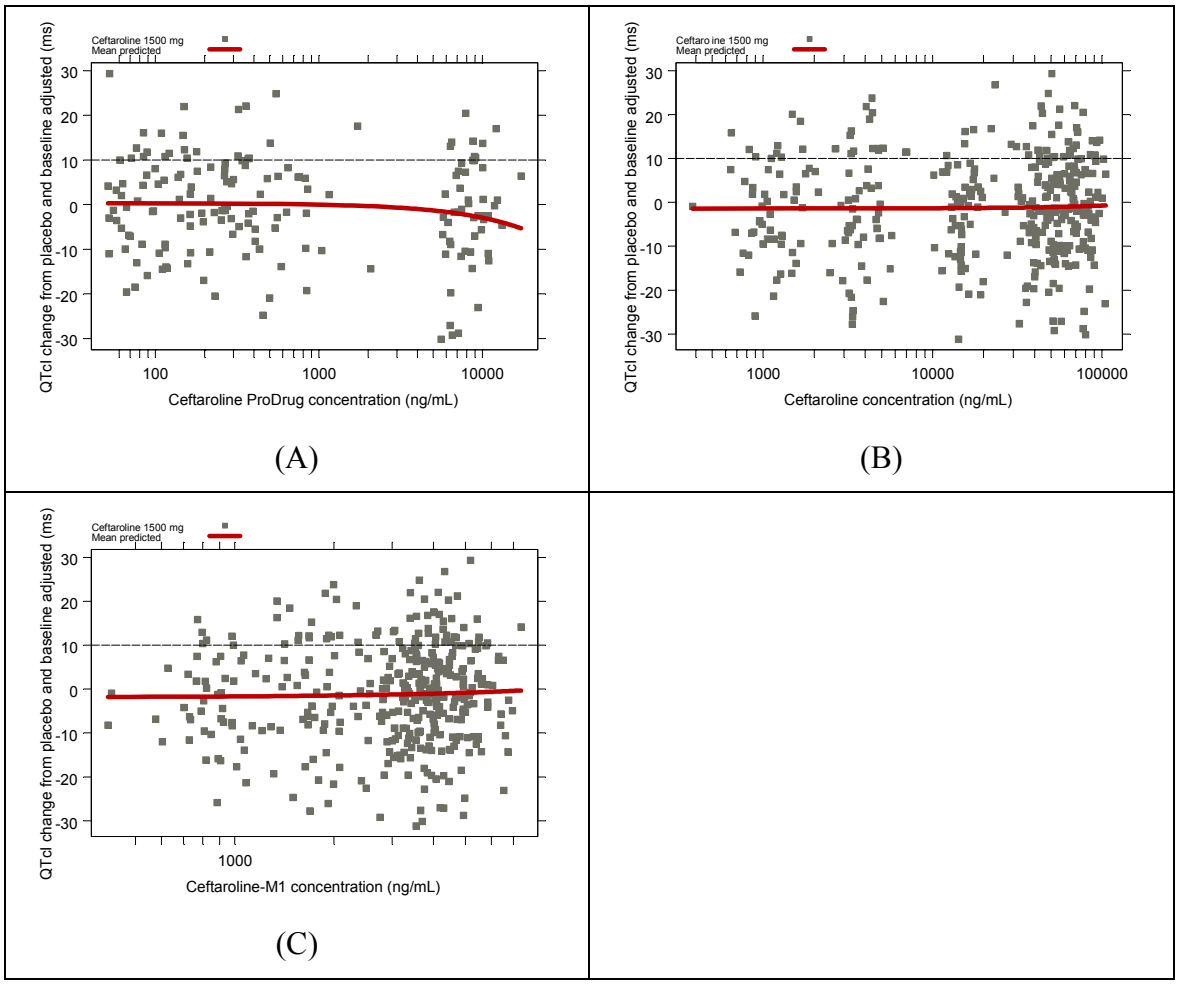
Table 11: Analysis Results of ΔQRS and ΔΔQRS for Ceftaroline 1500 mg and Moxifloxacin 400 mg

		Treatment Group					
		Ceftaroline 1500 mg			Moxifloxacin 400 mg		
	Placebo	ΔQRS	ΔΔQRS		ΔQRS	ΔΔQRS	
Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
1	0.8	0.1	-0.7	(-1.5, 0.1)	0.9	0.2	(-0.7, 1.0)
1.25	0.5	0.4	-0.0	(-0.7, 0.7)	0.4	-0.0	(-0.7, 0.6)
1.5	0.4	-0.0	-0.4	(-1.1, 0.3)	0.3	-0.0	(-0.8, 0.7)
2	0.3	0.0	-0.2	(-1.0, 0.5)	0.3	0.0	(-0.7, 0.7)
4	0.3	-0.0	-0.4	(-1.1, 0.4)	-0.2	-0.5	(-1.3, 0.2)
8	-0.2	-0.9	-0.7	(-1.6, 0.1)	-0.6	-0.4	(-1.3, 0.4)
12	0.9	0.3	-0.6	(-1.5, 0.3)	0.4	-0.5	(-1.4, 0.4)
24.5	-1.6	-1.6	0.0	(-1.0, 1.1)	-1.1	0.5	(-0.5, 1.6)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean ceftaroline fosamil, ceftaroline, and ceftaroline M-1 concentration-time profile is illustrated in **Figure 1**. The relationship between ΔΔQTcI and ceftaroline fosamil , ceftaroline, and ceftaroline M-1 concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5: ΔΔ QTcI vs. Ceftaroline Fosamil (Ceftaroline ProDrug) (A), Ceftaroline (B), and Ceftaroline M-1 (C) Concentrations



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics, over 95% of the ECGs were annotated in the primary lead (II), with less than 0.1% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Variable	Value		Study Reference
Therapeutic dose	600 mg q12 hr (normal or mild renal impairment) 400 mg q12 hr (moderate renal impairment) Dose for severe renal impairment has not been determined		P903-02 (renal impairment) P903-03 (Phase 2 cSSSI)
Maximum tolerated dose	No MTD was detected at the highest doses evaluated Highest dose tested: > 1000 mg (single) > 600 mg q12 hr daily for 14 days		P903-01 (Phase 1 PK healthy subjects) P903-03 (Phase 2 cSSSI)
Principal adverse events	The most common AE reported with ceftaroline treatment was headache. No trends of concern were identified in ceftaroline subjects compared to comparator (vancomycin) subjects for liver function tests, white blood cell count, platelet count, serum creatinine or QTc intervals. Creatine phosphokinase values were comparable between ceftaroline and vancomycin. No unusual trends or patterns in vital sign measurements, ECG tracings, or physical findings were observed in the Phase 2 study. There were two reports of bradycardia considered probably or possibly related to ceftaroline; one was mild in severity, the other moderate. Hypotension, probably or possibly related to study drug was reported in two subjects receiving ceftaroline (one was mild in severity, the other moderate) and one subject receiving comparator (mild), and no postural changes in blood pressure were reported.		P903-03 (Phase 2 cSSSI)
Maximum dose tested	Single dose	1000 mg	P903-01 (Phase 1 PK healthy subjects)
	Multiple dose	600 mg q12 hr for 13½ days	P903-03 (Phase 2 cSSSI)
Exposures achieved at maximum tested dose	Single dose	C_{max} = 30.2 (15.8%) µg/mL, AUC = 80.5 (11.3%) hr*µg/mL	P903-01 (PK report p18)
	Multiple dose	C_{max} = 21.0 (20.1%) µg/mL, AUC = 55.7 (16.4%) hr*µg/mL	P903-01 (PK report p23)

Range of linear PK	Single doses of 50 to 1000 mg		P903-01 (PK report p107)
Accumulation at steady state [a]	1.02 (12.5%) at 600 mg q12 hr		P903-01 (PK report p23)
Metabolites	Ceftaroline-M-1 (inactive open ring)		
Absorption	Not Applicable (Expected to be 100% for IV drug)		Not applicable
Distribution	V_{ss}/F (L)	22.2 (26%)	P903-HP-002 (p7)
	% bound	20% (1% to 28%)	P0903-P-001 P0903-P-003
Elimination	Route (% dose)	51.7 (33.1%) in urine as ceftaroline 7.4 (23.9%) in urine as ceftaroline-M-1	P903-01 (PK report p18 [ceftaroline], p20 [ceftaroline-M-1])
	Terminal $t_{½}$ (h)	2.41 (17.2%) for ceftaroline 4.51 (35.1%) for ceftaroline M1	
	CL/F_m (mL/min)	185 (22.1%) for ceftaroline 590 (26.9%) for ceftaroline M1	
Intrinsic factors	Age	TBD	Not applicable
	Sex	9% higher AUC in female (based on limited data in a population PK analysis)	P0903-P-002 (p30)
	Race	TBD	Not applicable
	Hepatic impairment	TBD	Not applicable
	Renal impairment	11% higher C_{max} and 52% higher AUC in subjects with moderate renal impairment	P903-02 (PK report p17
Extrinsic factors	Drug interaction	TBD	Not applicable
	Food effect	No food effect expected	Not applicable
Expected high clinical exposure scenario	In subjects with severe renal impairment, the clearance of ceftaroline is expected to be reduced to half, AUC will increase but there is no significant effect on Cmax However, appropriate dosing adjustment will be needed for moderate or severe renal impairment		Not applicable
The mean (%CV) were presented TBD: to be determined [a] Accumulation = $AUC_{0-\tau}$ (last dose)/ $AUC_{0-\tau}$ (first dose), where τ is one dosing interval			

6.2 TABLE OF STUDY ASSESSMENTS

Table 9.5.1–1. Schedule of Assessments and Procedures

Scheduled Event		*Study Day*								
		Screen	*Baseline*[a]	*Period 1*		*Period 2*		*Period 3*		*EOS*
		-21 to -2	-1 to 1	1	2	6	7	11	12	17 (± 1)
		Admitted to CRU (Study Days -2 to 12)[b]								
	Informed consent[c]	X								
	Medical and surgical history for the previous 5 years	X	X[d]							
Clinical	Prior and concomitant medications	X[e]	X	X	X	X	X	X	X	X
Clinical	Physical examination	X		X[f]		X[f]		X[f]	X	
Clinical	Vital signs[g]	X		X	X	X	X	X	X	
Clinical	Record weight	X							X	
Clinical	Record height	X								
Clinical	12-lead safety ECG	X		X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
Clinical	12-lead digital Holter ECG[i]		X	X	X	X	X	X	X	
Clinical	Record AEs and SAEs			X	X	X	X	X	X	X
Laboratory	Blood for comprehensive metabolic panel[j]	X	X		X	X	X	X	X	
Laboratory	Blood for hematology evaluations[j]	X	X		X	X	X	X	X	
Laboratory	Blood for direct and indirect antiglobulin tests		X			X[k]		X[k]	X	
Laboratory	Urine for UA and microscopy[j]	X	X		X	X	X	X	X	
Laboratory	Pregnancy test[j]	X	X						X	
Laboratory	Urine test for drugs of abuse	X	X							
Laboratory	Hepatitis and HIV tests[m]	X								
	Estimate creatinine clearance[n]	X	X							
	Study drug administration sequence randomization			X[o]						
	Administration of study drug[p]			X		X		X		
	Blood for PK analyses[q]			X	X	X	X	X	X	

Abbreviations: TEAE = treatment-emergent adverse event; CRU = clinical research unit; ECG = electrocardiogram; EOS = end-of-study; HIV = human immunodeficiency virus; PK = pharmacokinetic; SAE = serious adverse event; UA = urinalysis.

a Baseline assessments were performed within the 24 hours preceding the first study drug administration.

b Subjects were admitted to the CRU on Study Day -2 and remained in CRU until discharge on Study Day 12.

c Informed consent was obtained before initiating any study procedures.

d Medical and surgical history was updated since screening visit.

e Prior medications taken within the 4 weeks preceding randomization were recorded.

f A complete physical examination was performed within 4 hours before study drug administration on Study Days 1 (Period 1), 6 (Period 2), 11 (Period 3), and at 24 hours after the start of study drug administration in Period 3.

g Vital signs were measured at screening, within the 15 minutes proceeding to each study drug administration, and at 1.5, 2, 4, and 24 hours after the start of each study drug administration.

h A single 12-lead safety ECG recording was obtained less than 4 hours before each study drug administration, at 1.5 to 2 hours after the start of each study drug administration, and at 24 hours after the start of each study drug administration.

i Digital ECG recordings using a 12-lead Holter ECG monitor were obtained continuously for pre-specified time frames during baseline, Period 1, Period 2, and Period 3 (Appendix 2). The ECG study manual was referenced for detailed instructions on the Holter monitor and how to manage subjects before and during ECG extraction time points.

j Blood was collected for comprehensive metabolic panel and hematology, and urine collected for UA and urine microscopy at screening, at baseline, and within 24 hours before and 24 hours after the start of each study drug administration.

k Blood was collected for direct and indirect antiglobulin tests within 24 hours before study drug administration on Study Days 6 and 11.

l A urine pregnancy test was performed for women of childbearing potential, or those less than 1 year postmenopausal.

m HBV surface antigen, HCV antibody, and HIV antibody were screened.

n Creatinine clearance was estimated using the Cockroft-Gault formula to determine subject eligibility.

o It was verified that the subject met all study inclusion and exclusion criteria before randomization. Randomization occurred just before study drug preparation and as close to study drug infusion as possible. Subjects were randomized to one of six administration sequences for supratherapeutic ceftaroline fosamil, placebo, and moxifloxacin in a three-period crossover.

p Subjects received a single supratherapeutic dose (1500 mg) of IV ceftaroline fosamil (Study drug A), a single dose of IV saline placebo (Study drug B), and a single dose (400 mg) of IV moxifloxacin (Study drug C) in one of six randomized administration sequences in Periods 1, 2, and 3. Study drug was administered in the morning.

q Blood was collected for PK analyses at the following times:

Immediately preceding (within 15 minutes before) the start of each study drug administration

At 30 (± 5) minutes after the start of each study drug administration

Within 5 minutes before the end of each study drug administration

At 65 and 75 minutes and 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hours (± 5 minutes of the scheduled time points) after the start of each study drug administration (all time points must be postinfusion)

The ECG study manual was referenced for detailed instructions when PK sample time points occurred at the same time as digital ECG extraction time points. If the maximum plasma concentration occurred at a time point for which there was no corresponding ECG extraction (eg, 65 minutes), T_{max} was assigned to the nearest ECG extraction time point with the highest plasma concentration (eg, either 60 min or 75 min).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEVI KOZELI on behalf of JOANNE ZHANG
08/03/2010

MOH JEE NG
08/03/2010

SUCHITRA M BALAKRISHNAN
08/03/2010

HAO ZHU
08/03/2010
Dr. Venkatesh Autl Bhattaram is the primary clinical pharmacology reviewer

NORMAN L STOCKBRIDGE
08/04/2010

DSI CONSULT: Request for Clinical Inspections

Date: March 9, 2010

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2
Jean Mulinde, M.D., Acting Team Leader, GCP2
Kassa Ayalew, M.D., GCP2
Division of Scientific Investigations
Office of Compliance/CDER

Through: Ariel Porcalla, MD, MPH, Medical Officer, DAIOP
Janice Pohlman, MD, MPH, Medical Team Leader, DAIOP

From: Carmen DeBellas, PharmD

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 200327
Applicant/ Applicant contact information (to include phone/email):
Cerexa, Inc.
Bruce Lu, RPh RAC, Senior Director Regulatory Affairs
2100 Franklin St, Suite 900
Oakland CA, 94612
P: 510-285-9325
F: 510-282-9482
Drug Proprietary Name: (b) (4) ceftaroline fosamil for injection
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication: Complicated skin and skin structure infections (cSSSI), Community-acquired bacterial pneumonia (CABP)

PDUFA: December 29, 2009
Action Goal Date: October 29, 2010
Inspection Summary Goal Date: July 15, 2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #0002 Purvi Mahra eStudy Site 752 Medical Center Ct #105 Chula Vista, CA 91911 pmehra@estudysite.com P: 619 955 5246 F: 619 656 9761	P903-06	Screened: 137 Enrolled: 120	cSSSI
Site #5007 Sergey Goryunov Filatov Municipal Hospital #15 23, Veshnyakovskaya str. Moscow, Russia 111539 gav@hospital15.com or sergei.goryunov@mail.ru P: 7 495 375 1490 or 7 903165 92 56 F: 7 495 375 1400	P903-06	Screened: 56 Enrolled: 56	cSSSI
Site #5014 Alexander Konychev V Municipal Hospital #14 19, Kosinova St. St. Petersburg, Russia Doctor.Kira@list.ru P: 7 812 786 4397 F: 7 812 786 4397	P903-07	Screened: 75 Enrolled: 75	cSSSI
Site # 0037 Joseph Surber Southeast Regional Research Group 5210 Armour Rd, Suite 400 Columbus, GA 31904 joesurber@serrg.com P: 706-321-0495 F: 706-321-0477	P903-07	Screened: 46 Enrolled: 46	cSSSI

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site # 7030 Lyudmyla Yashyna F H Yanovskyi Phthisiology and Pulmonology Institute 10 Amosova Vul Kyiz, Ukraine 03680 diagnost@ifp.kiev.ua P: 38 044 275 05 68 F: 38 044 275 05 68 (same as phone number)	P903-08	Screened: 26 Enrolled: 25	CABP
Site # 5428 Revas Tabukashvili 9 Tsinandall Str. Internal Medicine Clinic of Georgian Patriarchate Tbilisi, Georgia 0144 reavas_tabukashvili@yahoo.com P: 995 99 53 21 73 F: 995 32 74 83 55	P903-08	Screened: 24 Enrolled: 24	CABP
Site # 7004 Oleg Kraydashenko Zaporizhzhya State Medical University, City Clinical Hospital #6 26 Mayakovskoho Pr. AND34, Stalevariv vul. Zaporizhzhya, Ukraine, 69035 krayd@ukr.net P: 0038 0612 34 25 58 F: 0038 0612 34 25 58 (same as phone number)	P903-09	Screen: 38 Enroll: 38	CABP
Site # 5011 Veronika B. Popova Saint George Municipal Hospital, Therapy Department #1 1 Severny pr. St. Petersburg, Russia 194354 veronika965@list.ru P: 007 812 596 10 85 F: 007 812 596 10 85 (same as phone number)	P903-09	Screen: 40 Enroll: 37	CABP

III. Site Selection/Rationale

Ceftaroline fosamil is a new molecular entity (NME) developed by Cerexa, Inc, a pharmaceutical company founded in 2005. In 2007, Cerexa became a wholly-owned subsidiary of Forest Laboratories. The Sponsor has submitted a New Drug Application (NDA 200327) for two indications: complicated skin and skin structure infections and community-acquired bacterial pneumonia.

These inspections are requested for clinical sites that have participated in one of the four pivotal clinical trials; two clinical trials to support the cSSSI indication (P903-06, P903-07) and two clinical trials for the CABP indication (P903-08, P903-09). A non-inferiority study design was used for all four pivotal trials. Efficacy endpoints for these trials are primarily based on a clinical assessment of the patient by the investigator and are somewhat subjective.

The vast majority of clinical investigation sites in the two CABP clinical trials (P903-08 and P903-09) were located outside the U.S. The reason for the large number of foreign sites, according to the applicant, was based on inability to recruit patients from the US because of U.S. sites would not enroll patients in a CABP trial without a macrolide as part of the treatment regimen, as recommended by the IDSA treatment guidelines for CAP. However, even in P903-08, where macrolide treatment was allowed for the first 24 hours, participation by US sites was minimal (i.e., only 4% of patients were enrolled at U.S. sites).

Domestic Inspections:
(Complicated skin infection only)
Reasons for inspections (please check all that apply):

- __X__ Enrollment of large numbers of study subjects (P903-06 Mehra)
- __X__ High treatment responders (specify): differential treatment effect favoring study therapy, ITT population (both sites)
- ____ Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- __X__ Other (specify): high number of protocol violations (P903-07 Surber), both sites involved in multiple trials, no DSI inspections at either site

International Inspections:

Reasons for inspections (please check all that apply):

- X There are insufficient domestic data (only 23/591 or 4% of patients enrolled in P903-08 were from the U.S.)
- X Only foreign data are submitted to support an application (for P903-09)
- ____ Domestic and foreign data show conflicting results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- X Other (specify) This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites. Eastern European sites have high efficacy rates (100%) and low numbers of protocol deviations reported. The sites selected were also based on sites at which the highest number of patients had baseline respiratory pathogens isolated (this is important with a shift in emphasis to the microbiologically positive analysis populations.

* Site #5007 Sergey Goryunov (Moscow) inspection was requested based on participation in the cSSSI trial (P903-06). However, there were also 6 patients enrolled in the CABP trial (P903-09) at that site.

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons:

- New molecular entity
- Design of clinical trials for both indications (non-inferiority)
- Endpoint based on clinical assessment by the investigator, rather then definitive, objective endpoint
- High efficacy rates at eastern European sites and paucity of US participation in the CABP trials
- Sites not previously inspected by DSI

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

In light of recent discussions regarding appropriate clinical trial design for cSSSI and CABP indications, in the face of developing scientific justification for the non-inferiority margins used to evaluate treatments, new primary efficacy endpoints and timing of assessment are being explored for these indications.

New information that ultimately may be used to determine clinical efficacy and therefore important to obtain information on during inspections includes:
Complicated skin infections: in addition to clinical observations and assessment at test-of-cure (currently used endpoint), vital signs (i.e., temperature) and clinical observations of the primary

infection site during therapy including measurement of the area of erythema (approximately Day 3, if available) and at the end of therapy are also important.

Community-acquired bacterial pneumonia: Increasingly, interest in assessment of the primary efficacy endpoint on Day 3-5 of treatment is being emphasized. In order to assess clinical efficacy or success, objective criteria that may be available during this period (e.g., temperature, heart rate, and respiratory rate) and clinician assessment of "well-being" of the patient are being considered to define clinical efficacy. Work on how to assess "well-being" of the patient is currently being defined, however it will likely be based on clinical appearance and signs that are observable by the investigator (such as tachypnea, cyanosis, mental status, ability to ambulate, and take nutrition and fluids orally) are things that may be considered. Additionally, the primary analysis population has shifted to the microbiological intent-to-treat population (i.e., patients with a typical respiratory pathogen isolated from baseline culture) and secondarily or supportively, the microbiologically evaluable population.

Should you require any additional information, please contact Carmen DeBellas, PharmD at 301-796-1203 or Ariel Porcalla, MD, MPH at 301-796-4215.

Concurrence: (as needed)

Janice Pohlman, MD, MPH	Medical Team Leader
Katie Laessig, MD	Deputy Division Director (for foreign inspection requests or requests for 5 or more sites only)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

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/s/

JANICE K POHLMAN
03/10/2010

KATHERINE A LAESSIG
03/11/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 200327		
Proprietary Name: (b) (4) Established/Proper Name: ceftaroline fosamil Dosage Form: Injection Strengths: 400 mg and 600 mg		
Applicant: Cerexa, Inc		
Date of Application: 12/30/09 Date of Receipt: 12/30/09 Date clock started after UN:		
PDUFA Goal Date: 10/30/10	Action Goal Date (if different): 10/29/10	
Filing Date: 2/28/10	Date of Filing Meeting: 2/19/10	
Chemical Classification: 1S		
Proposed indication(s)/Proposed change(s): Complicated Skin and Skin Structure Infections Community Acquired Pneumonia		
Type of Original NDA: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	x 505(b)(1) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	X Standard ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	
Collaborative Review Division (*if OTC product*):		

List referenced IND Number(s): 71, 371				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	x			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	x			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment** ***Not Applicable***
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		x		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		x		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		x		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**x**			
Index: Does the submission contain an accurate comprehensive index?	**x**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	**x**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		**x**		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #		**x**		

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	x			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	x			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	x			

Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	x			

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	x			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	x			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		x		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	x			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	x			
Is the PI submitted in PLR format?	x			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	x			
REMS consulted to OSE/DRISK?				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	x			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	x			

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** October 24, 2006 ***If yes, distribute minutes before filing meeting***	x			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** July 7, 2009 ***If yes, distribute minutes before filing meeting***	x			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			x	

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 19, 2010

BLA/NDA/Supp #: NDA 200327

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: ceftaroline fosamil

DOSAGE FORM/STRENGTH: 400 mg and 600 mg

APPLICANT: Cerexa

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

Community Acquired Pneumonia
Skin and Skin Sturcture Infections

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Carmen DeBellas	Y
	CPMS/TL:	Frances Le Sane	N
Cross-Discipline Team Leader (CDTL)	Janice Pohlman		Y
Clinical	Reviewer:	Ariel Porcalla Neil Rellosa	Y
	TL:	Janice Pohlman	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Avery Goodwin	N
	TL:	Frederic Marsik	N

Clinical Pharmacology	Reviewer:	Aryun Kim Jiang Liu	Y
	TL:	Charles Bonapace	Y
Biostatistics	Reviewer:	Daniel Rubin Christopher Kadoorie	Y
	TL:	Thamban Valappil Scott Komo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Ellis	Y
	TL:	Wendy Schmidt	N
Product Quality (CMC)	Reviewer:	Andrew Yu	Y
	TL:	Rapti Madurawe	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Pawar Vinayak	N
	TL:	James McVey	N
OSE/DMEPA (proprietary name)	Reviewer:	Shirley Zeigler	N
	TL:	Brantley Dorch Tselaine Jones-smith	N
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	N
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Jean Mulinde	Y
	TL:		

Other reviewers DDMAC	Sharon Watson	N
Other attendees	Wiley Chambers Acting Division Director John Farley Deputy Office Director Sumathi Nambiar	Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	X Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	X Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the***	X YES Date if known: TBA – August? ☐ NO ☐ To be determined Reason:

drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease	

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter

Comments:	

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable X YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Edward Cox – Office Director **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): Review Classification: X Standard Review ☐ Priority Review
ACTIONS ITEMS	
X	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARMEN L DEBELLAS
02/22/2010