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# Phase 2 Study of Ceftaroline versus Standard Therapy in Treatment of Complicated Skin and Skin Structure Infections▽

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**Ceftaroline, the bioactive metabolite of ceftaroline fosamil (previously PPI-0903, TAK-599), is a broad-spectrum cephalosporin with potent in vitro activity against multidrug-resistant gram-positive aerobic pathogens, including methicillin-resistant *Staphylococcus aureus*. A randomized, observer-blinded study to evaluate the safety and efficacy of ceftaroline versus standard therapy in treating complicated skin and skin structure infections (cSSSI) was performed. Adults with cSSSI, including at least one systemic marker of inflammation, were randomized (2:1) to receive intravenous (i.v.) ceftaroline (600 mg every 12 h) or i.v. vancomycin (1 g every 12 h) with or without adjunctive i.v. aztreonam (1 g every 8 h) for 7 to 14 days. The primary outcome measure was the clinical cure rate at a test-of-cure (TOC) visit 8 to 14 days after treatment. Secondary outcomes included the microbiological success rate (eradication or presumed eradication) at TOC and the clinical relapse rate 21 to 28 days following treatment. Of 100 subjects enrolled, 88 were clinically evaluable; the clinical cure rate was 96.7% (59/61) for ceftaroline versus 88.9% (24/27) for standard therapy. Among the microbiologically evaluable subjects (i.e., clinically evaluable and having had at least one susceptible pathogen isolated at baseline), the microbiological success rate was 95.2% (40/42) for ceftaroline versus 85.7% (18/21) for standard therapy. Relapse occurred in one subject in each group (ceftaroline, 1.8%; standard therapy, 4.3%). Ceftaroline exhibited a very favorable safety and tolerability profile, consistent with that of marketed cephalosporins. Most adverse events from ceftaroline were mild and not related to treatment. Ceftaroline holds promise as a new therapy for treatment of cSSSI and other serious polymicrobial infections.**

Selection of an appropriate treatment option for many skin and skin structure infections (SSSI) has become increasingly difficult as *Staphylococcus aureus* and other causative pathogens have developed increasing resistance to commonly used antimicrobial agents. Since the first report of methicillin-resistant *S. aureus* (MRSA) infection in the United States in 1968, the proportion of *S. aureus* isolates from the United States resistant to methicillin has risen continuously (3, 10). The appearance of community-associated MRSA has further compounded this therapeutic challenge (11, 13, 17).

Ceftaroline (also referred to as PPI-0903M, T-91825; Cerexa, Inc., Alameda, CA) is the bioactive metabolite of ceftaroline fosamil (PPI-0903, TAK-599), an *N*-phosphonoamino water-soluble cephalosporin prodrug. Ceftaroline exhibits time-dependent, bactericidal activity in vitro and in vivo (1; H. S. Sader, P. R. Rhomberg, and R. N. Jones, poster F-334, presented at the 44th Intersci. Conf. Antimicrob. Agents Chemother., 2004). Unlike marketed β-lactam antibiotics, ceftaroline is very active in vitro against MRSA, *S. aureus* intermediately susceptible to vancomycin, and methicillin-resistant coagulase-negative staphylococci ($MIC_{90}$ ≤1 μg/ml) (15; H. S. Sader, G. Moet, T. R. Fritsche, and R. N. Jones, poster E-0121, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother., 2006). Ceftaroline's in vitro spectrum also includes streptococci (including ceftriaxone- and penicillin-resistant *Streptococcus pneumoniae*), β-lactam-resistant *Haemophilus influenzae*, *Moraxella catarrhalis*, the majority of pathogenic enteric bacilli, and some gram-positive anaerobic bacteria (15; S. Mushtaq, M. Warner, K. Kaniga, Y. Ge, and D. M. Livermore, poster F-1451, presented at the 45th Intersci. Conf. Antimicrob. Agents Chemother., 2005; H. S. Sader, G. Moet, T. R. Fritsche, and R. N. Jones, poster E-0121, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother., 2006).

In previous phase 1 studies with healthy subjects, ceftaroline was safe and showed a predictable pharmacokinetic profile (Y. Ge, R. Redman, L. Floren, S. Liao, and M. Wikler, poster A-1936, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother; Y. Ge, R. Redman, L. Floren, S. Liao, and M. Wikler, poster A-1937, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother.; Y. Ge, D. Thye, S. Liao, and G. H. Talbot, poster A-1939, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother.). As part of the continuing clinical development of ceftaroline, a phase 2 study was performed to evaluate its safety and efficacy versus that of a standard therapy regimen in the treatment of complicated SSSI (cSSSI).

(The results of this study were presented in part at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 2006).

## MATERIALS AND METHODS

This randomized, observer-blinded, multinational phase 2 clinical study was conducted at 15 clinical sites in the United States, South America, South Africa, and Russia. The study protocol and the informed consent form were approved by the appropriate local institutional review board/ethics committee prior to implementation, and the study was conducted in accordance with good clinical practice, the Declaration of Helsinki, and the requirements of local authorities.

Adults (≥18 years old) with an SSSI requiring initial hospitalization and treatment with intravenous (i.v.) antimicrobials were eligible for study partici-

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pation if the SSSI involved deeper soft tissue and/or required significant surgical intervention (e.g., surgical or traumatic wound infection, major abscess, infected ulcer, or deep and extensive cellulitis) or had developed on a lower extremity in a subject with diabetes mellitus or well-documented peripheral vascular disease. The subjects were further required to have at least two local signs of cSSSI (purulent or seropurulent drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, swelling/induration) plus at least one systemic sign (oral temperature of >38°C, white blood cell count of >10,000/mm$^3$, >10% immature neutrophils).

Reasons to exclude subjects from participation included hypersensitivity reactions to any β-lactam antibiotic or vancomycin, history of red man syndrome or epilepsy, more than a single prior dose of a nonstudy antimicrobial within the 96 h prior to randomization unless there was clear evidence of failure, suspected anaerobic pathogens or *Pseudomonas aeruginosa*, ischemic ulcer due to peripheral vascular disease, decubitus ulcer, diabetic foot ulcer present for more than 7 days, third-degree burn or a burn covering more than 5% of the total body surface area, human or animal bites, necrotizing fasciitis, AIDS, or any significant or life-threatening organ or systemic condition or disease. In addition, pregnant or nursing women or those of childbearing potential not using highly effective birth control were excluded from the study.

Once enrolled, the subjects were randomized (2:1) to receive ceftaroline (600 mg infused over 60 min every 12 h) or i.v. standard therapy for 7 to 14 days. Up to 21 days' treatment was permitted for subjects with a severe infection that required extended i.v. antibiotic therapy, but only with the approval of the medical monitor for the study. The subjects randomized to standard therapy initially received vancomycin (1 g every 12 h). When the baseline culture indicated a gram-positive organism that was susceptible to a penicillinase-resistant penicillin (PRP; e.g., *Streptococcus pyogenes* or methicillin-susceptible *S. aureus* [MSSA]), therapy with vancomycin could be switched to a PRP within the first 72 h after initiation of therapy. If the presence of a gram-negative pathogen was suspected at baseline, concomitant administration of aztreonam (1 g every 8 h) was allowed only in the standard therapy group. Use of oral antibiotic therapy was not allowed during the study. The investigators evaluating clinical response and safety were blinded to the treatment allocations.

Clinical assessments were performed at baseline (within 24 h prior to study drug administration) and daily through the end-of-therapy (EOT) visit. The test-of-cure (TOC) visit assessments were conducted 8 to 14 days after administration of the last dose of the study drug. At the late follow-up (LFU) visit (21 to 28 days after the last dose of the study drug), subjects cured at TOC were assessed for relapse of the cSSSI. At each evaluation, investigators assessed the extent of the cSSSI, surgical procedures performed on the infection site, physical examination and vital signs, laboratory tests (not at the LFU visit), concomitant medications, and adverse events (AEs). In addition, a standard 12-lead electrocardiogram (ECG) was performed at baseline, day 3, EOT, and TOC. Microbiological assessments included collection of infection site specimens for Gram's stain and culture at baseline, to be repeated when medically indicated, and blood culture at baseline. All subjects were monitored for the occurrence of AEs and serious AEs (SAEs).

No analysis was performed in the intention-to-treat (ITT) population. The modified ITT (MITT) analysis population comprised randomized (ITT) subjects who received any amount of the study drug; this population was used for safety analyses. The clinical MITT (cMITT) population comprised all subjects in the MITT population with a confirmed cSSSI. The microbiological MITT (mMITT) population comprised all subjects who had at least one bacterial pathogen identified from a blood culture or a culture of an adequate microbiological sample from the cSSSI site at baseline. The clinically evaluable (CE) population comprised all subjects in the cMITT population who had no confounding factors that interfered with the assessment of outcome. In addition, the subjects in the CE population must have received 80 to 120% of the intended study drug doses, received at least 48 h (for failure evaluation) or 96 h (for success evaluation) of therapy, and had the outcome assessment performed within 7 to 20 days after the end of therapy or were determined to be a clinical failure at an earlier time point. The microbiologically evaluable (ME) population comprised all subjects in the CE population who met the criteria for inclusion in the mMITT population and whose baseline pathogen was subjected to antimicrobial susceptibility testing. At least one of the isolates had to be susceptible to at least one of the study drugs received.

The primary efficacy outcome measure was the clinical cure rate at the TOC visit in the CE and cMITT populations (co-primary outcomes). The subjects were considered clinically cured if the blinded investigator determined that there had been resolution of all signs and symptoms of the cSSSI or improvement of the infection such that no further antimicrobial therapy was necessary. Failure was defined as either (i) persistence, incomplete resolution, or worsening of signs and symptoms of the cSSSI that required further antimicrobial therapy; (ii) an unplanned surgical intervention performed as an adjunctive or follow-up therapy due to failure of the study drug to adequately treat the infection; (iii) new signs and symptoms associated with the original cSSSI or a new cSSSI at the same anatomical site; (iv) requirement for additional antibiotic therapy to treat the cSSSI, including oral step-down therapy; (v) a switch to a PRP >72 h after initiation of therapy with the study drug for subjects receiving vancomycin whose baseline isolate was a methicillin-susceptible pathogen; or (vi) death wherein cSSSI was considered causative.

The clinical cure rate at the EOT visit was assessed to support the findings at the TOC visit. The microbiological response at the TOC visit was evaluated for the ME and mMITT populations. The favorable outcomes per pathogen were eradication and presumed eradication. Safety analyses were conducted with the MITT population.

This exploratory study was not powered for inferential statistical analyses. However, descriptive statistics were provided for the efficacy and safety analyses; when appropriate, 95% confidence intervals were calculated for observed rates of response to treatment using the method described by Clopper and Pearson (4). With the observed sample size and response rates, there was only a 40% power to detect the superiority of ceftaroline over standard therapy, assuming a two-sided alpha of 0.05.

TABLE 1. Disposition of subjects

| Subject disposition | No. (%) of subjects in indicated treatment group: | |
|---|---|---|
| | Ceftaroline | Standard therapy |
| Subjects randomized | 67 | 33 |
| Treated (MITT population) | 67 (100.0) | 32 (97.0) |
| Not treated | 0 (0.0) | 1 (3.0) |
| Subjects completing study through EOT | 65 (97.0) | 29 (87.9) |
| Subjects completing study through TOC | 61 (91.0) | 28 (84.8) |
| Subjects completing study through LFU | 59 (88.1) | 26 (78.8) |
| Subjects terminating from study before LFU | 8 (11.9) | 7 (21.2) |
| Primary reason for early discontinuation of study drug or withdrawal from study | | |
| Randomized, did not receive study drug | 0 (0.0) | 1 (14.3) |
| At request of subject, investigator, or sponsor[a] | 1 (12.5) | 0 (0.0) |
| Withdrew consent | 2 (25.0) | 2 (28.6) |
| Lost to follow-up | 3 (37.5) | 1 (14.3) |
| Noncompliance with study drug | 0 (0.0) | 1 (14.3) |
| Unsatisfactory response | 0 (0.0) | 1 (14.3) |
| ≥100% increase of baseline creatinine | 0 (0.0) | 1 (14.3) |
| QTc interval of >500 ms[b] | 1 (12.5) | 0 (0.0) |
| Other adverse event[c] | 1 (12.5) | 0 (0.0) |
| Subjects in cMITT population | 67 (100.0) | 32 (97.0) |
| Subjects in mMITT population | 51 (76.1) | 27 (81.8) |
| Subjects in CE population | 61 (91.0) | 27 (81.8) |
| Subjects in ME population | 42 (62.7) | 21 (63.6) |

[a] Postrandomization, the subject was determined to have met the exclusion criterion of a seizure history and was withdrawn at the request of the sponsor.

[b] Subsequent centrally read ECGs showed the baseline QTc's (Bazett's correction) to be 470, 463, and 448 msec, with a study day 3 predose QTc (Bazett) of 501 msec.

[c] Recurrence of infection, which was recorded as an SAE.

## RESULTS

**Baseline characteristics.** The disposition and distribution of the subjects by analysis population are shown in Table 1. The ceftaroline and standard therapy groups were balanced for baseline subject characteristics in the MITT population: mean age (41.6 versus 44.0 years, respectively), gender (55.2% versus 59.4% males, respectively), race/ethnicity, and infection type.

TABLE 2. Types of infection among subjects in study

| Infection type | No. (%) of subjects receiving indicated treatment: | |
|---|---|---|
| | Ceftaroline ($n$ = 67) | Standard therapy ($n$ = 32) |
| Major abscess | 30 (44.8) | 16 (50.0) |
| Deep, extensive cellulitis | 23 (34.3) | 12 (37.5) |
| Infected wound | 7 (10.4) | 1 (3.1) |
| Lower extremity cSSSI[a] | 4 (6.0) | 0 (0.0) |
| Infected ulcer | 1 (1.5) | 0 (0.0) |
| Infected bite | 0 (0.0) | 2 (6.3) |
| Infected burn | 0 (0.0) | 0 (0.0) |
| Other | 2 (3.0) | 1 (3.1) |
| Total | 67 (100.0) | 32 (100.0) |

[a] Diabetes mellitus or peripheral vascular disease present.

The most common infection types were major abscess, deep extensive cellulitis, and infected wounds (Table 2).

**Course of treatment.** The mean length of therapy was 7.8 days (range, 0.4 to 19.5 days) in the ceftaroline group and 8.0 days (range, 2.0 to 20.5 days) in the standard therapy group. Only one subject was switched from vancomycin to a PRP (cloxacillin). Adjunctive aztreonam therapy was given for a mean of 5.1 days (range, 1.0 to 12.1 days) to a total of seven subjects in the standard therapy group.

**Efficacy.** Clinical cures were achieved at TOC in 96.7% of CE subjects who received ceftaroline and 88.9% who received standard therapy (Table 3). Similar findings were observed at EOT (98.4% and 96.3%, respectively). Relapse after cure at TOC was documented in one (1/57, 1.8%) ceftaroline subject and one standard therapy subject (1/23, 4.3%) who returned for LFU. Results at EOT, TOC, and LFU for the cMITT, mMITT, and ME populations were consistent with those for the CE subjects. Among the ME subjects, the microbiological success rate was 95.2% (40/42) for ceftaroline versus 85.7% (18/21) for standard therapy. The clinical cure rate by pathogen for the CE subjects is provided in Table 4.

Six subjects in each treatment group had MRSA identified as a baseline pathogen, and five of these subjects from each group were included in the ME population. Five of five standard therapy subjects and four of five ceftaroline subjects with MRSA infection achieved clinical cures. The single subject in the ceftaroline group who was considered a failure was a 45-year-old Hispanic male with a cSSSI in his left foot associated with a diabetic foot ulcer. His relevant medical history included diabetes mellitus, peripheral vascular disease, osteomyelitis, tobacco and alcohol use, and hepatitis C infection. At entry, the wound was deep, with moderate erythema, moderate swelling, severe tenderness, moderate warmth, and mild fluctuance measuring 14 × 20 cm. The infection improved so markedly with therapy that ceftaroline was discontinued after 13 days of treatment, and the patient was assessed as a clinical cure at EOT. However, 8 days later, the subject was readmitted with worsened symptoms, including left foot osteomyelitis with overlying cellulitis, and eventually underwent excision of the fifth metatarsal of the left foot approximately 2 weeks later.

TABLE 3. Primary outcomes at TOC visit

| Assessment of investigator | No. (%) of CE population receiving indicated treatment: | | No. (%) of cMITT population receiving indicated treatment: | |
|---|---|---|---|---|
| | Ceftaroline ($n$ = 61) | Standard therapy ($n$ = 27) | Ceftaroline ($n$ = 67) | Standard therapy ($n$ = 32) |
| Cure | 59 (96.7) | 24 (88.9) | 59 (88.1) | 26 (81.3) |
| Failure | 2 (3.3) | 3 (11.1) | 2 (3.0) | 3 (9.4) |
| Indeterminate[a] | NA | NA | 6 (9.0) | 3 (9.4) |
| 95% CI | 88.7–99.6 | 70.8–97.6 | 77.8–94.7 | 63.6–92.8 |

[a] By definition, responses in the CE population cannot be indeterminate. NA, not applicable.

TABLE 4. Clinical cure rate by pathogen

| Organism | Clinical cure rate[a] (%) of CE population receiving indicated treatment: | |
|---|---|---|
| | Ceftaroline ($n$ = 61) | Standard therapy ($n$ = 27) |
| *S. aureus* | 29/30 (96.7) | 16/17 (94.1) |
| MSSA | (25/25) (100) | 11/12 (91.7) |
| MRSA | 4/5 (80) | 5/5 (100) |
| Streptococci | | |
| *S. pyogenes* | 8/8 (100) | 2/2 (100) |
| *Viridans* group streptococcus | 3/3 (100) | 0 |
| *S. intermedius* | 3/3 (100) | 0 |
| *S. agalactiae* | 1/1 (100) | 1/2 (50.0) |
| *S. anginosus* | 1/1 (100) | 0 |
| *S. anginosus*/"*milleri*" | 1/1 (100) | 0 |
| *S. oralis* | 1/1 (100) | 0 |
| Group C streptococcus | 1/1 (100) | 0 |
| *Staphylococcus haemolyticus* | 1/1 (100) | 0 |
| *Peptococcus prevotii* | 1/1 (100) | 0 |
| *Pediococcus* sp. | 1/1 (100) | 0 |
| *Enterococcus faecalis* | 1/1 (100) | 0 |
| *Enterococcus faecium* | 0/1 (0) | 0 |
| *Enterobacteriaceae* | | |
| *Enterobacter cloacae* | 1/1 (100) | 0 |
| *Klebsiella pneumoniae* | 1/1 (100) | 0 |
| *Proteus mirabilis* | 0/1 (0) | 1/1 (100) |
| *Citrobacter freundii* | 0/1 (0) | 0 |

[a] Ratio of number of subjects cured to number of subjects in study group.

In the ME population, 4.8% (2/42) of subjects in the ceftaroline group and 14.3% (3/21) in the standard therapy group had bacteremia at baseline, as documented by blood cultures. Bacteremia was caused by either MSSA (one subject) or MRSA (one subject) in the ceftaroline group and by MSSA (two subjects) or *Streptococcus agalactiae* (one subject) in the standard therapy group. The subject with *S. agalactiae* bacteremia was not cured with standard therapy. Both bacteremic ceftaroline subjects were cured.

**Safety and tolerability.** The proportion of subjects in the MITT group ($n$ = 99) experiencing an AE during the study was similar between the treatment groups: 61.2% (ceftaroline) versus 56.3% (standard therapy). For ceftaroline, the majority (138/157, 87.9%) of AEs reported were mild, versus 70.8% (63/89) for standard therapy. For both treatment groups, only three AEs (gangrene, recurrent skin infection, and interstitial nephritis) were assessed as severe by the investigators and were also considered to be SAEs (discussed below). Related AEs

TABLE 5. Most common related adverse events[a]

| Adverse event | No. (%) of MITT population receiving indicated treatment: | |
|---|---|---|
| | Ceftaroline ($n$ = 67) | Standard therapy ($n$ = 32) |
| Crystals in urine | 6 (9.0) | 5 (15.6) |
| Elevated level of blood creatine phosphokinase | 5 (7.5) | 2 (6.3) |
| Elevated level of alanine aminotransferase | 4 (6.0)) | 4 (12.5) |
| Elevated level of aspartate aminotransferase | 4 (6.0) | 3 (9.4) |
| Headache | 4 (6.0) | 2 (6.3) |
| Insomnia | 4 (6.0) | 2 (6.3) |
| Nausea | 4 (6.0) | 0 (0.0) |
| Rash[b] | 1 (1.5) | 2 (6.3) |

[a] >5% in either treatment group. Infusion-associated AEs are discussed in the text.

[b] Does not include one subject who reportedly had "mononucleosis syndrome" but for whom the major manifestation was a maculopapular rash.

that occurred in at least 5% of subjects in either treatment group are shown in Table 5. For both treatment groups, the presence of urinary crystals on routine urinalysis was the most frequently reported AE. These crystals were composed of amorphous material or calcium oxalate and did not suggest the presence of crystallized drug. Increased levels of creatine phosphokinase observed in samples from both treatment groups were also exclusively a laboratory finding, unaccompanied by clinical evidence of muscle or cardiac signs or symptoms. The related events of nausea in four (6.0%) ceftaroline subjects were assessed as mild (three, 4.5%) or moderate (one, 1.5%) by the investigators. Two (3.0%) ceftaroline subjects discontinued therapy due to a related AE, as did one (3.1%) standard therapy subject.

Five SAEs were reported in five (5.1%) subjects. In the ceftaroline group, the unrelated SAEs of recurrent skin infection, pulmonary edema, and gangrene in the right toe were reported by three (4.5%) subjects. In the standard therapy group, interstitial nephritis (related) and reinfection (not related) were reported by two (6.3%) subjects. All SAEs resolved. No death occurred during the study.

Ceftaroline infusion was well tolerated, with two (3.0%) subjects reporting infusion site pain, one (1.5%) subject reporting swelling, and one (1.5%) subject reporting thrombosis at the infusion site. In the standard therapy group, three (9.4%) subjects reported infusion site phlebitis, one (3.1%) subject reported infusion site pruritus and erythema, and one (3.1%) subject reported infusion site swelling and erythema. In addition, no subject in the ceftaroline group experienced a generalized infusion reaction, whereas three (9.4%) subjects in the standard therapy group experienced mild, related AEs suggestive of red man syndrome. Overall, four (6.0%) ceftaroline subjects and eight (25.0%) standard-therapy subjects experienced an infusion-associated local or systemic AE, of which two (3.0%) and eight (25.0%), respectively, were considered related to study medication.

No trends causing concern were observed in any laboratory test values of ceftaroline subjects compared with standard therapy subjects, including a comprehensive metabolic panel. Digitally acquired and centrally analyzed ECG data showed no trend to an increase in the mean heart rate-corrected QT interval (QTc) or the number of QTc outlier values, which would have suggested a QTc prolongation effect of ceftaroline.

## DISCUSSION

From 1999 to 2000, an estimated 125,969 hospitalizations with a diagnosis of MRSA infection occurred annually in the United States, accounting for 3.95 of every 1,000 hospital discharges (12). MRSA is a worldwide problem, with the rate of infections due to MRSA continuing to rise in many countries (6). Furthermore, cSSSI developing in patients with diabetes mellitus and other major comorbidities may involve not only staphylococci, including MRSA, but also gram-negative pathogens (7). Many newer or investigational antibiotics (e.g., daptomycin, linezolid, dalbavancin, telavancin, oritavancin) are effective against only gram-positive pathogens (2, 8, 9, 14; R. G. Corey, M. Stryjewski, W. O'Riordan, V. Fowler, A. Hopkins, M. Kitt, and S. Barriere, poster LB-17, presented at the 44th Ann. Meet. Infect. Dis. Soc. Am.). Although tigecycline, a glycylcycline recently approved for treatment of cSSSI, has a broader spectrum of activity, its use may be limited by substantial rates of nausea and vomiting (16). New antibiotics that are effective against both MRSA and gram-negative pathogens and that have excellent safety and tolerability profiles would be welcome additions to the therapeutic armamentarium for SSSI and other community and hospital infections.

In this phase 2 cSSSI study, the investigational cephalosporin ceftaroline was safe, well-tolerated, and efficacious in the treatment of cSSSI. The efficacy results were consistent across all analyzed populations and outcomes and for clinically relevant cSSSI pathogens. As might be expected for a member of the cephalosporin class of antimicrobials, no major safety issues were identified. Ceftaroline was well tolerated, with the majority of AEs reported as mild. Gastrointestinal and venous tolerabilities were good, and in no case did poor tolerability limit treatment or result in premature discontinuation.

Currently marketed β-lactam antimicrobials, including cephalosporins and carbapenems, are characterized by poor in vitro and in vivo activity against MRSA and other methicillin-resistant staphylococci. In contrast to these older agents, ceftaroline exhibits excellent activity against these organisms, including MRSA and methicillin-resistant coagulase-negative staphylococci, in preclinical in vitro and in vivo models (1, 15; C. Jacqueline, O. Grossi, V. Le Mabecque, D. Bugnon, J. Caillon, Y. Ge, and G. Potel, poster B-1819, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother.; H. S. Sader, G. Moet, T. R. Fritsche, and R. N. Jones, poster E-0121, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother.). This enhanced activity correlates well with the very high level of binding of ceftaroline to penicillin-binding protein 2a, the altered bacterial cell wall synthesis enzyme responsible for resistance to other β-lactams (data on file; Cerexa, Inc.). Phase 1 studies with ceftaroline determined that a dosing regimen of 600 mg i.v. every 12 h produces pharmacokinetic exposures achieving a clinically relevant percentage of time above the MIC, based on current pharmacokinetic/pharmacodynamic principles for cephalosporin antibiotics (5; Y. Ge, R. Redman, L. Floren, S. Liao, and M. Wikler, poster A-1936,

presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother.; Y. Ge, R. Redman, L. Floren, S. Liao, and M. Wikler, poster A-1937, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother.; Y. Ge, D. Thye, S. Liao, and G. H. Talbot., poster A-1939, presented at the 46th Intersci. Conf. Antimicrob. Agents Chemother.)

The current study included a robust standard therapy regimen. Vancomycin was utilized to ensure initial therapy effective against MRSA, while a switch to a PRP was allowed if warranted by the susceptibility of the isolated gram-positive pathogen(s). The standard therapy regimen performed as expected with regard to efficacy and safety/tolerability, providing confidence in the validity of the study design and the clinical relevance of the enrolled subject population. A challenging population of subjects was enrolled, with rigorously defined cSSSIs and at least one systemic marker of inflammation in addition to multiple local signs and symptoms of infection. Ceftaroline therapy resulted in a high clinical cure rate.

The major limitation of this study was its sample size, which did not permit inferential statistical testing of the primary or secondary efficacy outcomes. This limitation is characteristic of phase 2 studies of new antimicrobial agents. In fact, the sample size of this study was larger than that of some other recent phase 2 studies of antibacterial compounds and was adequate, especially with the 2:1 randomization scheme, to provide meaningful insight into ceftaroline's safety and tolerability.

Based on the results of this study and on other preclinical and clinical data, ceftaroline has been advanced to phase 3 clinical studies and has the potential to become a safe and effective treatment option for cSSSI and other serious community- and hospital-acquired infections.

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