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MAJOR ARTICLE

Ceftriaxone+Sulbactam+Disodium EDTA Versus Meropenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: PLEA, a Double-Blind, Randomized Noninferiority Trial

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Background. CSE is a novel combination of ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid (EDTA) with activity against multidrug-resistant Gram-negative pathogens.

Methods. Adult patients aged ≥18 years with a diagnosis of complicated urinary tract infections (cUTIs), including acute pyelonephritis (AP), were randomized 1:1 to receive either intravenous CSE (1000 mg ceftriaxone/500 mg sulbactam/37 mg disodium EDTA) every 12 hours or intravenous meropenem (1000 mg) every 8 hours for up to 14 days. The primary objective was to show the noninferiority of CSE to meropenem at the test-of-cure visit (8–12 days after the end of therapy), with a noninferiority margin of 10%.

Results. Of 230 randomized patients, 74 of 143 and 69 of 143 were treated with CSE and meropenem, respectively. Of these, 98% were ceftriaxone nonsusceptible and 83% were ESBL-positive at baseline. Noninferiority of CSE to meropenem was demonstrated for both the US Food and Drug Administration-defined coprimary endpoints of (1) symptomatic resolution at test-of-cure (71 of 74 [95.9%] patients vs 62 of 69 [89.9%]; treatment difference, 6%; 95% confidence interval [CI] −2.6% to 16%) and (2) symptomatic resolution as well as microbiological eradication at test-of-cure (70 of 74 [94.6%] vs 60 of 69 [87.0%]; treatment difference, 7.6%; 95% CI, −2.0% to 18.4%). Microbiological eradication at test-of-cure (European Medical Agency's primary endpoint) was observed in 70 of 74 (94.6%) vs 61 of 69 (88.4%) (treatment difference, 6.2%; 95% CI, −3.2% to 16.6%) patients treated with CSE and meropenem, respectively. Safety profile of CSE was consistent with that of ceftriaxone alone.

Conclusions. The results support the use of CSE as a carbapenem-sparing treatment for patients suffering from cUTI/AP caused by resistant Gram-negative pathogens.

Keywords. acute pyelonephritis; ceftriaxone-sulbactam-disodium EDTA; complicated urinary tract infections; meropenem.

Multidrug-resistant bacterial (MDR) infections are an important public health problem, and urinary tract infections (UTIs) represent a substantial burden of these infections, causing significant morbidity and mortality [1]. There is a rapid increase in MDR strains across the globe [2, 3], especially in the Southeast Asian region, including India [1, 4], where extended-spectrum β-lactamase (ESBL) prevalence varies between 17% and 70% [5–7]. Extended-spectrum β-lactamases are typically plasmid-encoded, inhibitor-susceptible β-lactamases that hydrolyze penicillins, cephalosporins, and aztreonam [8]. Extended-spectrum β-lactamase-producing organisms exhibit cross-resistance to many other classes of antibiotics, resulting in limited therapeutic options to treat such infections. Carbapenems are structurally stable against ESBL enzymes and are therefore considered to have a very important place in the therapeutic regimen for these MDR infections. However, the rise of carbapenem-resistant bacteria over the past decade has undermined the effectiveness of carbapenems in treating such drug-resistant infections [9].

As an interim solution, the concept of using antibiotic resistance breakers to revive the potency of existing antibiotics has been widely discussed in the recent literature [3, 10, 11]. Antibiotic resistance breakers, also referred as antibiotic adjuvants, are nonantibiotic moieties that do not carry any antimicrobial activity on their own, but, when combined with antibiotics, they help overcome various resistance barriers and repurpose them for better antimicrobial activity. CSE, a

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novel combination of ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid ([EDTA] a known metal chelator), was developed for the treatment of various bacterial infections. The addition of sulbactam and disodium EDTA expands the in vitro activity of ceftriaxone against Ambler class A (bla_{TEM}, bla_{SHV}, bla_{CTX-M}), class B (metallo-enzymes, eg, bla_{VIM}, bla_{NDM}, bla_{IMP}), and some class D β-lactamase-producing bacteria [12, 13]; it is not active against serine carbapenemases [14]. Furthermore, in in vitro studies, CSE has shown activity against other resistance mechanisms such as efflux pumps [15, 16], bacterial biofilms [17], membrane impermeability [18], and horizontal gene transfer by means of conjugation [19], although the clinical relevance of these is unproven. Preclinical efficacy of CSE has been previously described in a *Klebsiella pneumoniae* lung infection model in rats [20]. Acute dose (up to 500 mg/kg) and subacute dose toxicity (150 mg/kg daily for 28 consecutive days) studies performed in Swiss albino mice and Sprague-Dawley rats showed no adverse effects [21, 22]. Furthermore, intravenous infusion of disodium EDTA at 12.91 mg/kg for 90 minutes in New Zealand rabbits did not show any significant change in heart rate, heart rhythm, QT interval, corrected QT interval (QTc), and serum electrolyte levels over the observation period of 120 minutes postadministration. A no-observable-adverse-effect limit was established at a dose of 4.2 mg/kg human-equivalent dose (≈250 mg for a 60-kg adult; data on file). This provides a ≈7× safety margin over the current dose of 37 mg. CSE was approved in India on the basis of a phase 3 multiple indication trial (CTRI/2010/091/000174) evaluating efficacy and safety of CSE versus ceftriaxone for the treatment of various bacterial infections, including complicated UTIs (cUTIs) [23, 24]. The preserving life of existing antibiotics (PLEA) clinical study was conducted to demonstrate the noninferiority of CSE versus meropenem in adults with cUTI, including acute pyelonephritis (AP).

MATERIALS AND METHODS

Study Design and Study Population

PLEA was a phase 3, prospective, randomized, multicenter, double-blind, double-dummy, parallel-group, noninferiority trial designed and conducted in accordance with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance for cUTI trials and good clinical practice guidelines [25, 26] and reported in accordance with CONSORT 2010 recommendations [27]. This trial was registered at www.clinicaltrials.gov under registration number NCT03477422 and at http://ctri.nic.in under registration number CTRI/2013/11/004133. All patients (or their legally acceptable representatives) provided written informed consent prior to initiation of any study-related procedures. The informed consent and study protocol were reviewed and approved by an independent ethics committee or institutional review board at each participating site.

The full inclusion and exclusion criteria are listed in Supplementary Appendix S1. In brief, patients aged >18 years with clinically suspected cUTI caused by Gram-negative pathogens, judged by the investigator to require intravenous antibiotic therapy for 5–14 days, were recruited into the study. Complicated UTI included AP, UTIs in men with a documented history of chronic urinary retention, or UTI associated with obstruction, foreign bodies, recent urinary instrumentation, or urologic abnormalities. Diagnosis of cUTI was established based on the criteria defined in the FDA guidance document [25]. Patients were only enrolled in the study if it were expected that all catheters will be discontinued during study treatment, urine cultures will be positive for Gram-negative bacteria at $\geq 10^5$ colony-forming units/mL, and the study drugs were considered appropriate for empiric therapy.

Key exclusion criteria included patients with the following: perinephritic abscess or renal corticomedullary abscess; polycystic kidney disease; only 1 functional kidney; chronic vesicoureteral reflux; uncomplicated UTI; creatinine clearance ≤30 mL/minutes.

Randomization and Blinding

Eligible patients were randomized 1:1 to CSE 1000 mg/500 mg/37 mg every 12 hours or meropenem 1000 mg every 8 hours (see Supplementary Appendix S4 for dose adjustment protocol) using a computer-generated central randomization code and an interactive web response system. Both CSE and meropenem were administered for 5–14 days as 30-minute intravenous infusions; matching placebos were added at 8 hours and 16 hours in the CSE arm and at 12 hours in the meropenem arm to maintain blinding.

Study Procedures and Assessments

The study procedures (listed in Supplementary Appendix S2) included urine collection for quantitative cultures, as well as blood cultures, at baseline and as clinically needed. Routine pathogen isolation, identification, and susceptibility testing were carried out at local laboratories using disk diffusion methodology as per Clinical and Laboratory Standards Institute (CLSI) standards; combined disc diffusion test was used to detect ESBL production [28, 29]. All isolates were shipped to a central reference laboratory (Department of Cell Culture & Microbial Biotechnology, VMRC, HP, India) for CLSI broth microdilution susceptibility testing and polymerase chain reaction for the identification of β-lactamases.

Assessments (Supplementary Appendix S3) included a clinical assessment on the basis of a patient symptom assessment questionnaire, derived programmatically each day. Clinical outcomes were defined as cure, failure, or indeterminate. Microbiological outcomes were classified as eradication, failure/persistence, superinfection, or indeterminate. Composite outcomes were defined as favorable (both clinical cure and

microbiological eradication), unfavorable (clinical and/or microbiological failure), or indeterminate.

Clinical and microbiological outcomes were assessed at the end of treatment ([EOT] 5–14 days postrandomization), test-of-cure ([TOC] 8–12 days post-EOT), and late follow-up ([LFU] 5–9 days post-TOC). Intravenous to oral switch was not permitted in the study.

Primary Endpoints

The primary efficacy endpoints of this study were defined separately to adhere to the varying regulatory guidelines of the FDA and EMA. The FDA coprimary endpoints were (1) the proportion of patients with clinical cure at TOC in the microbiologic modified intent-to-treat (mMITT) population and (2) the proportion of patients with clinical cure and microbiological eradication at TOC in the mMITT population. The EMA primary endpoint was microbiological eradication at TOC in the mMITT population.

Secondary Endpoints

Secondary endpoints included per-patient and per-pathogen clinical and microbiological response at EOT and LFU; per-patient and per-pathogen clinical and microbiological response at EOT, TOC, and LFU in patients infected with an ESBL-producing pathogen. Various other prespecified secondary efficacy outcome variables (Supplementary Appendix S5) were also analyzed to ascertain the consistency of the results across different visits and in different populations. Safety and tolerability were assessed by monitoring reported adverse events (AEs). A sensitivity analysis was performed for all primary endpoints on the basis of the type of infection (cUTI or AP), baseline pathogens, age, and sex.

Statistical Analysis

The mMITT population was used for primary analysis and included patients with evidence of cUTI caused by eligible baseline pathogen(s) susceptible to both study drugs. Other population sets (Supplementary Appendix S6 and S8), namely, microbiologically evaluable, clinically evaluable, and extended microbiologically evaluable, were used to verify the primary analysis, and perform secondary and exploratory analyses.

Assuming that both treatments had an underlying true response of >96% for each coprimary endpoint and that mMITT analysis set included 60% of randomized patients (assuming a dropout rate/postrandomization withdrawal of 40% due to ESBL-negative or β-lactamase-negative or Gram-positive pathogens), a sample size of 228 patients ensured at least 85% power to demonstrate noninferiority at a margin of –10%.

Between-group treatment differences and 2-sided 95% confidence intervals (CIs) were calculated using the unstratified method of Miettinen and Nurminen [30]. Noninferiority was considered proven if the lower limit of the 2-sided 95% CI of the treatment difference (CSE minus meropenem) was greater than –10% (FDA/EMA) in the mMITT analysis set. Although superiority was not specified as an objective, superiority can be tested in a planned noninferiority trial without a need for type 1 error (α) correction. The superiority was concluded if the lower bound of the CI was greater than 0%. All analyses were performed using SAS version 9.1 or higher (SAS Institute, Cary, NC).

RESULTS

Patient Disposition: Baseline Characteristics

Between December 2013 and April 2017, 230 patients (from different regions of India with majority from North India) were randomized at 17 sites (tertiary care hospitals) (Supplementary Appendix S7); 227 received ≥1 intravenous dose of either study drug (Figure 1). The mMITT population comprised 143 patients; 91 (63.6%) had cUTI and 52 (36.4%) had AP.

The baseline characteristics were similar across the study populations in the 2 treatment groups, with females aged between 18 and 45 years constituting the highest proportion of randomized patients (Table 1 and Supplementary Appendix S13). Patients presented with a median of 4 symptoms (range, 1–7 for CSE and 2–10 in meropenem) with fever as the most common symptom.

Most patients presented with a monomicrobial urine infection with Escherichia *coli* (n = 113, 80.7%) (Table 2). In the mMITT population, ceftriaxone nonsusceptible pathogens were identified in 140 (97.9%) patients (CSE, n = 72; meropenem, n = 68); ESBL-producing pathogens in 119 (83.2%) patients (CSE, n = 63; meropenem, n = 56); multidrug-resistant pathogens in 100 (69.9%) patients (CSE, n = 55; meropenem, n = 45); most were *E coli* or Pseudomonas *aeruginosa*.

Duration of Treatment

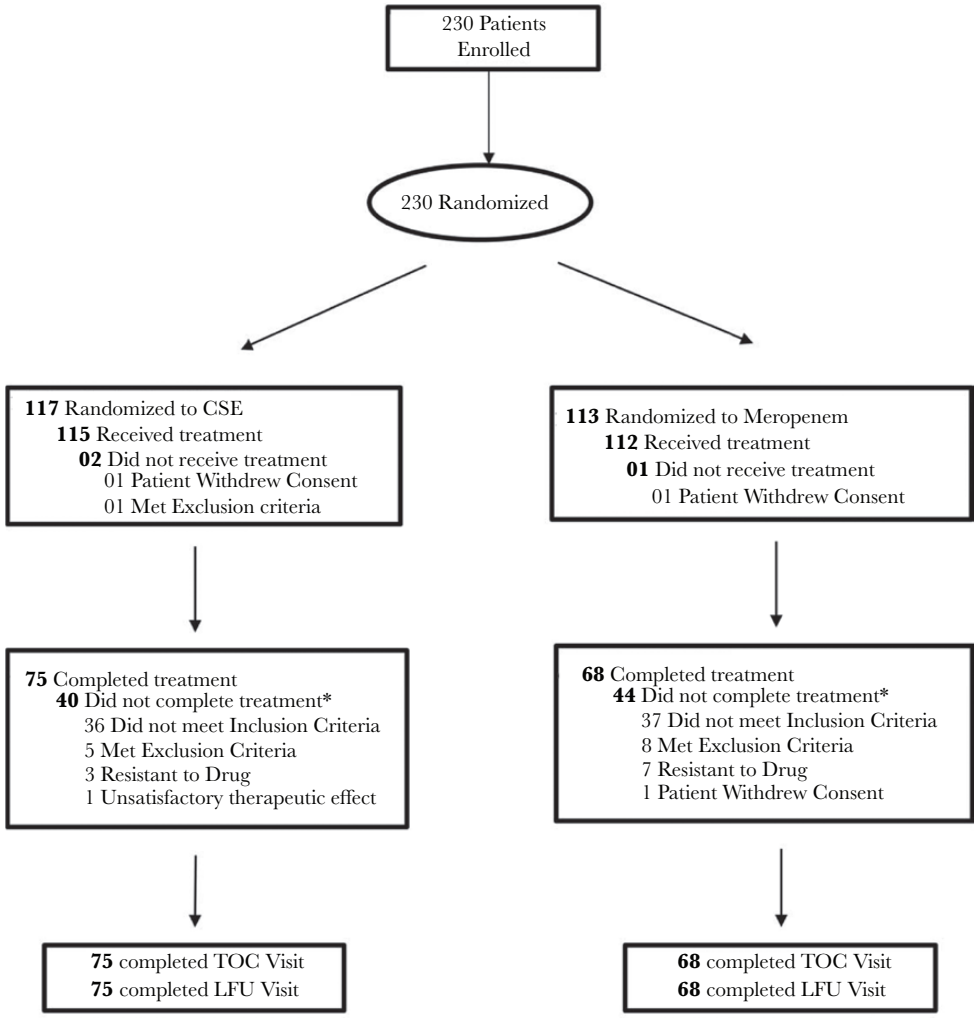
Treatment duration was comparable across the 2 arms with an overall median (range) duration of approximately 6.5 (5–14) days. The proportion of patients with 5 days therapy was higher in the CSE arm compared with the meropenem arm (32.9% vs 27.5%). Overall, almost 78% of the patients received ≤7 days of intravenous therapy.

Efficacy Evaluation

Primary Endpoints

The efficacy results are summarized in Table 2. CSE demonstrated noninferiority to meropenem for both the FDA coprimary endpoints as well as the EMA primary endpoint (Supplementary Appendix S9) at the prespecified noninferiority margin of –10%.

Furthermore, across all the 3 resistant phenotypes (ceftriaxone nonsusceptible; multidrug-resistant; ESBL-positive), the point estimates of the treatment difference for both clinical and microbiological outcomes favored CSE (Table 2), and the 95% CI



*One patient may have had more than one response.; Abbreviations: TOC: Test of Cure Visit; LFU: Late Follow-up Visit; CSE: ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid

Figure 1. Flowchart representing the patient disposition and study populations.

shows noninferiority of CSE compared with meropenem. In the ESBL subgroup, the lower bound of the 95% CI was greater than zero for both clinical and microbiological endpoints (Table 2).

Sensitivity analyses of the primary endpoints (Supplementary Appendix S10) were generally consistent across baseline patient characteristics, and the point estimates of the treatment difference generally favored CSE; the exception being patients in the age group of 65–74.

Secondary and Exploratory Endpoints

In all evaluable populations, the clinical cure and microbiological eradication rates were comparable between the 2 treatment arms at the end of treatment (Supplementary Appendix S12). In the extended microbiologically evaluable population, 2 of 3 (66.6%) patients with a meropenem-resistant baseline pathogen reported a clinical cure and microbiological eradication at the TOC visit, whereas 1 patient had a recurrence at TOC due to superinfection. Overall, the results were consistent across all visits, with CSE demonstrating noninferiority to meropenem at the −10% noninferiority margin.

Table 3 presents the minimum inhibitory concentration (MIC) distribution versus clinical/microbiological outcome data for CSE and meropenem, respectively. The modal MIC of CSE and meropenem was 2 μg/mL and ≤0.25 μg/mL, respectively. The MIC distribution of CSE was more predictive of clinical outcome with >97% cure rate observed for MICs ≤4 μg/mL (provisional breakpoint), compared with the meropenem arm where the clinical cure was reported in ≈90% of all patients up to the breakpoint MIC of ≤1 μg/mL. In both treatment groups, patients that failed therapy had baseline MICs towards the higher side of the MIC distribution (Table 3). In two patients (both *E coli*) who had failed therapy in the meropenem group, a ≥4-fold increase in baseline MICs of both study drugs was observed. Polymerase chain reaction was used to investigate

Table 1. Baseline Patient Characteristics: Microbiologic Modified Intent-to-Treat Population

	CSE, 1034 (N = 74)	Meropenem (N = 69)
Characteristics	n (%)	n (%)
Gender		
Male	32 (43.2)	29 (42.0)
Female	42 (56.7)	40 (58.0)
Age		
≥18 to ≤45	39 (52.7)	41 (59.4)
≥46 to ≤64	31 (41.9)	20 (29.0)
≥65	4 (5.4)	8 (11.6)
Body mass index, kg/m^2; mean (SD)	23.1 (3.4)	22.9 (3.0)
Diagnosis		
Pyelonephritis	26 (35.1)	26 (37.7)
cUTI	48 (64.9)	43 (62.3)
With removable source of infection[a]	25 (33.8)	24 (34.8)
With nonremovable source of infection	23 (31.1)	19 (27.5)
Common Signs and Symptoms[b]		
Fever	65 (87.8)	51 (73.9)
Urinary frequency	54 (73.0)	49 (71.0)
Urinary urgency	53 (71.6)	48 (69.6)
Dysuria	42 (56.8)	43 (62.3)
Suprapubic pain	43 (58.1)	41 (59.4)
Creatinine clearance (mL/min); mean (SD)[c]	85.5 (29.1)	87.0 (28.0)
Renal Status		
Normal renal function/mild impairment (CrCl >50 mL/minute)	69 (93.2)	66 (95.7)
Moderate impairment (CrCl 31–50 mL/minute)	5 (6.8)	3 (4.3)
Diabetes mellitus	9 (12.2)	5 (7.2)
Systemic inflammatory response syndrome[d]	44 (59.5)	42 (60.9)
Baseline Pathogen in Urine		
Enterobacteriaceae	67 (90.5)	64 (92.7)
Escherichia coli	57 (77)	56 (81.2)
Klebsiella pneumoniae	3 (4.1)	4 (5.8)
Proteus mirabilis	3 (4.1)	3 (4.3)
Enterobacter spp	4 (5.4)	1 (1.4)
Other Gram-Negative Pathogens	7 (9.5)	5 (7.2)
Acinetobacter baumannii	0 (0)	2 (2.9)
Pseudomonas aeruginosa	7 (9.5)	3 (4.3)

Abbreviations: CSE, ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

[a]Removable source of infection includes urinary catheter or removable kidney stones.

[b]Most common presenting signs and symptoms with incidence >50% has been reported.

[c]CrCl was calculated by using the Cockcroft-Gault method based on local laboratory data.

[d]SIRS was defined as the occurrence of ≥2 of fever (temperature >38°C [100.4°F]) or temperature <36°C (96.8°F); heart rate >90/minutes; respiratory rate >20/minutes or arterial carbon dioxide tension <32 mmHg; abnormal white blood cell count (>12000/μL or <4000/μL or >10% immature [band] forms).

differences between the baseline and TOC isolates in these cases. In both *E coli*, there was an acquisition of carbapenemase genes bla_{KPC} and bla_{OXA-25}, in addition to the other resistance genes identified at baseline (Supplementary Appendix S14). No significant changes in the posttreatment MICs were noted in the CSE group.

Safety Evaluation

A total of 15 AEs were reported in 13 patients (11.3%) receiving CSE, compared with 17 AEs reported in 14 patients (12.5%) receiving meropenem. The most common AEs included general weakness (3.1%), thrombophlebitis (1.8%), phlebitis (0.9%), gastritis (1.3%), and vomiting (0.9%) (Table 4). Adverse events associated with laboratory parameters included decreased hemoglobin in 2 patients and rise in total leukocyte count in 1 patient in the CSE group (none in the meropenem group). Most of the AEs were mild to moderate in intensity and were resolved.

Serious AEs were reported in 1 patient (0.8%) who witnessed multiple organ dysfunction syndrome and septic shock in the CSE arm, 1 week after withdrawal of the study drug. Both of the serious AEs were continuous, life threatening, and resulted in patient death; however, both the events and death were deemed unrelated to the study drug by the treating investigator. No deaths related to the study drugs were observed. Due to the chelating property of disodium

Table 2. Summary of Primary and Secondary Efficacy Endpoints: Microbiologic Modified Intent-to-Treat Population[a]

Endpoints	Visit	CSE-1034[b] n/N (%)	Meropenem n/N (%)	Difference, % (95% CI)
Primary Analysis				
FDA Coprimary Endpoints[c]				
Clinical cure[d] and microbiological eradication[e]	TOC	70/74 (94.6)	60/69 (87.0)	7.6 (−2.0 to 18.4)
Clinical cure		71/74 (95.9)	62/69 (89.9)	6.0 (−2.6 to 16)
EMA Primary Endpoint[f]				
Microbiological eradication	TOC	70/74 (94.6)	61/69 (88.4)	6.2 (−3.2 to 16.6)
Secondary Endpoints				
Clinical cure	EOT	72/74 (97.3)	68/69 (98.6)	−1.3 (−8.1 to 5.4)
	LFU	71/74 (95.9)	62/69 (89.9)	6.0 (−2.6 to 16.0)
Microbiological eradication	EOT	73/74 (98.6)	68/69 (98.6)	0.0 (−6.0 to 6.6)
	LFU	70/74 (94.6)	61/69 (88.4)	6.2 (−3.2 to 16.6)
Per-Pathogen Microbiological Eradication				
Enterobacteriaceae	TOC			
Escherichia coli		53/57 (93.0)	49/56 (87.5)	5.5 (−6.1 to 17.7)
Klebsiella pneumoniae		3/3 (100)	4/4 (100)	0.0 (−59.9 to 52.8)
Proteus mirabilis		3/3 (100)	2/3 (66.7)	33.3 (−40.3 to 81.5)
Enterobacter species		4/4 (100)	1/1 (100)	0.0 (−54.6 to 82.8)
Other Gram-Negative Pathogens				
Acinetobacter baumannii		-	2/2 (100)	NE
Pseudomonas aeruginosa		7/7 (100)	3/3 (100)	0.0 (−37.9 to 58.7)
Subgroup Analysis				
Ceftriaxone Nonsusceptible				
Clinical cure	TOC	69/72 (95.8)	62/68 (91.2)	4.7 (−4.0 to 14.4)
Microbiological eradication		68/72 (94.4)	61/68 (89.7)	4.7 (−4.7 to 15.0)
Multidrug Resistant				
Clinical cure	TOC	53/55 (96.4)	40/45 (88.9)	7.5 (−3.0 to 20.4)
Microbiological eradication		52/55 (94.5)	39/45 (86.7)	7.9 (−3.8 to 21.6)
Extended-Spectrum β-Lactamase[g] Positive				
Clinical cure	TOC	63/63 (100)	50/56 (89.3)	10.7 (4.6 to 21.5)
Microbiological eradication		62/63 (98.4)	49/56 (87.5)	10.9 (2.3 to 22.3)

Abbreviations: CI, confidence interval; CFU, colony-forming units; CSE, ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid; EMA, European Medicines Agency; EOT, end-of-treatment; ESBL, extended-spectrum β-lactamase; FDA, US Food and Drug Administration; LFU, late follow-up (7 ± 2 days after TOC); TOC, test of cure (10 ± 2 days after EOT); MDR, multidrug resistant; mMITT, microbiological modified intention to treat; NE, not estimable.

[a]Denominators are the total numbers in each group unless shown otherwise.

[b]CSE-1034 nonsusceptibility was defined as a central microbiology reference laboratory minimum inhibitory concentration ≥8 μg/mL or local laboratory disk diffusion diameter of ≤19 mm for Enterobacteriaceae and ≤13 mm for non-Enterobacteriaceae (*Acinetobacter baumannii* and *Pseudomonas aeruginosa*).

[c]Coprimary endpoints for the FDA: the sponsor concluded noninferiority if the lower limit of the 95 CI at TOC was greater than −15. The FDA noninferiority margin was a lower limit of the 95% CI greater than −10.0.

[d]Clinical Cure: all or most pretherapy signs and symptoms of the index infection had improved or resolved such that no additional antibiotics were required.

[e]Microbiological eradication: a urine culture taken within 48 hours before randomization and compared with the culture from the EOT, TOC, or LFU visit shows growth of the original uropathogen $<10^4$ CFU/mL (for FDA) or $<10^3$ CFU/mL (for EMA), and the patient was not bacteremic (if the patient was bacteremic at screening, the bacteremia has resolved).

[f]Primary endpoint for the EMA: the sponsor concluded noninferiority if the lower limit of the 95% CI at TOC was greater than −15. The EMA noninferiority margin was a lower limit of the 95% CI greater than −10.0.

[g]ESBL detection was carried out using the combined disc diffusion test at the site-of-care and later confirmed using the genotypic characterization using polymerase chain reaction. Data presented are as per the site-of-care results.

EDTA, patients were monitored for their serum electrolyte changes, serum calcium and magnesium levels, postural hypotension, and electrocardiography changes; however, no significant changes from baseline were noted (data not shown). The safety profile of CSE was consistent with that of ceftriaxone alone. There were no new safety concerns reported for meropenem during the study.

DISCUSSION

The findings of the PLEA clinical trial demonstrate that CSE is microbiologically and clinically effective and well tolerated by patients and the dosing regimen of CSE (1000 mg/500 mg/37 mg every 12 hours) is noninferior to meropenem (1000 mg every 8 hours) for the treatment of hospitalized adults suffering from cUTI. The CI around the treatment difference for both the FDA- and EMA-defined endpoints at TOC visit demonstrated noninferiority of CSE versus meropenem at 5% level of significance. Consistent with the primary analysis, a more stringent conservative analysis (indeterminate outcomes were classified as unfavorable in the CSE group and favorable in the meropenem group) also demonstrated the noninferiority of CSE across all

Table 3. Outcomes by Baseline MIC at Test-of-Cure: Microbiologic Modified Intent-to-Treat Population

	CSE-1034 (N = 74)			Meropenem (N = 69)	
	Clinical Cure	Microbiological Eradication		Clinical Cure	Microbiological Eradication
MIC	n/N (%)	n/N (%)	MIC	n/N (%)	n/N (%)
<0.25	16/16 (100)	16/16 (100)	<0.25	20/22 (90.9)	21/22 (95.4)
0.25	4/4 (100)	4/4 (100)	0.25	12/12 (100)	11/12 (91.7)
0.5	3/3 (100)	2/3 (66.7)	0.5	14/14 (100)	13/14 (92.7)
1	9/10 (90)	9/10 (90)	1	16/21 (76.2)	16/21 (76.2)
2	23/23 (100)	23/23 (100)			
4	16/17 (94.1)	16/17 (94.1)			
8	0/1 (0)	0/1 (0)			
Overall	71/74 (95.9)	70/74 (94.6)	Overall	62/69 (89.9)	61/69 (88.4)

Abbreviations: CSE, ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid; MIC, minimum inhibitory concentration.

primary endpoints (Supplementary Appendix S11), thus suggesting that the efficacy results were insensitive to the handling of missing data and indeterminate outcomes. Subgroup analyses in resistant subpopulations showed that clinical cure and microbiological eradication rates were higher in patients who received CSE than those who received meropenem. Meropenem was a reliably active comparator because of its efficacy against ESBL-producing Gram-negative bacteria, including ceftriaxone-resistant pathogens, and its availability across all study regions. Of note, previous trials in cUTI had only a limited number of patients in the resistant subgroup (14.7% ESBL-positive in ASPECT-cUTI; 19.6% ceftazidime-nonsusceptible in RECAPTURE), whereas in this study, approximately 98% of the mMITT population presented with a ceftriaxone-nonsusceptible pathogen [31, 32]. Furthermore, because patients infected with a meropenem-resistant pathogen

Table 4. Summary of Adverse Events (AEs) and Serious AEs: Safety Population

	CSE-1034 (N = 115)	Meropenem (N = 112)
System Organ Class	No. of Patients[a] (%)	No. of Patients (%)
Patients with at least 1 AE	13 (11.3)	14 (12.5)
Gastrointestinal Disorders	3 (2.6)	6 (5.4)
Constipation	1 (0.9)	-
Diarrhoea	-	1 (0.9)
Feces discolored	1 (0.9)	-
Gastritis	1 (0.9)	2 (1.8)
Nausea	-	1 (0.9)
Vomiting	-	2 (1.8)
General Disorders and Administration Site Conditions	5 (4.3)	5 (4.5)
Asthenia	4 (3.5)	3 (2.7)
Catheter site erythema	-	1 (0.9)
Injection site swelling	-	2 (1.8)
Multiple organ dysfunction syndrome[b]	1 (0.9)	-
Infections and Infestations	1 (0.9)	1 (0.9)
Candida infection	-	1 (0.9)
Septic shock[b]	1 (0.9)	-
Investigations	3 (2.6)	-
Hemoglobin decreased	2 (1.7)	-
White blood cell count increased	1 (0.9)	-
Nervous System Disorders	-	1 (0.9)
Headache	-	1 (0.9)
Vascular Disorders	3 (2.6)	3 (2.7)
Thrombophlebitis	3 (2.6)	3 (2.7)

Abbreviations: CSE, ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid; SOC, system organ class.

NOTE: Patients may have reported more than 1 event per SOC or preferred term. Patients with multiple AEs were counted once for each SOC and/or preferred term. Patients with AEs in >1 category are counted once in each of those categories. Adverse events were coded using MedDRA version 20.0 or later; zero frequencies were presented by "-".

[a]Percentages were calculated by taking count of corresponding column header group as denominator.

[b]Serious AEs.

were excluded from the mMITT population, the higher cure rate in the CSE group is therefore unrelated to meropenem resistance.

Fewer patients in the CSE group than in the meropenem group reported microbiological recurrence (3% vs 10%) or clinical relapse (1% vs 7%) at LFU. Clinical relapse associated with carbapenem therapy has previously been reported in cUTI patients receiving meropenem in the EPIC trial (7.1% relapse rate) and in patients receiving doripenem (8.5% relapse rate) in the RECAPTURE trial [32, 33]. Most patients received the intravenous therapy for the prespecified duration, and, unlike recent cUTI trials, a switch to an oral drug was not permitted in the study. Hence, the higher composite cure rate and a lower posttreatment recurrence of infection observed in the CSE group is not confounded by a switch to oral therapy.

Baseline pathogens were typical of cUTI and comparable between treatment groups with *E coli* reported in almost 80% of the patients in the mMITT population. Overall, almost 92% of the patients had Enterobacteriaceae, whereas the other 8% comprised nonfermenters such as *P aeruginosa* and *A baumannii*. Previous studies in cUTI patients have shown similar results with Enterobacteriaceae reported in ≥90% of the patients in the mMITT analyses sets [32–34]. The microbiological results observed for CSE are consistent with previous in vitro and preclinical studies [12, 35, 36] and clinical data [23, 37, 38]. However, although the difference in trial designs does not permit direct comparisons, in a previous clinical study comparing CSE versus ceftriaxone, clinical cure and microbiological eradication rates in the CSE group were 100% and 97%, respectively in cUTI patients [38].

Safety assessment of CSE demonstrated a safety and tolerability profile comparable to meropenem. The AEs reported in this study are consistent with postmarketing surveillance data in incidence, causality, and severity [37]. Most of the AEs were mild and moderate in nature and were eventually resolved. Moreover, no new safety concerns were reported during the study. All of the AEs reported in the CSE arm have previously been reported for ceftriaxone [24, 39, 40]. The results are also in line with the rate of incidence of AEs reported in previous trials on CSE [23, 37, 38].

A limitation of this trial is that it did not include patients from outside India. However, the pharmacokinetics of ceftriaxone and sulbactam are not expected to vary by ethnic group or region.

Further research in patients with baseline bacteremia or nosocomial infection due to metallo-β-lactamase-positive pathogens is needed to add greater insight into the spectrum of patients in whom CSE (either monotherapy or in combination) offers a clinical advantage. However, such populations are extremely difficult to recruit in a randomized controlled trial, but we look forward to investigator-initiated studies to collect such difficult-to-obtain, yet extremely important, data.

CONCLUSIONS

In conclusion, CSE met the primary objective of showing noninferiority against meropenem in the treatment of patients with cUTI, including AP. The susceptibility profile of pathogens isolated in this study highlights the increasing antibiotic resistance trend and warrant a need for new effective antimicrobials. The results support the use of CSE as a potential alternative to carbapenems in the treatment of patients with cUTI or AP, including infections caused by ESBL-producing Gram-negative bacteria.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. All authors had full access to all trial data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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