2.0 SYNOPSIS

Name of Sponsor/Company: Cerexa, Inc. 2100 Franklin St, Suite 900 Oakland, CA 94612	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Ceftaroline fosamil-avibactam	**Volume:**	
Name of Active Ingredients: ceftaroline fosamil and avibactam (the latter previously referred to as NXL104)	**Page:**	
Study Number: CXL-MD-02		
Title of Study: A Phase 2, Multicenter, Randomized, Double-blind, Comparative Study to Evaluate the Efficacy and Safety of Intravenous Coadministered Ceftaroline fosamil and NXL104 Versus Intravenous Doripenem in Adult Subjects With Complicated Urinary Tract Infection		
Investigators: Multicenter study; a complete list of investigators is provided in Appendix 16.1.4.1		
Study Centers: 28 study centers enrolled subjects: 4 in Bulgaria, 3 in Germany, 1 in Lebanon, 8 in Poland, 8 in Russia, 2 in Turkey, and 2 in the United States		
Publication (reference): None at the time of this report		
Study Period (years): First Subject First Visit: 28 Dec 2010 Last Subject Last Visit: 07 May 2012	**Development Phase:** 2	

Objectives:

The primary objectives of the study were:

- Determine the microbiological response in the Microbiologically Evaluable (ME) Population at Test-of-Cure (TOC)
- Evaluate the safety of coadministered intravenous (IV) ceftaroline fosamil and avibactam (referred to hereafter as CXL) in subjects with complicated urinary tract infection (cUTI)

The secondary objectives of the study were:

- Determine the proportion of subjects with a clinical response of cure in the Clinically Evaluable (CE) Population at TOC
- Determine the proportion of subjects with a favorable microbiological response in the microbiological Intent-to-Treat (mITT) Population at TOC
- Determine the proportion of subjects with a clinical response of cure in the mITT Population at TOC
- Determine the proportion of subjects with a sustained favorable microbiological response in the ME Population at Late Follow-up (LFU)
- Determine the proportion of subjects with a clinical response of sustained clinical cure in the CE Population at LFU
- Determine the proportion of subjects with a favorable microbiological response in the ME Population at TOC and the proportion of subjects with a clinical cure in the CE Population at TOC in subjects with complicated lower urinary tract infection (cLUTI) or acute pyelonephritis (AP)
- Evaluate the per-pathogen outcome in the mITT and ME Populations at TOC
- Determine the proportion of subjects with a favorable microbiological response in the ME Population at End-of-Therapy (EOT)
- Determine the proportion of subjects with a clinical response of cure in the CE Population at EOT
- Determine the incidence of emergent infections
- Evaluate the pharmacokinetics of ceftaroline fosamil (prodrug), ceftaroline, ceftaroline M-1 (inactive metabolite), and avibactam in subjects with cUTI

Study Design: Phase 2, multicenter, randomized (1:1:1), double-blind study comparing efficacy and safety in adult subjects with cUTI receiving 600 mg ceftaroline fosamil/600 mg avibactam (ie, CXL 600 mg/600mg) every 8 hours (q8h), CXL 600 mg/600 mg every 12 hours (q12h), or doripenem 500 mg q8h (referred to hereafter as the CXL q8h, CXL q12h, and doripenem groups, respectively).

Diagnosis and Main Criteria for Inclusion: Male and female patients ≥ 18 years of age; pyuria; local urine Gram stain demonstrating the presence of gram-negative bacilli; clinical signs and/or symptoms of cUTI, defined as AP or cLUTI; pretreatment baseline urine culture specimen obtained within 48 hours before start of administration of the first dose of study drug; infection requiring initial treatment with IV antibiotics; initial hospitalization required to manage the cUTI by the standard of care

Number of Subjects:
72 subjects randomized to CXL q8h, 73 subjects randomized to CXL q12h, 73 subjects randomized to doripenem in the Intent-to-Treat (ITT) Population

Analyzed for efficacy:

- mITT Population: 51 CXL q8h, 42 CXL q12h, 51 doripenem
- ME Population: 46 CXL q8h, 37 CXL q12h, 44 doripenem
- CE Population: 45 CXL q8h, 37 CXL q12h, 47 doripenem

Analyzed for safety:

- Safety Population: 71 CXL q8h, 71 CXL q12h, 73 doripenem

Investigational Product, Dose and Mode of Administration, Batch Number:

- CXL 600 mg/600 mg administered in 60-minute IV infusion q8h
- CXL 600 mg/600 mg administered in 60-minute IV infusion q12h

Adjustments to doses of CXL were made as necessary based on the estimated creatinine clearance (CrCl).

Reference Therapy, Dose and Mode of Administration, Batch Number:

- Doripenem 500 mg administered in 60-minute IV infusion q8h

Adjustments to doses of doripenem were made as necessary based on the estimated CrCl.

Duration of Treatment: 7 to 10 days

Criteria for Evaluation:

Efficacy:

Primary: The primary efficacy outcome measure was the proportion of subjects with a favorable microbiological response in the ME Population at TOC

Secondary:

The secondary efficacy outcome measures were the following:

- Proportion of subjects with a clinical response of cure in the CE Population at TOC
- Proportion of subjects with a favorable microbiological response in the mITT Population at TOC
- Proportion of subjects with a clinical response of cure in the mITT Population at TOC
- Proportion of subjects with a sustained favorable microbiological response in the ME Population at LFU
- Proportion of subjects with a clinical response of sustained clinical cure in the CE Population at LFU
- Proportion of subjects with a favorable microbiological response in the ME Population at TOC and the proportion of subjects with a clinical response of cure in the CE Population at TOC in subjects with cLUTI or AP
- Per-pathogen outcome in the mITT and ME Populations at TOC
- Proportion of subjects with a favorable microbiological response in the ME Population at EOT
- Proportion of subjects with a clinical response of cure in the CE Population at EOT
- Incidence of emergent infections

Safety: Safety measures included the subject incidences of adverse events (AEs), including serious adverse events [SAEs] and deaths, monitored from signing of informed consent through TOC; ongoing AEs, new SAEs, and deaths monitored through LFU (or 28 days after last dose if no LFU visit occurred); and changes in clinical laboratory evaluations, electrocardiograms (ECGs), and vital signs, recorded at prespecified times throughout the study and analyzed in the Safety Population.

Pharmacokinetic: Pharmacokinetic measures included plasma concentrations of ceftaroline, ceftaroline fosamil (prodrug), ceftaroline M-1 (inactive metabolite), and avibactam in samples collected on Study Days 1 and 3 from all subjects

Statistical Methods:
The following study populations were defined:
ITT Population: all randomized subjects

Safety Population: all randomized subjects who received any amount of study drug

mITT Population: randomized subjects for whom 1 or 2 bacterial pathogens were isolated from an appropriate microbiological urine specimen at baseline

ME Population and CE Population: subsets of subjects in the mITT Population who met all the following criteria:

- Met the protocol definition of cUTI
- Received ≥ 80% of the intended doses of study drug therapy based on the number of days on study drug therapy
- Received ≥ 72 hours of therapy in order to be considered an evaluable failure
- Received ≥ 96 hours of therapy in order to be considered an evaluable success
- Did not receive any amount of an alternative (nonstudy) systemic antibiotic that was potentially effective for the treatment of cUTI prior to the TOC Visit, for a reason other than treatment failure
- Had no violations of entry exclusion criteria 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 in Section 8.2 of the Protocol (Appendix 16.1.1)
- Did not receive any amount of study drug from the treatment arm to which they were not randomly assigned

The subjects in the ME Population also met the following criterion:

- Had an interpretable urine culture within the appropriate TOC Visit window (5 to 11 days after EOT for a favorable microbiological response; 1 to 11 days after EOT for an unfavorable microbiological response).

The subjects in the CE Population also met the following criteria:

- Had an outcome assessment performed within the appropriate TOC Visit window (5 to 11 days after EOT for clinical cure; 1 to 11 days after EOT for clinical failure)
- The blind remained unbroken until after database lock

Disposition: A detailed description of subject disposition (enrollment, discontinuations from study drug. withdrawal from study) was provided for the ITT, mITT, and ME Populations.

Demographics and Other Baseline Characteristics: Descriptive statistics for demographics and other baseline characteristics were provided for the mITT and ME Populations.

Efficacy: The primary efficacy analysis was based on the ME Population. The secondary efficacy analyses were based on the ME, mITT, and CE Populations. Descriptive statistics were generated for all primary and secondary efficacy endpoints. Ninety-five percent confidence intervals (CIs) were generated for the proportion of subjects with favorable microbiological responses and clinical cures in each treatment group at TOC and other specified visits, as well as for all pairwise differences between treatment groups. The 2 CXL treatment groups also were combined and summarized ("CXL Total" column in the data tables; referred to hereafter as the combined CXL groups). Differences of proportions between the combined CXL groups and the doripenem group also were performed using the same method. No formal hypothesis testing was conducted.

Safety: All safety data were summarized for the Safety Population. The incidence of treatment-emergent adverse was summarized by system organ class and preferred term, by relationship to study drug, and by severity. Descriptive statistics of clinical laboratory results and the change from baseline were presented. A summary of abnormal ECG findings were provided.

Pharmacokinetic: Plasma concentrations of ceftaroline, ceftaroline fosamil, ceftaroline M-1, and avibactam were summarized.

SUMMARY OF RESULTS:

Disposition: A total of 218 subjects were randomized to receive study drug (72 to CXL q8h, 73 to CXL q12h, and 73 to doripenem) (ITT Population). Of these subjects, 215 (99%) received study drug and were included in the Safety Population. A total of 144 randomized subjects (66%) had 1 or 2 bacterial pathogens isolated from an appropriate microbiological urine specimen at baseline and were included in the mITT Population. Of note, a higher percentage of subjects in the CXL q12h group (43%) did not have a study-qualifying pretreatment baseline urine culture and were excluded from the mITT Population than in the CXL q8h (29%) and doripenem (30%) groups. A subset of 127 subjects in the mITT Population (58% of the ITT Population) met the criteria for inclusion in the ME Population (the primary efficacy population), and a subset of 129 subjects in the mITT Population (59% of the ITT Population) met the criteria for inclusion in the CE Population. Approximately 73% of the subjects in the study completed study drug treatment, and approximately 88% of the subjects completed the study.

Demographics and Other Baseline Characteristics: Demographic and baseline characteristics for the ME Population were generally balanced across treatment groups. Most of the subjects in this population were Caucasian and female. The mean (range) age was 60 (18 to 90) years, and the mean (range) body mass index was 28.5 (18.1 to 48.9) kg/m^2. The CXL groups had higher percentages of subjects $\geq$ 65 years of age than the doripenem group (approximately 20% to 25% differences). Most subjects had normal renal function or mild renal impairment. Only 1 of the subjects (in the doripenem group) received prior antibiotic therapy within 96 hours before the baseline urine culture. Bacteremia (defined as having pathogen[s] isolated from both urine and blood [this definition does not require that the same species be present in both urine and blood]) was present at baseline for 6% of the subjects (no subjects in the CXL q8h group had bacteremia, compared with 11% of subjects in the CXL q12h group and 9% of subjects in the doripenem group). Approximately 49% of the subjects had cLUTI, and approximately 51% of the subjects had AP. Demographic characteristics of the mITT and Safety Populations were generally similar to those of the ME Population.

Efficacy Results:

Per-Subject Microbiological Response at the Test-of-Cure, End-of-Treatment, and Late Follow-up Visits ME Population

Visit *Outcome*	*Doripenem*	*CXL q8h*	*CXL q12h*
Test-of-Cure, N	44	46	37
Favorable, n (%)	32 (72.7)	34 (73.9)	25 (67.6)
Unfavorable, n (%)	12 (27.3)	12 (26.1)	12 (32.4)
Difference in % favorable (vs. doripenem)	—	1.2	–5.2
95% CI for the difference (vs. doripenem)	—	–17.2, 19.6	–25.2, 14.7
End-of-Treatment, N	44	46	37
Favorable, n (%)	42 (95.5)	46 (100)	37 (100)
Unfavorable, n (%)	0	0	0
Difference in % favorable (vs. doripenem)	—	4.5	4.5
95% CI for the difference (vs. doripenem)	—	–3.4, 15.2	–5.2, 15.2
Late Follow-up, N	32	34	25
Sustained favorable, n (%)	19 (59.4)	27 (79.4)	22 (88.0)
Recurrence, n (%)	12 (37.5)	7 (20.6)	2 (8.0)
Indeterminant, n (%)	1 (3.1)	0	1 (4.0)
Difference in % sustained favorable (vs. doripenem)	—	20.0	28.6
95% CI for the difference (vs. doripenem)	—	–2.4, 41.0	5.3, 48.7

Abbreviations: CI = confidence interval; ME = Microbiologically Evaluable; N = number of subjects in the specified population; n = number of subjects within a specific category.

Note: Percentages are calculated as 100 × (n/N).

- The primary efficacy outcome measure was the proportion of subjects in the ME Population with a favorable microbiological response (ie, eradication of all baseline pathogens) at the TOC visit (5 to 11 days after EOT). The favorable microbiological response rates at TOC in this population were high and comparable across treatment groups (73.9% CXL q8h, 67.6% CXL q12h, 72.7% doripenem). Analyses of differences in favorable microbiological response rates between the treatment groups (each CXL group versus doripenem and CXL q12h versus CXL q8h) and the corresponding 95% CIs suggested that favorable response rates were similar across the treatment groups.
- Clinical cure rates in the CE Population at TOC were higher than the favorable microbiological response rates in the ME Population and were comparable between treatment groups (≥ 91.5% in each group).

- *Escherichia coli* was the most common baseline uropathogen in the ME Population and was eradicated at TOC at a high rate in all treatment groups (80.0% CXL q8h, 69.2% CXL q12h, 66.7% doripenem). *Klebsiella pneumoniae* was the second most common baseline uropathogen and was eradicated at TOC at a numerically lower rate in the CXL groups (57.1% CXL q8h, 55.6% CXL q12h) than in the doripenem group (81.8%). Because the number of subjects with *K. pneumoniae* baseline pathogens was low (n = 27 [CXL q8h = 7, CXL q12h = 9, doripenem = 11]), conclusions about these differences are difficult to make.
- Clinical cure rates at TOC for subjects in the CE Population with *E. coli* were high (≥ 92.3% in each treatment group). Clinical cure rates at TOC for subjects with *K. pneumoniae* also were high, but were more variable between treatment groups (ranging from 81.8% [doripenem group] to 100.0% [both CXL groups]). It is of note that while the favorable microbiological response rate at TOC for subjects with *K. pneumoniae* baseline pathogen was numerically lower in the CXL groups than in the doripenem group, the opposite was true for the clinical cure rate, with numerically higher cure rates in the CXL groups than in the doripenem group.
- Favorable microbiological response rates at TOC in the ME Population and clinical cure rates at TOC in the CE Population also were summarized by subgroups defined by primary diagnosis (AP or cLUTI) and age groups (< 65 years or ≥ 65 years and < 75 years or ≥ 75 years). Within each primary diagnosis subgroup, the favorable microbiological response and clinical cure rates were high and similar across the treatment groups. Some numerical differences between treatment groups were observed within some of the age subgroups; however, for each subgroup (except the ≥ 75 years subgroup, for which such analyses were not performed due to its small size), analyses of differences between the treatment groups and the corresponding 95% CIs suggested that favorable microbiological response rates and clinical cure rates were similar across all treatment groups. Favorable microbiological response rates and clinical cure rates at TOC also were analyzed by region/country. Some numerical differences between treatment groups were observed within some of the regions/countries; however, the analyses of differences between the treatment groups and the corresponding 95% CIs suggested that the rates were similar across all treatment groups within the regions/countries large enough to be analyzed.
- Favorable microbiological response rates in the ME Population at EOT were high (≥ 95.5%) and comparable across the treatment groups. At LFU, the sustained favorable response rate was numerically higher in the CXL groups (≥ 79.4%) than in the doripenem group (59.4%). However, analyses of differences between the treatment groups and the corresponding 95% CIs suggested that sustained response rates were similar across all treatment groups.
- Clinical cure rates in the CE Population at EOT, like the microbiological favorable rates in the ME Population, were high (≥ 97.9%) and comparable between treatment groups. At LFU, for most subjects in each treatment group (≥ 88.4%), the cure was sustained at LFU.
- In support of the analyses for the ME and CE Populations, additional analyses also assessed favorable microbiological response and clinical cure rates at EOT, TOC, and LFU in the mITT Population. Results for this population were comparable with those for the ME and CE Populations.
- Efficacy also was assessed in subjects in the ME Population with presumed ceftaroline-hydrolyzing β-lactamase (CHBL)-producing baseline pathogens (defined as pathogens that had a minimum inhibitory concentration (MIC) ≥ 2 µg/mL for ceftaroline and MIC < 1 µg/mL for CXL). Among these subjects, the favorable microbiological response rate at TOC was numerically lower in the CXL groups (53.8% CXL q8h, 60.0% CXL q12h) than in the doripenem group (81.3%). Because the number of subjects with presumed CHBL-producing pathogens was low (n = 44 [CXL q8h = 13, CXL q12h = 15, doripenem = 16]), conclusions about the differences in microbiological response rates are difficult to make. Imbalances in confounding factors, including invasive urologic procedures performed during the study and treatment allocation by center, existed between the subjects with these baseline pathogens in the CXL and doripenem groups. Furthermore, among the subjects with presumed CHBL-producing baseline pathogens in the CE Population, the clinical cure rate at TOC was high in all treatment groups (92.3% CXL q8h, 100% CXL q12h, 93.8% doripenem), indicating that many of the microbiological unfavorable responses in all treatment groups represented asymptomatic bacteriuria.

- Results of efficacy analyses at TOC for the similar subset of subjects in the ME Population with baseline pathogens phenotypically identified as extended-spectrum β-lactamase (ESBL) producers (ie, either confirmed as ESBL-producing [ceftazidime and/or ceftriaxone resistant and the addition of clavulanate reduced the MIC for ceftazidime and/or cefotaxime by at least 3 doubling-dilutions] or considered possible ESBL producers [ceftazidime and/or ceftriaxone resistant and addition of clavulanate did not reduce the MIC for ceftazidime and/or cefotaxime by at least 3 doubling-dilutions]) were comparable with those for subjects with presumed CHBL-producing pathogens. Pathogens from all the subjects with confirmed or possible ESBL producing baseline pathogens were also examined using pulsed-field gel electrophoresis (PFGE) to precisely identify recurrent/persistent pathogens at TOC. Analysis of microbiological response at TOC based on PFGE data had similar results to the initial response analysis based on genus and species, though with an additional subject in each CXL group having a favorable response than in the initial analysis. (The response rate remained the same in the doripenem group.)

Pharmacokinetic Results: Individual plasma concentrations of ceftaroline fosamil, ceftaroline, ceftaroline M-1, and avibactam are presented in Listing 16.2.11. Note that plasma concentration data for ceftaroline fosamil, ceftaroline, and avibactam from this study were combined with data from other studies and used in population pharmacokinetic pharmacokinetic/pharmacodynamic analyses. Results of these analyses are reported separately.

Safety Results: The median duration of CXL or doripenem therapy for the Safety Population was 8 days, and most subjects in all treatment groups received 7 to 10 days of study drug therapy. Similar percentages of subjects in each treatment group had ≥ 1 treatment-emergent adverse event (TEAE) (38.0% CXL q8h, 36.6% CXL q12h, 39.7% doripenem). Because the subject incidence of TEAEs was similar in the 2 CXL groups, the presentation of safety information focused on the combined CXL groups. TEAEs that occurred with a ≥ 2% subject incidence in either the combined CXL groups or the doripenem group were headache, constipation, diarrhea, anemia, nausea, insomnia, hypotension, vomiting, abdominal pain, sepsis, blood creatine phosphokinase increased, blood magnesium decreased, back pain, and cough. The only TEAE that occurred with a ≥ 2% higher subject incidence in the combined CXL groups compared with the doripenem group was anemia (2.1% and 0, respectively). Events that occurred with a ≥ 2% higher incidence in the doripenem group compared with the combined CXL groups included headache, nausea, vomiting, abdominal pain, sepsis, blood creatine phosphokinase increased, blood magnesium decreased, back pain, and cough. Most TEAEs were mild to moderate in severity. Seven percent of subjects in the CXL groups and 2.7% of subjects in the doripenem group had TEAEs that were reported as severe. No severe TEAE was reported by > 1 subject in any treatment group.

Study drug-related TEAEs were reported for 10.6% of subjects in the combined CXL groups and 12.3% of subjects in the doripenem group. A higher percentage of subjects in the CXL q12h group (14.1%) had a study drug-related TEAE than in the CXL q8h group (7.0%). Study drug-related TEAEs reported for ≥ 2% of subjects in either the combined CXL groups or doripenem group were diarrhea (2.1% CXL, 1.4% doripenem), nausea (2.1% CXL, 2.7% doripenem), vomiting (0 CXL, 2.7% doripenem), headache (1.4% CXL, 2.7% doripenem), and blood creatine phosphokinase increased (0 CXL, 2.7% doripenem).

Similar percentages of subjects in each treatment group had SAEs (5.6% each CXL group, 4.1% doripenem). None of the SAEs were reported as study drug-related. Study drug discontinuations due to TEAEs occurred for a higher percentage of subjects in the in the combined CXL groups (4.2%) than in the doripenem group (0%). The only event leading to study drug discontinuation for > 1 subject was nausea, which led to discontinuation of 2 subjects in the CXL q12h group. No TEAEs related to *Clostridium difficile* were reported, and other TEAEs of interest occurred with similar subject incidences across treatments. One subject (1.4%) in the CXL q8h group and 2 subjects (2.7%) in the doripenem group died on study. The deaths were not reported as related to study drug, and the causes of death could be attributed to underlying disease or unrelated comorbidities.

Review of descriptive statistics and shifts from baseline for all laboratory parameters over time, as well as relevant potentially clinically significant (PCS) laboratory values, generally showed overall low incidences and no meaningful differences between the combined CXL and doripenem groups, with a few exceptions, as described below. The most common relevant PCS hematology findings (occurring in > 3% of subjects in either the combined CXL groups or the doripenem group) were decreased hemoglobin (6.1% CXL, 4.2% doripenem), decreased red blood cell count (3.1% CXL, 2.9% doripenem), and direct Coombs test seroconversions. Direct Coombs test seroconversions occurred in approximately 30% of subjects in the combined CXL groups and no subjects in the doripenem group. No evidence of hemolytic anemia or hemolysis was identified in the subjects who had Coombs seroconversion, or in any subject in the study. The only relevant PCS chemistry value that occurred in more than 1 subject in either the combined CXL groups or the doripenem group was increased creatine kinase (0 CXL, 4.2% doripenem). The subject incidence of relevant PCS coagulation values was low: Increased activated partial thromboplastin time values occurred in 6.0% and 3.0% of subjects in the combined CXL and doripenem groups, respectively, and an increased international normalized ratio occurred in 1.5% and 3.0% of subjects, respectively. No clinically meaningful changes from baseline were noted for urinalysis parameters, with the exception of changes consistent with responses to treatment of the subjects' cUTIs. No subjects met laboratory criteria for potential Hy's Law. The subject incidences of PCS postbaseline systolic blood pressure, diastolic blood pressure, and pulse values were low and similar across treatments. No potential association between study drug therapy and QTc prolongation was apparent. Only 1 subject, who was in the doripenem group, had both a QTcB interval value of > 500 msec and increase from baseline of > 60 sec; this subject did not have any cardiac TEAEs. No subjects had such a QTcF value.

CONCLUSIONS: