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Efficacy and Safety of CEM-102 in a Phase 2, Randomized, Double-Blind Study in Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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Abstract

Background: CEM-102, sodium fusidate, is a fusidane antibiotic under development for treatment of gram-positive ABSSSI. Sodium fusidate has been used for many years outside the US to treat infections caused by *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA).

Methods: This was a Phase 2, randomized, double-blind, multi-center study to evaluate the efficacy and safety of an oral CEM-102 loading dose regimen (CEM-102 LD), 1500 mg BID Day 1 followed by 600 mg BID, compared to oral linezolid (LZ) 600 mg BID, both administered for 10 to 14 days. Patients must not have received prior antibacterial therapy or must have failed other therapy (≥ 48 hours) to be eligible. Primary efficacy endpoints were clinical success in the intent to treat (ITT) and clinically evaluable (CE) populations at the test of cure (TOC) visit.

Results: 155 patients with cellulitis (n=100 [65%]) or wound infections (n=55 [35%]) were randomized to CEM-102 LD (n=78 [24 failed prior therapy]) or LZ (n=77 [22 failed prior therapy]). Clinical success rates at TOC were 85.9% CEM-102 LD and 94.8% LZ in the ITT population and 92.3% CEM-102 LD and 98.5% LZ in the CE population. *S. aureus* was isolated in 72% of patients, of which 70% were MRSA. MRSA eradication in the microbiologically evaluable (ME) population was CEM-102 LD 30/31 and LZ 37/37; methicillin-susceptible *S. aureus* (MSSA) eradication CEM-102 LD 16/17, LZ 10/11. Both drugs were well tolerated and AEs were comparable (62% CEM-102 LD and 64% LZ); gastrointestinal (GI) AEs (40% CEM-102 LD and 42% LZ).

Conclusion: Clinical success rates for CEM-102 LD and LZ in treatment of ABSSSI were comparable in the ITT and CE populations at TOC; ME eradication rates for MRSA and MSSA were also comparable. Safety analyses demonstrated a favorable safety and tolerability profile for CEM-102 LD.

Introduction

Treatment options for serious gram-positive ABSSSI warranting systemic antibacterial therapy have become more limited in recent years as resistance patterns in *S. aureus* have evolved, with far more of these infections now involving MRSA. There is an increasing need for effective and safe empirical oral antibacterials with demonstrated efficacy in treating both MSSA and MRSA infections.

Sodium fusidate is a potentially valuable systemic treatment option due to its unique profile of broad gram-positive antimicrobial spectrum, high oral bioavailability, a long history of safety, and its unique mechanism of action. The CEM-102 (sodium fusidate) oral loading dose regimen (CEM-102 LD) tested in this study was identified by pharmacokinetic/pharmacodynamic modeling and selected to balance optimal PK parameters for efficacy while maintaining favorable safety and tolerability, with trough plasma CEM-102 levels of approximately 80 µg/mL within the first 24 hours of dosing. The CEM-102 non-loading dose regimen (CEM-102 NL) studied is similar to that frequently used outside the U.S., reported in the European literature to be efficacious in the treatment of skin and soft tissue infections. Linezolid (LZ), an antibiotic with established efficacy in ABSSSI, was used as the active comparator.

Materials and Methods

This phase 2, adaptive design, randomized, double-blind, multi-center study enrolled 198 patients with ABSSSI at 16 US centers between August 2009 and March 2010. Patients were randomized using a sequence stratified by type of infection (cellulitis or wound). The first 127 patients were randomized 1:1:1 to CEM-102 NL (CEM-102 600 mg BID), CEM-102 LD (CEM-102 1500 mg BID on Day 1 followed by 600 mg BID), or LZ (600 mg BID), each administered orally for 10 to 14 days. Interim analysis after 127 patients were enrolled demonstrated comparable tolerability of the three study medication regimens; the CEM-102 NL dose regimen was dropped (N=43), and the remaining patients were randomized 1:1 to CEM-102 LD or LZ. A double-dummy design was used to maintain the blind.

Inclusion criteria: Men or non-pregnant women ≥18 years of age with ABSSSI ≤7 days duration suspected or proven to be caused by a gram-positive pathogen. Eligible ABSSSIs were cellulitis measuring at least 100 cm^2, with or without a focal abscess, and surgical or traumatic wound infections with local inflammation at the wound and surrounding soft tissues, all requiring 10-14 days of a systemic antibacterial. At least 3 local/systemic symptoms/signs of infection were required.

Exclusion criteria: Superficial or minor infections; human or animal bites, burns, or chronic diabetic foot ulcers; suspected polymicrobial infection involving *Pseudomonas aeruginosa*; significant hepatic or renal dysfunction; prior potentially effective antimicrobial therapy unless failing therapy or had gram-positive pathogen non-susceptible to prior therapy; inability to swallow the blinded medication whole.

Clinical and microbiological assessments: In-clinic assessments at baseline, Day 3, Day 7, Day 10, end-of-therapy (EOT), test-of cure (TOC; 7-14 days after EOT). Late follow-up (LFU; 7-21 days after TOC and ≥ 30 days after the first dose of study medication) was by telephone unless a clinic visit was indicated. Infection site specimens and blood cultures obtained at baseline; subsequent specimens obtained as clinically indicated.

Efficacy endpoints: The primary endpoint was clinical response at TOC in the ITT and in the CE populations. Clinical success was defined as total resolution of local and systemic signs and symptoms of the ABSSSI such that no further antibiotic therapy was required. Secondary efficacy analyses included the clinical success at the EOT for the ITT and CE populations, at the EOT and TOC for the microbiological intent to treat (MITT) and ME populations, at the EOT and TOC by baseline pathogen for the MITT and ME populations; by-pathogen microbiological success at the EOT and TOC for the MITT and ME populations, by-subject microbiological success at the EOT and TOC for the MITT and ME populations.

Safety: Safety assessments included adverse events (AEs), vital signs, clinical laboratory tests, and baseline and post-treatment electrocardiograms (ECGs).

Results

155 patients were randomized to CEM-102 LD or LZ (ITT population) and all received ≥ 1 dose of study medication; 78 patients received CEM-102 LD, and 77 patients received LZ. The two groups were comparable in demographics, baseline characteristics (Table 1), and percentages of ITT population in MITT, CE and ME populations (Table 2).

Comparable percentages of patients in each group completed study drug therapy (CEM-102 LD 73 of 78 [94%]; LZ 76 of 77 [99%]). The mean duration of study drug exposure was similar in the two treatment groups (CEM-102 LD 11.3 days and LZ 11.5 days).

Table 1. Demographics and Baseline Characteristics (ITT)

Characteristic	CEM-102 LD (N=78)	LZ (N=77)
Sex, n (%)		
Male	56 (72)	50 (65)
Female	22 (28)	27 (35)
Age (years)		
Mean ± SD	41.5 ± 16.7	40.6 ± 11.8
Range	18-80	19-74
Race, n (%)		
White	57 (73)	55 (71)
Black	16 (21)	17 (22)
Other	5 (6)	5 (7)
Infection type, n (%)		
Cellulitis	51 (65)	49 (64)
Wound	27 (35)	28 (36)
Duration of ABSSSI (days)	4.1	4.5

Table 2. Study Populations

Population	No. (%) of patients CEM-102 LD (N=78)	No. (%) of patients LZ (N=77)
ITT	78 (100)	77 (100)
MITT	59 (76)	58 (75)
CE	65 (83)	68 (88)
ME	50 (64)	49 (64)

Baseline cultures of the ABSSSI site identified at least one gram-positive pathogen (121 isolates) in 59 of 78 patients (76%) in the CEM-102 LD and in 58 of 77 patients (75%) in the linezolid groups. 111 were *S. aureus*,

The clinical 10 were β-hemolytic streptococci (CEM-102 LD 1 patient with group A streptococus [GAS], 5 patients with group B streptococcus [GBS], 1 patient with β-hemolytic streptococcus not typed; LZ 3 patients with GAS). 4 patients had polymicrobial infections (CEM-102 LD 3 patients with MSSA and GBS; LZ 1 patient with MSSA, GAS and *Acinetobacter lwoffii*). Two LZ patients had baseline bacteremia, one with MSSA (success) and one with MRSA (indeterminate; lost to follow-up after Day 10). success rates for CEM-102 loading-dose were comparable to those of linezolid in the ITT, CE MITT and ME populations (Table 3). No clinical failure was associated with decreased susceptibility of the causative pathogen post-therapy to either sodium fusidate or linezolid. One CEM-102 LD patient with a successfully treated lower extremity wound infection had superficial swab specimens before and during therapy demonstrating MSSA with an increase in sodium fusidate minimum inhibitory concentration from 0.12 µg/mL at baseline to 8 µg/mL on day 11 of 14 of treatment. The isolates appeared to be genetically related; the latter isolate demonstrated a *fusE* mutation in the L6 protein and a significant decrease in fitness (JMI Laboratories, North Liberty, IA).

There were no clinically relevant differences between groups in the incidence. types or frequency of AEs, including gastrointestinal events (Table 4). Three patients in the CEM-LD group discontinued study drug due to an AE (nausea and chills; blister and maculo-papular rash; nausea, vomiting, and anorexia). Three CEM-102 LD patients had ≥1 SAE, none considered likely related to study drug (herpes simplex; pyelonephritis; head injury and back pain). There were no deaths. Laboratory, vital sign and ECG analyses demonstrated no clinically important differences between groups or safety concerns.

Table 3. Clinical Success Rates by Study Population

Population	CEM-102 LD No. of patients	CEM-102 LD Success rate, % (95% CI)	LZ No. of patients	LZ Success rate, % (95% CI)
ITT	67/78	86 (76.2-92.7)	73/77	95 (87.2-98.6)
MITT	52/59	88 (79.9-95.1)	54/58	93 (83.3-98.1)
CE	60/65	92 (83.0-97.5)	67/68	99 (92.1-100)
ME	48/50	96 (86.3-99.5)	48/49	98 (89.2-100)
Early Response* (ITT)	60/63	95	63/65	97
***S. aureus* (ME)**	46/48	96	47/48	98
MRSA (ME)	30/31	97	37/37	100

*Day 3: Cessation of spread of lesion; afebrile; patients with baseline lesion ≥75 cm^2

Table 4. Adverse Events in ≥ 5% of Patients in Either Treatment Group

	No. (%) of patients CEM-102 LD (N=78)	No. (%) of patients LZ (N=77)
Any adverse event	48 (62)	49 (64)
Nausea	17 (22)	20 (26)
Vomiting	10 (13)	7 (9)
Diarrhea	10 (13)	10 (13)
Dyspepsia	6 (8)	2 (3)
Headache	4 (5)	9 (12)

Conclusions

- The CEM-102 loading dose regimen demonstrated efficacy comparable to that of linezolid in the ITT, CE, MITT, and ME populations in the treatment of ABSSSI.
- The safety and tolerability of the CEM-102 loading dose regimen was comparable to that of linezolid.
- These findings of comparable efficacy, safety and tolerability of the oral CEM-102 loading dose regimen compared to oral linezolid support further study of the CEM-102 loading dose regimen in Phase 3 clinical studies of the treatment of ABSSSI.

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