Supplemental Online Content

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eTable 1. Study Populations Analyzed in the Phase 3 Study

eTable 2. Description of Clinical and Microbiological Outcomes Used in the Phase 3 Study

eTable 3. Listing of All Secondary Outcomes Assessed in the Phase 3 Study Not Presented in This Report

eTable 4. Demographic and Baseline Characteristics of Patients in the Primary Analysis Set

eTable 5. Overall Success, Clinical Cure and Microbiological Eradication in Patients Without Exclusion Based on Susceptibility

eTable 6. Overview of Adverse Events in All Patients Receiving at Least One Dose of Study Drug

eTable 7. Listing of Adverse Events Leading to Discontinuation of Study Drug in All Patients Receiving at Least One Dose of Study Drug

eBox. Exclusion and Inclusion criteria Used Among 1107 Patients Assessed for Study Eligibility

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Study Populations Analyzed in the Phase 3 Study

Name of study population in study protocol and statistical analysis plan	Study population presented in this report	Criteria for study population
Intent to Treat (ITT)	Not presented in this report	All randomized patients
Modified Intent to Treat (MITT)	All patients who received at least one dose of study drug	All patients who were randomized and received at least one dose of study drug. All adverse event analyses were based on actual treatment received.
Microbiological-Modified Intent to Treat (m-MITT)	Primary analysis set	The primary analysis set included all randomized patients who received at least one dose of study drug and who had a baseline gram-negative pathogen $\geq 10^5$ CFU/ml in urine culture or the same pathogen present in concurrent blood and urine cultures that caused the complicated UTI that was not resistant to cefepime/enmetazobactam (minimum inhibitory concentration ≤8 µg/ml; minimum inhibitory concentration determined with enmetazobactam at a fixed concentration of 8 µg/ml) or piperacillin/tazobactam (minimum inhibitory concentration ≤64 µg/ml). If ≥3 bacterial isolates were identified, the culture was considered contaminated regardless of colony count unless one of the isolates that grew in the urine, even if $\geq 10^5$ CFU/ml, was also isolated from a blood culture obtained within 48 hours prior to randomization. Any patient with only a gram-positive pathogen or a bacterial species typically not expected to respond to both study drugs at $\geq 10^5$ CFU/ml, was excluded from the primary analysis set. Patients with contaminated screening and baseline samples were also excluded from the primary analysis set.
Microbiological-Modified Intent to Treat + Resistant (m-MITT+R)	Patients without exclusion based on susceptibility	All randomized patients who met criteria for the primary analysis set including patients with isolates resistant to cefepime/enmetazobactam (minimum inhibitory concentration >8 µg/ml; minimum inhibitory concentration determined with enmetazobactam at a fixed concentration of 8 µg/ml) or piperacillin/tazobactam (minimum inhibitory concentration >64 µg/ml), or with a missing minimum inhibitory concentration determination (i.e. minimum inhibitory concentration unknown).
Clinically Evaluable (CE)	Not presented in this report	The clinically evaluable population included all patients who received at least one dose of study drug and who met the following important components of the study as specified in the protocol: • Received a total duration of antibacterial therapy of at least 15 consecutive doses of study drug or were classified as clinical failures after completing at least 9 doses of intravenous study drug therapy

Name of study population in study protocol and statistical analysis plan	Study population presented in this report	Criteria for study population
		• Had a clinical assessment at Day 14[a], unless criteria for clinical failure were met at an earlier time point • Did not receive concomitant antibacterial therapy with a non-study antibacterial drug to which the uropathogen was susceptible between the time of the baseline culture and Day 14, unless criteria for clinical failure were met • Did not have any other major protocol violations that would have affected assessment of efficacy
Microbiologically Evaluable (ME)	Not presented in this report	All patients who met the definition for both the primary analysis set and clinically evaluable population. In addition, patients must not have had a microbiological outcome of indeterminate at Day 14. Concomitant administration of narrow-spectrum gram-positive active agents to patients who had gram-positive and gram-negative co-infection did not affect patient evaluability in the clinically evaluable or microbiologically evaluable populations.
Microbiologically Evaluable + Resistant (ME+R)	Not presented in this report	All patients who met the definition for patients without exclusion based on susceptibility and the clinically evaluable population. In addition, patients must not have had a microbiological outcome of indeterminate at Day 14. Concomitant administration of narrow-spectrum gram-positive active agents to patients who had gram-positive and gram-negative co-infection did not affect patient evaluability in the clinically evaluable or microbiologically evaluable + resistant populations.

[a]Day 14 occurred 7 [±2] days after end of treatment (i.e. the test of cure visit).

eTable 2. Description of Clinical and Microbiological Outcomes Used in the Phase 3 Study

Category	Criteria
Clinical outcome	
Cure	The complete resolution (or return to premorbid state) of the baseline signs and symptoms of complicated UTI or acute pyelonephritis that were present at screening (and no new urinary symptoms or worsening of symptoms), such that no further antimicrobial therapy to treat the of complicated UTI or acute pyelonephritis was warranted. Symptom resolution did not necessarily include baseline symptoms associated with anatomic abnormalities that predispose to cUTI, such as symptoms associated with the presence of an indwelling urinary catheter. **This outcome category could have been used at Day 3 of treatment, end of treatment, Day 14[a], Day 21[b], and early termination.**
Improvement	Lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms of complicated UTI or acute pyelonephritis,but continued intravenous therapy for management of complicated UTI or acute pyelonephritis was warranted. **This outcome category could only have been used at Day 3 of treatment.**
Failure	Patients who experienced any 1 of the following: • At Day 3 of treatment and end of treatment, worsening of baseline clinical signs and symptoms of complicated UTI or acute pyelonephritis or the development of new clinical signs and symptoms of infection, sufficient to stop study drug and initiate non-study antimicrobial; • At Day 14 and Day 21, persistence, incomplete resolution of baseline clinical signs and symptoms of infection, requiring additional antibiotic therapy; • Withdrawal from the study drug due to an adverse event or due to lack of clinical improvement; or • Death of the patient during the study. Note: Withdrawal from the study drug due to an adverse event or due to lack of clinical improvement or death of the patient during the study led to clinical failure for the subsequent time points but did not change the previous time point assessment. **This outcome category could have been used at Day 3 of treatment, end of treatment, Day 14, Day 21, and early termination.**
Indeterminate	Clinical outcome could not be determined. **This outcome category could have been used at Day 3 of treatment, end of treatment, Day 14, Day 21, and early termination.**
Microbiological outcome	
Eradication	The baseline qualifying Gram-negative pathogen(s) was reduced to $<10^3$ CFU/ml in urine culture; AND a negative blood culture for a Gram-negative pathogen that was identified as a uropathogen (if repeated after positive baseline blood culture).
Persistence	Demonstration that one or more of the baseline Gram-negative pathogen(s) remained continuously present in urine culture at $\geq 10^3$ CFU/ml; OR a continuously positive blood culture with an organism that was identified as a Gram-negative uropathogen.
Recurrence	Isolation of the same baseline Gram-negative pathogen(s) from urine culture after a response of eradication; OR a positive blood culture with the same baseline Gram-negative pathogen that was identified as a uropathogen after a response of eradication.
Indeterminate	No urine culture was available, or the culture could not be interpreted for any reason.

[a]Day 14 occurred 7 [±2] days after end of treatment (i.e. the test of cure visit).
[b]Day 21 occurred 14 [±2] days after end of treatment (i.e. the late follow-up visit).

eTable 3. Listing of All Secondary Outcomes Assessed in the Phase 3 Study Not Presented in This Report

The composite outcome for the clinically evaluable and microbiologically evaluable populations.
The composite outcome for the microbiologically evaluable + resistant population.
The number and percentage of patients in the microbiologically evaluable, and microbiologically evaluable + resistant populations with composite outcomes (success, failure, or indeterminate) at day 3 of treatment, end of treatment and at Day 21[a] will be summarized by treatment group.
The number and percentage of patients in the microbiologically evaluable, and microbiologically evaluable + resistant populations with clinical outcomes (cure, improvement, failure, and indeterminate) at day 3 of treatment, end of treatment, at Day 14[b], and at Day 21 will be summarized by treatment group.
The number and percentage of patients in the microbiologically evaluable, and microbiologically evaluable + resistant populations with per-patient microbiological outcomes (eradication, persistence, recurrence, and indeterminate) at day 3 of treatment, end of treatment, at Day 14 , and at Day 21 will be summarized by treatment group.
The per-pathogen microbiological outcomes (eradication, persistence, recurrence, and indeterminate) at day 3 of treatment, end of treatment, at Day 14, and at Day 21 by baseline pathogen will be summarized by treatment group in the primary analysis set, patients without exclusion based on susceptibility results, microbiologically evaluable, and microbiologically evaluable + resistant populations.
Clinical cure rates at day 3 of treatment, end of treatment, at Day 14, and at Day 21 by baseline pathogen will be summarized in the primary analysis set, patients without exclusion based on susceptibility results, microbiologically evaluable, and microbiologically evaluable + resistant populations as the proportion of patients with a clinical cure for each baseline pathogen isolated.
Clinical outcomes at day 3 of treatment, end of treatment, at Day 14, and at Day 21 will be summarized for the subset of patients infected with baseline extended spectrum β-lactamase-producing isolates of Enterobacterales in the primary analysis set, patients without exclusion based on susceptibility results, microbiologically evaluable, and microbiologically evaluable + resistant populations.
Per-patient microbiological outcomes at day 3 of treatment, end of treatment, at Day 14, and at Day 21 will be summarized for the subset of patients infected with baseline extended spectrum β-lactamase-producing isolates of Enterobacterales in the primary analysis set, patients without exclusion based on susceptibility results, microbiologically evaluable, and microbiologically evaluable + resistant populations.
Composite outcomes (success, failure, or indeterminate) at day 3 of treatment, end of treatment, at Day 14, and at Day 21 will be summarized for the subset of patients infected with baseline extended spectrum β-lactamase-producing isolates of Enterobacterales in the primary analysis set, patients without exclusion based on susceptibility results, microbiologically evaluable, and microbiologically evaluable + resistant populations.
Clinical cure at Day 14 will be summarized for discrete minimum inhibitory concentration values in the primary analysis set, patients without exclusion based on susceptibility results, microbiologically evaluable, and microbiologically evaluable + resistant.
Per-patient microbiological Eradication at Day 14 will be summarized for discrete cefepime/enmetazobactam and piperacillin/tazobactam baseline minimum inhibitory concentration values by baseline pathogen in the primary analysis set, patients without exclusion based on susceptibility results, microbiologically evaluable, and microbiologically evaluable + resistant populations.
Composite outcomes at Day 14 will be summarized for discrete cefepime/enmetazobactam and piperacillin/tazobactam baseline minimum inhibitory concentration values by baseline pathogen in the primary analysis set, patients without exclusion based on susceptibility results, microbiologically evaluable, and microbiologically evaluable + resistant populations.

[a]Day 21 occurred 14 [±2] days after end of treatment (i.e. the late follow-up visit).
[b]Day 14 occurred 7 [±2] days after end of treatment (i.e. the test of cure visit).

eTable 4. Demographic and Baseline Characteristics of Patients in the Primary Analysis Set

Demographic/Characteristic Category/Statistic	Cefepime/ enmetazobactam (N=345)	Piperacillin/ tazobactam (N=333)
Age in years, mean (SD)	55.4 (18.7)	52.4 (19.7)
Age group, n (%)		
<65 years	209 (60.6)	220 (66.1)
65 to <75 years	85 (24.6)	70 (21.0)
≥75 years	51 (14.8)	43 (12.9)
Sex		
Male	144 (41.7)	127 (38.1)
Female	201 (58.3)	206 (61.9)
Race, n (%)		
Asian	3 (0.9)	1 (0.3)
Black	1 (0.3)	0 (0.0)
White	327 (94.8)	316 (94.9)
Other[a]	14 (4.1)	16 (4.8)
Weight in kg, mean (SD) [n]	75.7 (16.9) [344]	74.3 (17.6) [333]
Height in cm, mean (SD) [n]	168.2 (9.6) [345]	167.9 (9.0) [333]
BMI (kg/m^2), mean (SD) [n]	26.7 (5.6) [344]	26.3 (5.5) [333]
eGFR at baseline (ml/min/1.73 m^2), mean (SD) [n]	71.3 (22.3) [331]	71.5 (24.6) [312]
eGFR group at baseline, n (%)		
Severe: <30 ml/min/1.73 m^2	2 (0.6)	5 (1.5)
Moderate: 30-59 ml/min/1.73 m^2	79 (22.9)	75 (22.5)
Mild: 60-89 ml/min/1.73 m^2	187 (54.2)	166 (49.8)
Normal: ≥90 ml/min/1.73 m^2	63 (18.3)	66 (19.8)
Type of infection, n (%)		
Acute pyelonephritis	171 (49.6)	178 (53.5)
Complicated UTI with removable source of infection	75 (21.7)	73 (21.9)
Complicated UTI without removable source of infection but with other risk factors	99 (28.7)	82 (24.6)
Prior antibiotic therapy, n (%)		
Short-acting antibiotic up to 24 hours	25 (7.2)	23 (6.9)
No prior antibiotic therapy	320 (92.8)	310 (93.1)
Region, n (%)		
Eastern Europe	238 (69.0)	240 (72.1)
Americas	21 (6.1)	22 (6.6)
Other countries	85 (24.6)	71 (21.3)
Country category, n (%)		
US	1 (0.3)	0 (0.0)
Non-US	344 (99.7)	333 (100.0)
Charlson Comorbidity Index at baseline, n (%)		
<3	198 (57.4)	205 (61.6)
≥3	145 (42.0)	125 (37.5)
Presence of concurrent bacteremia at baseline, n (%)	38 (11.0)	28 (8.4)
Diabetes at baseline, n (%)	55 (15.9)	41 (12.3)
Enterobacterales baseline pathogen, extended spectrum β-lactamase-producing, n (%)	76 (22.0)	66 (19.8)
Baseline pathogen, 5 most common		
Escherichia coli	264 (76.5)	254 (76.3)
Klebsiella pneumoniae	34 (9.9)	32 (9.6)
Proteus mirabilis	19 (5.5)	19 (5.7)
Pseudomonas aeruginosa	13 (3.8)	11 (3.3)
Enterobacter cloacae	7 (2.0)	3 (0.9)

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation

[a]Other includes unknown or was not identified.

eTable 5. Overall Success, Clinical Cure and Microbiological Eradication in Patients Without Exclusion Based on Susceptibility

Response at visit	Cefepime/ enmetazobactam (N=388) n (%)	Piperacillin/ tazobactam (N=383) n (%)	Treatment difference[a] % (95% CI)
Day 3 of treatment			
Overall success[b]	352 (90.7)	331 (86.4)	4.2 (-0.5, 8.8)
Clinical cure	19 (4.9)	19 (5.0)	0.0 (-3.2, 3.3)
Improvement[c]	357 (92.0)	347 (90.6)	not determined
Microbiological eradication	357 (92.0)	338 (88.3)	3.6 (-0.8, 8.0)
End of therapy			
Overall success	354 (91.2)	357 (93.2)	-2.1 (-6.0, 1.8)
Clinical cure	362 (93.3)	362 (94.5)	-1.3 (-4.9, 2.2)
Microbiological eradication	371 (95.6)	369 (96.3)	-0.9 (-3.9, 2.1)
Day 14[d]			
Overall success	305 (78.6)	225 (58.7)	20.7 (14.1, 27.0)
Clinical cure	356 (91.8)	340 (88.8)	3.1 (-1.2, 7.4)
Microbiological eradication	321 (82.7)	247 (64.5)	19.0 (12.8, 25.0)
Day 21[e]			
Overall success	265 (68.3)	226 (59.0)	10.3 (3.5, 17.0)
Clinical cure	334 (86.1)	324 (84.6)	1.5 (-3.6, 6.6)
Microbiological eradication	291 (75.0)	252 (65.8)	10.0 (3.6, 16.4)

[a]Treatment difference was determined using the stratified Newcombe method.
[b]Overall success was determined as a composite outcome of clinical cure (complete resolution of the baseline signs and symptoms present at screening) and microbiological eradication ($<10^3$ CFU/ml of qualifying baseline pathogen in urine).
[c]Improvement was defined as lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms, but continued intravenous therapy was warranted. This outcome category was only used at Day 3 of treatment.
[d]Day 14 occurred 7 [±2] days after end of treatment (i.e. the test of cure visit).
[e]Day 21 occurred 14 [±2] days after end of treatment (i.e. the late follow-up visit).

eTable 6. Overview of Adverse Events in All Patients Receiving at Least One Dose of Study Drug

Category	Cefepime/ enmetazobactam (N=516) n (%)	Piperacillin/ tazobactam (N=518) n (%)
Patients with any adverse event	277 (53.7)	242 (46.7)
Patients with adverse event		
Any treatment-emergent adverse event	258 (50.0)	228 (44.0)
Drug-related treatment-emergent adverse event	102 (19.8)	75 (14.5)
Patients with treatment-emergent adverse event		
Mild (CTCAE Grade 1)	174 (33.7)	153 (29.5)
Moderate (CTCAE Grade 2)	58 (11.2)	49 (9.5)
Severe (CTCAE Grade 3)	20 (3.9)	22 (4.2)
Life-threatening (CTCAE Grade 4)	3 (0.6)	1 (0.2)
Death (CTCAE Grade 5)	3 (0.6)	3 (0.6)
Drug-related treatment-emergent adverse event		
Mild (CTCAE Grade 1)	74 (14.3)	54 (10.4)
Moderate (CTCAE Grade 2)	20 (3.9)	16 (3.1)
Severe (CTCAE Grade 3)	8 (1.6)	5 (1.0)
Life-threatening (CTCAE Grade 4)	0 (0.0)	0 (0.0)
Death (CTCAE Grade 5)	0 (0.0)	0 (0.0)
Patients with death	3 (0.6)	3 (0.6)
Patients with serious adverse event		
Any serious adverse event	22 (4.3)	19 (3.7)
Treatment-emergent serious adverse event	22 (4.3)	19 (3.7)
Drug-related treatment-emergent serious adverse event	1 (0.2)	3 (0.6)
Patients with discontinuation of study drug due to treatment-emergent adverse event		
Any treatment-emergent adverse event	9 (1.7)	4 (0.8)
Drug-related treatment-emergent adverse event	5 (1.0)	2 (0.4)

Abbreviations: CTCAE, common terminology criteria for adverse events

eTable 7. Listing of Adverse Events Leading to Discontinuation of Study Drug in All Patients Receiving at Least One Dose of Study Drug

Treatment/ Patient number	Adverse Event[a] (Preferred Term)	Severity	Related to Study Drug	Outcome
Cefepime/enmetazobactam				
325-007	Urinary retention	Grade 3	Yes	RD
	Abdominal pain	Grade 3	Yes	RD
401-002	Bacterial infection	Grade 1	No	RD
406-003	Pneumonia	Grade 2	No	RD
	Transaminases increased	Grade 3	Yes	RD
425-020	Insomnia	Grade 2	No	RD
521-003	Urinary tract infection	Grade 2	No	RD
620-001	Nausea	Grade 3	Yes	RD
	Eructation	Grade 2	Yes	RD
	Restlessness	Grade 3	Yes	RD
701-004	Headache	Grade 3	Yes	RD
922-013	Pyelonephritis acute	Grade 3	No	RD
923-009	Dermatitis allergic	Grade 3	Yes	RD
Piperacillin/tazobactam				
400-016	Lung carcinoma cell type unspecific recurrent	Grade 5	No	Fatal
620-002	Septic shock	Grade 5	No	Fatal
924-016	Abdominal pain upper	Grade 2	Yes	RD
	Vomiting	Grade 2	Yes	RD
	Diarrhea	Grade 2	Yes	RD
930-032	Hypersensitivity	Grade 2	Yes	RD

Abbreviations: RD, Recovered/Resolved.
[a]Adverse events were distinguished as occurring on or after the first dose of study drug. Coding was based on the Medical Dictionary for Regulatory Activities Version 21.0.

eBox. Exclusion and Inclusion criteria Used Among 1107 Patients Assessed for Study Eligibility

Inclusion criteria not met by assessed patients:

- Baseline urine culture specimen
- Pyuria
- Expectation that any implanted urinary instrumentation will be surgically removed or replaced
- Expectation that the patient's complicated urinary tract infection (UTI) or acute pyelonephritis will require hospitalization and initial treatment
- Female patient who is no longer of childbearing potential must meet 1 of the described criteria
- Clinical signs and/or symptoms of complicated UTI or acute pyelonephritis

Exclusion criteria met by assessed patients:

- QT interval corrected using the Fridericia formula >450 ms
- Impairment of kidney function with estimated glomerular filtration rate <30 mL/min/1.73 m^2
- At screening, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or total bilirubin level >3 times the upper limit of normal, or current clinically significant liver disease
- Any condition or circumstance that would compromise the safety of the patient or the quality of data
- Unable or unwilling, in the judgment of the investigator, to comply with the protocol
- At screening, platelet count <50 ×10^3/μL, absolute neutrophil count <1000/μL, or hemoglobin level <8 g/dL
- Immunocompromising condition or immunosuppressive therapy
- Known urine culture with gram-positive primary pathogen or suspected gram-positive pathogen
- Likely to require the use of an antibiotic for complicated UTI or acute pyelonephritis prophylaxis
- Receipt of potentially effective systemic antibacterial drug therapy for a continuous duration >24 hours
- Presence of disease or condition that may confound the assessment of efficacy
- Complete, permanent obstruction of the urinary tract
- History of significant hypersensitivity or allergic reaction
- Patient considered unlikely to survive the approximately 6-week study period
- Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned
- Weight >180 kg
- Any rapidly progressing disease or immediately life-threatening illness
- Complicated UTI known at study entry to be caused by pathogens resistant to the study antibiotics
- Intractable UTI at baseline
- Pregnant or expecting to conceive, breastfeeding, or plans to breastfeed