This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. SYNOPSIS

SPONSOR COMPANY NAME: Cubist Pharmaceuticals, Inc.	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:** **VOLUME:** **PAGE:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT: CXA-101 for injection **NAME OF ACTIVE INGREDIENT:** CXA-101		

TITLE OF STUDY:

A Multicenter, Double-blind, Randomized, Phase 2 Study to Compare the Safety and Efficacy of Intravenous CXA-101 and Intravenous Ceftazidime in Complicated Urinary Tract Infection, Including Pyelonephritis

INVESTIGATORS AND STUDY CENTERS:

A total of 20 sites, (6 in the United States [US], and 7 each in Germany and Poland) enrolled 129 subjects.

PUBLICATION (REFERENCE):

None at the time of this report. Important publications are cited in this report.

STUDIED PERIOD:

Initiation Date (first subject enrolled): 17 August 2009
Completion Date (last subject completed): 11 March 2010

PHASE OF DEVELOPMENT:

Phase 2

PRIMARY OBJECTIVE:

- To determine the microbiological response at 6 to 9 days after treatment with CXA-101 in subjects with complicated urinary tract infection (cUTI) including pyelonephritis following a 7- to 10-day treatment regimen.

SECONDARY OBJECTIVES:

- Evaluate the safety of CXA-101 in subjects with cUTI including pyelonephritis;
- Determine the clinical response at 6 to 9 days after treatment in subjects with cUTI including pyelonephritis following a 7- to 10-day treatment regimen;
- Evaluate the population plasma pharmacokinetic (PK) profile in subjects with cUTI.

METHODOLOGY:

This was a Phase 2, multicenter, prospective, randomized, double-blind, comparative efficacy and safety study of intravenous (IV) CXA-101 (1000 mg every 8 hours [q8h]) versus IV ceftazidime (1000 mg q8h) for 7 to 10 days in hospitalized adult subjects with cUTI including pyelonephritis. Block randomization using an interactive voice response system, stratified by complicated lower UTI (cLUTI) or pyelonephritis, was used to assign subjects (2:1) to the IV CXA-101 or IV ceftazidime groups.

Urine specimens for culture were collected from all patients within 48 hours prior to receipt of the first dose of study drug. Blood cultures were required if subjects presented with pyelonephritis, were suspected to have bacteremia or had indwelling catheters and their baseline urine specimen was obtained from the indwelling urinary catheter. Post therapy urine specimens for culture were required to document eradication of the baseline pathogen(s).

The minimum duration of study therapy was 7 days. No switch to oral antibiotics was permitted in this study. Outpatient parenteral antibiotic therapy was allowed in a subset of pre-approved sites and only in patients who met strict protocol specified criteria. The maximum duration of therapy was 10 days with the exception of subjects post removal of an indwelling catheter that was present at baseline, subjects undergoing bladder instrumentation, and subjects following successful treatment of a bladder obstruction.

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Clinical and microbiological response assessments were performed at the end of therapy (EOT), test of cure (TOC), and late follow up (LFU) visits (21 -28 days after the EOT). Safety assessments were performed regularly throughout the study.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED):

120 planned: 80 CXA-101 and 40 ceftazidime

129 randomized: (86 CXA-101, 43 ceftazidime); 127 received study drug (modified intent-to-treat [MITT]), 103 treated subjects had at least 1 qualifying baseline pathogen (microbiological MITT [mMITT]), and 82 were microbiologically evaluable (ME) at TOC.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Hospitalized male or female subjects 18 to 90 years inclusive, with a creatinine clearance (CrCl) $\geq$ 50 mL/min, with clinical signs and/or symptoms of cUTI (including pyelonephritis) and a study qualifying pre-treatment urine specimen (obtained within 48 hours prior to receipt of first dose of study drug) were eligible for the study. Isolation of an acceptable bacterial uropathogen with a colony count $\geq 10^5$ colony forming unit (CFU)/mL from the baseline urine specimen was required for a subject to continue receiving study drug.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER(S):

CXA-101 for Injection, 1000 mg, administered by IV infusion over 1 hour every 8 hours (q8h). Lot number of CX-101: [redacted] for all sites and also [redacted] for sites in Germany and Poland.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER(S):

Ceftazidime for Injection, 1000 mg administered by IV infusion over 1 hour q8h. Lot number of ceftazidime: [redacted] for sites in the US and [redacted] for sites in Germany and Poland.

DURATION OF TREATMENT:

7 to 10 days (exceptions: subjects post removal of indwelling catheter that was present at baseline, subjects undergoing bladder instrumentation and subjects following successful treatment of bladder obstruction)

CRITERIA FOR EVALUATION:

EFFICACY:

Efficacy analyses were conducted on the mMITT and ME populations:

- mMITT population: comprised of all subjects in the MITT population who had at least one acceptable causative pathogen from a study-qualifying pretreatment baseline urine specimen.
- ME population: comprised of all subjects in the mMITT population who also met pre-specified criteria including confirmation of the cUTI, receipt of study treatment as randomized for at least 5 days, compliance with dosing, availability of a qualified urine culture at the TOC visit to assess response, and who did not receive potentially effective non-study antibiotics. Other criteria were also applied (see Section **Error! Reference source not found.**).

Primary Efficacy Endpoint: Per-subject microbiological eradication rate at the TOC visit in the mMITT and ME populations

Secondary Efficacy Endpoint: Per-subject clinical response rate at the TOC visit in the mMITT and ME populations

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SAFETY:

Safety analyses were conducted on the MITT population which comprised all randomized subjects who received any amount of study drug. Safety was assessed via monitoring of adverse events (AEs), vital signs, physical examinations, and laboratory data (including serum chemistries, hematology, coagulation, and urinalysis).

STATISTICAL METHODS:

Inferential statistical analyses were not conducted.

The number and percentage of subjects determined to be a microbiological cure, microbiological failure, or indeterminate (mMITT only) at the TOC visit are tabulated. A two-sided exact 95% confidence interval (CI) for the per-subject microbiologic cure rate in each treatment group, calculated using the Clopper-Pearson method, is presented. Similarly, the number and percentage of subjects determined to be a clinical cure, clinical failure, or indeterminate (mMITT only) at the TOC visit are tabulated with the two-sided exact 95% CI. Concordance between clinical and microbiological response was assessed. Microbiological and clinical cure rates at the TOC visit are tabulated by baseline pathogen, geographic region and cUTI diagnosis. Emergent infections, microbiological recurrence, and clinical relapse are summarized.

Treatment-emergent adverse events (TEAE) are tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term overall and by severity (mild, moderate, and severe); Treatment-related TEAEs, serious adverse events (SAEs) and adverse events leading to discontinuation of study treatment also are tabulated.

Descriptive statistics at each study visit and the change from baseline to all study visits are presented for clinical laboratory data and vital signs. Shifts in toxicity grade (from the Division of Microbiology and Infectious Diseases Adult Toxicity Scale, November 2007) from baseline to Day 3, EOT, and TOC are presented for selected laboratory parameters. The number and percentage of subjects with an elevated transaminase level (> 3 × upper limit of normal [ULN], > 5 × ULN, and > 10 × ULN) or an elevated bilirubin level (> 1.5 × ULN and > 2 × ULN) are presented by study visit. A listing of subjects who met the laboratory criteria for Hy's rule is provided. Potentially clinically significant (PCS) vital signs values were defined and the incidence of PCS vital signs is summarized by study visit and treatment group.

SUMMARY AND CONCLUSIONS:

SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

In general, the demographic and baseline characteristics of the treatment groups were similar in the MITT, mMITT, and ME populations and were comparable between the 2 treatment groups.

In the MITT population, mean ages were 57 and 63 years in the CXA-101 and ceftazidime groups, respectively; age ranged from 19 to 88 years across the 127 subjects. In the CXA-101 group, 45.9% of the subjects were 65 years of age or older compared with 66.7% in the ceftazidime group. Most subjects in both treatment groups were male (50.6% and 61.9% in the CXA-101 and ceftazidime groups, respectively) and White (94.1% and 100%, respectively). Findings were similar in the mMITT and ME populations.

The distribution of subjects by baseline cUTI diagnosis was similar in the 2 treatment groups in the MITT population with 65.9% and 69.0% of subjects in the CXA-101 and ceftazidime groups, respectively, having cLUTI and 34.1% and 31.0%, respectively, having pyelonephritis. Following blinded review for subject evaluability, a higher proportion of subjects with cLUTI were excluded from the ME analysis set in the ceftazidime group resulting in an imbalance between the 2 treatment groups for cUTI diagnosis (72.7% and 59.3% with cLUTI in the CXA-101 and ceftazidime groups, respectively).

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As expected, *Escherichia coli* was the most common uropathogen, reported in 66.2% and 71.1% of subjects in the CXA-101 and ceftazidime groups, respectively, in the mMITT population. Six subjects, including 4 in the CXA-101 group (3 subjects with pyelonephritis and 1 with complicated lower urinary tract infection [cLUTI]) and 2 subjects in the ceftazidime group (1 with pyelonephritis and 1 with cLUTI), had bacteremia at baseline; all blood isolates were *E. coli*.

SUMMARY OF EFFICACY:

Both study drugs were comparably effective in achieving high microbiologic cure rates across the different analysis populations. In the mMITT population, microbiologic cure rates at TOC were 83.1% and 76.3% in the CXA-101 and ceftazidime groups, respectively, and in the ME population were 85.5% and 92.6%, respectively.

As expected, microbiological cure rates among subjects with cLUTI were lower than in subjects with pyelonephritis but were comparable between the treatment groups. In the mMITT population, microbiological cure rates at TOC were 81.8% and 73.1% in the CXA-101 and ceftazidime groups, respectively, for subjects with cLUTI, and 85.7% and 83.3%, respectively, for subjects with pyelonephritis.

Both study drugs showed excellent activity against *E. coli* with eradication rates at TOC of 91.7% in the CXA-101 group and 94.7% in the ceftazidime group.

As with microbiological response, both study drugs were comparably effective at achieving high clinical response rates at TOC: 90.8% and 92.1% in the CXA-101 and ceftazidime groups, respectively, in the mMITT population, and 92.7% and 100%, respectively, in the ME population.

New infections were reported in 7 (10.8%) subjects included in the mMITT population in the CXA-101 group and 2 (5.3%) of subjects in the ceftazidime group. New infections in the CXA-101 group were caused by *Enterococcus faecalis* (4 subjects), *E. coli* (2 subjects), and *Proteus mirabilis* (1 subject) and in the ceftazidime group by *Candida glabrata* and *Klebsiella pneumoniae*. One subject in each treatment group experienced a superinfection: *C. albicans* in the CXA-101 group and *E. faecalis* in the ceftazidime group.

The sustained clinical cure rates at the LFU visit were 98.0% for CXA-101 and 92.6% for ceftazidime. Microbiological recurrence was uncommon, reported in 6.4% and 12.0% in the CXA-101 and ceftazidime groups, respectively. The most frequent uropathogen isolated from subjects with microbiological recurrence was *E. coli*.

SUMMARY OF SAFETY:

The most commonly reported TEAEs (i.e., reported in 2 or more of subjects in either treatment group) regardless of relationship to study drug were constipation (9.4% and 4.8% in the CXA-101 and ceftazidime groups, respectively), sleep disorder (7.1% and 4.8%, respectively), nausea (5.9% and 0%, respectively), headache (5.9% and 0%, respectively), diarrhea (3.5% and 7.1%, respectively), insomnia (4.7% and 0%, respectively), pyrexia (3.5% and 2.4%, respectively), infusion site irritation (3.5% and 0%, respectively), abdominal pain (2.4% and 2.4%, respectively), back pain (2.4% and 2.4%, respectively), and infusion site erythema, infusion site extravasation, infusion site swelling, flank pain, urinary tract infection, hypertension, phlebitis, and cough (each 2.4% and 0%, respectively).

The majority of TEAEs were assessed by the Investigators as mild to moderate in severity. Four subjects, including 2 in each treatment group, had TEAEs reported that were assessed as severe including abdominal pain and worsening anemia in the CXA-101 group and chest pain and aggression in the ceftazidime group. All severe events were assessed as unrelated to study treatment.

There were no deaths in either treatment group. One SAE was reported during the study. This subject, in the

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CXA-101 group, who was initially successfully treated for pyelonephritis, relapsed 16 days post-treatment and required re-hospitalization. The subject recovered following antibiotic treatment and was subsequently discharged. The event was assessed as unrelated to study treatment.

Two subjects discontinued study drug due to adverse events, including 1 subject in the CXA-101 group whose CrCl decreased to <50 mL/min on Day 3 and 1 subject in the ceftazidime group who was discontinued due to vomiting and diarrhea.

No unexpected clinically significant changes were noted for hematology or coagulation parameters; results over time were similar in the CXA-101 and ceftazidime groups. The incidence and pattern of liver enzyme elevation and resolution were consistent with known experience with β-lactam therapy. No subject met the criteria for Hy's rule. There was an imbalance in the incidence of hyperglycemia severity grade shifts observed in the CXA-101 group; the shifts in serum glucose were transient, especially in non-diabetic patients, and serum glucose values were mostly below the upper limit of normal for non-fasting subjects.

No unexpected clinically significant changes in vital signs were noted.

CONCLUSIONS:

These results show the therapeutic effectiveness of the 1000 mg dose of CXA-101 administered IV q8h in adults with cUTI. The data provide evidence of its safety compared to ceftazidime and fully support its continued development as a useful therapeutic agent for the treatment of patients with serious infections

DATE OF THE REPORT: 8 July 2010