Exposure–Response Analyses to Support Optimal Dosing Regimens of Ceftolozane/Tazobactam in Patients With Hospital-Acquired Pneumonia (HAP)/Ventilator-Associated Pneumonia (VAP) in ASPECT-NP

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BACKGROUND

- Nosocomial pneumonia comprises hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) and is the most common nosocomial infection; mortality rates range from 3%–22% for nonventilated HAP (10%–40% for ventilated HAP) and from 6%–29% for VAP[1-3]
- Ceftolozane/tazobactam (C/T), a combination of the antipseudomonal cephalosporin ceftolozane and the β-lactamase inhibitor tazobactam, is approved in the European Union and United States for the treatment of complicated intra-abdominal and urinary tract infections and HAP/VAP[4,5]
- A 3-g C/T dose (2-g ceftolozane and 1-g tazobactam), or C/T dose adjusted based on renal function, was evaluated in patients with HAP/VAP in the phase 3 randomized, controlled, double-blind ASPECT-NP study (NCT02070757)
  - C/T was safe, and efficacy was noninferior to meropenem[6]
- An exposure–response analysis was performed to assess the potential relationship between ceftolozane and tazobactam plasma pharmacokinetics (PK) and clinical efficacy end points

METHODS

- Ceftolozane and tazobactam plasma exposure measures associated with the last dose were predicted for each patient using a population PK model and were utilized in the exposure–response analyses
- Exposure measures for efficacy analyses included:
  - Ceftolozane: the percentage of time the concentration of free ceftolozane in plasma exceeded the minimum inhibitory concentration (MIC) of the lower respiratory tract isolate (%fT>MIC)
    - The MIC value used in this analysis corresponded to the highest ceftolozane MIC for the relevant baseline pathogens identified for each patient
  - Tazobactam: the percentage of time the concentration of free tazobactam in plasma exceeded the threshold concentration (%fT>C_T)
- Efficacy end points included Day 28 all-cause mortality and clinical response at the test-of-cure (TOC) visit
  - Clinical outcome was determined by the blinded investigator based on an overall assessment of clinical status based on signs, symptoms, and available laboratory data
- Exposure measures, efficacy data, and study- and patient-specific information from ASPECT-NP were obtained for patients in the intention-to-treat (ITT) population who received C/T, had a baseline organism isolated, and had available exposure measures from the population PK model (**Table 1**)

Table 1. Number of Patients Included in the Exposure–Response Analyses by Renal Function Subgroup

Renal function subgroup[a]	Ceftolozane, mg	Tazobactam, mg	Patients (N=231), n (%)
CrCl ≥15 to 29 mL/min	500	250	9 (3.9)
CrCl ≥30 to ≤50 mL/min	1000	500	16 (6.9)
CrCl >50 mL/min	2000	1000	206 (89.2)

CrCl, creatinine clearance.
[a]CrCl was calculated using the Cockcroft-Gault equation.

- Exploratory data analyses of efficacy end points determined that the data did not support meaningful exploration of structural model analysis; therefore, only exploratory graphical analyses were performed to assess relationships between individual estimates of exposures and efficacy end points

RESULTS

Efficacy

- A total of 462 observations from 231 patients in ASPECT-NP were included in the exposure–response efficacy dataset
- Patient demographics and clinical characteristics of those included in the exposure–response efficacy set were comparable to the ITT population and are shown in **Table 2**

Table 2. Patient Demographics and Clinical Characteristics of the Exposure–Response Efficacy Analysis Set

Characteristic	ASPECT-NP analysis set (N=231)
Age, mean (SD), years	60.0 (16.4)
Age group, n (%), years	
<65	131 (56.7)
≥65	100 (43.3)
≥75	47 (20.3)
Male sex, n (%)	174 (75.3)
Baseline weight, mean (SD), kg	81.2 (16.6)
Baseline CrCl, mean (SD), mL/min[a]	108.5 (60.0)

CrCl, creatinine clearance.
[a]Calculated using the Cockcroft-Gault equation and local laboratory data.

- The exposure–response efficacy analysis set had an overall Day 28 all-cause mortality of 16% (n=36/231) and a clinical cure rate at the TOC visit of 65% (n=151/231)
- Efficacy response rates were comparable among patients with baseline Enterobacterales isolates and patients with baseline *Pseudomonas aeruginosa* isolates (**Table 3**)

Table 3. Summary Statistics of Exposure Measurements and Efficacy Response by Baseline Pathogen

Variable	Statistic	Enterobacterales[a] (n=154)	*P aeruginosa*[a] (n=43)	Overall[a,b] (N=191)
%fT>1 μg/mL for tazobactam	Mean (SD)	76.1 (24.6)	79.7 (23.1)	76.9 (24.3)
	Median (min–max)	87.2 (28.0–99.0)	94.4 (22.8–99.0)	87.2 (22.8–99.0)
%fT>MIC for ceftolozane	Mean (SD)	84.3 (32.8)	94.8 (16.1)	86.6 (30.3)
	Median (min–max)	99.0 (0.0–99.0)	99.0 (0.0–99.0)	99.0 (0.0–99.0)
Ceftolozane MIC, μg/mL	Mean (SD)	23.1 (58.8)	8.8 (39.2)	20.0 (55.4)
	Median (min–max)	0.5 (0.1–256.0)	1.0 (0.3–256.0)	0.5 (0.1–256.0)
Day 28 all-cause mortality,[c] n (%)	Death	20 (13.0)	10 (23.3)	30 (15.2)
Clinical response at TOC,[d] n (%)	Cure	104 (67.5)	28 (65.1)	132 (67.0)

%fT>1 μg/mL, percentage of time the threshold concentration of tazobactam exceeded 1 μg/mL; %fT>MIC, percentage of time the concentration of free ceftolozane in plasma exceeded the MIC that was determined in the presence of tazobactam; EOT, end of treatment; MIC, minimum inhibitory concentration; TOC, test of cure.
[a]The analysis set presented in this table is a subset of the exposure–response efficacy analysis set.
[b]Six patients had 2 baseline pathogens with the same highest MIC value and were included in both Enterobacterales and *P aeruginosa* groups.
[c]Mortality was assessed on Days 14 and 28; the Day 28 all-cause mortality end point accounted for deaths on or before Day 28.
[d]Clinical response assessments were performed at the EOT, TOC, and late follow-up visits. Determination of clinical response was based on an overall assessment of clinical status based on signs, symptoms, and available laboratory data. Clinical responses at EOT and TOC visits were classified as cure, failure, or indeterminate. "Clinical cure" was a favorable clinical response.

- All-cause mortality and clinical cure response rates were similar regardless of the MIC cutoff values evaluated (**Table 4**)
  - Day 28 all-cause mortality ranged from 6.3% to 25.6%
  - The clinical cure rate at TOC ranged from 27.3% to 75.0%

Table 4. Summary of Overall Response Rates by Ceftolozane/Tazobactam MIC Cutoff Values[a,b]

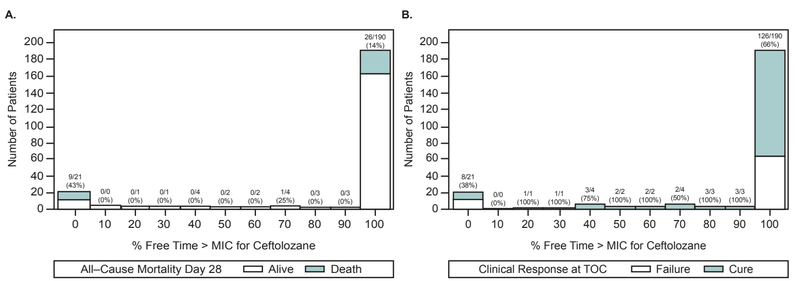
MIC, μg/mL	Day 28 all-cause mortality, n/N (%)	Clinical cure at TOC, n/N (%)
≤1	19/142 (13.4)	102/142 (71.8)
>1 to ≤2	3/19 (15.8)	11/19 (57.9)
>2 to ≤4	1/16 (6.3)	12/16 (75.0)
>4 to ≤8	2/11 (18.2)	3/11 (27.3)
>8 to ≤256	11/43 (25.6)	23/43 (53.5)

MIC, minimum inhibitory concentration; TOC, test of cure.
[a]Due to the small number of isolates at MIC cutoff values from >8 to ≤256 μg/mL, patients within this range were combined for analysis.
[b]The MIC value used in this analysis corresponded to the highest MIC for relevant pathogens identified at baseline for each patient.

Ceftolozane

- A total of 82% (n=190/231) of patients had a ceftolozane %fT>MIC of 99%
  - Of the remaining patients, 9% (n=21/231) had %fT>MIC of 0% due to high MIC values of the lower respiratory tract pathogen (64–256 μg/mL)
- Ceftolozane %fT>MIC values were similar among patients who died and those who survived to Day 28, with median values of 99% in both groups (**Figure 1A**)
- Ceftolozane %fT>MIC values were similar between patients who were clinically cured and patients who were not cured, with median values of 99% in both groups (**Figure 1B**)

Figure 1. Frequency Distributions of Exposure Measures for Ceftolozane (%fT>MIC) by (A) Day 28 All-Cause Mortality and (B) Clinical Response at TOC



%fT>MIC, percentage of time the concentration of free ceftolozane in plasma exceeded the MIC; MIC, minimum inhibitory concentration; TOC, test of cure.
The number under each bar represents the median of the range of values for that bar. The ratio of numbers represents the number of deaths/total number of patients in each bar (panel A) or number of clinical cures/total number of patients in each bar (panel B). The number in parentheses is the percentage of patients who died (panel A) or who were clinically cured (panel B).

- Ceftolozane exposure–response was analyzed in patients whose baseline lower respiratory tract isolate was at or below various MIC values (1, 2, 4, and 8 μg/mL; **Table 5**)
  - The all-cause mortality rate for patients with ceftolozane %fT>MIC of 99% was ~13% compared with 0.0% for patients with %fT>MIC of <99%
  - No exposure–response trend was observed for ceftolozane at TOC at any MIC cutoff
    - The clinical cure rate for patients with ceftolozane %fT>MIC of 99% was ~70% compared with 83.3%–100.0% for patients with %fT>MIC of <99%

Table 5. Summary of Efficacy Response for Ceftolozane by %fT>MIC and MIC Cutoff Values

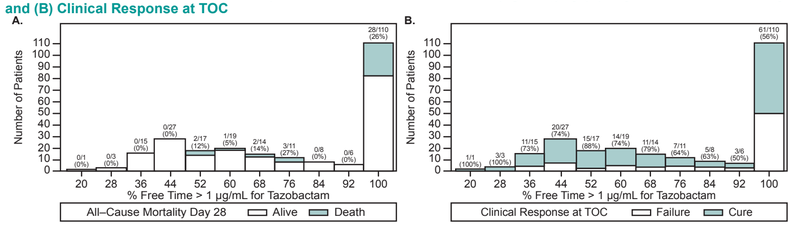
MIC cutoff, μg/mL	Exposure	n	%fT>MIC	Day 28 all-cause mortality, %	Clinical cure at TOC, %
≤1	%fT>MIC of 99.0%	141		13.5%	71.6%
	%fT>MIC <99.0%	1	86.1%	0.0%	100.0%
≤2	%fT>MIC of 99.0%	160		13.8%	70.0%
	%fT>MIC <99.0%	1	86.1%	0.0%	100.0%
≤4	%fT>MIC of 99.0%	173		13.3%	70.0%
	%fT>MIC <99.0%	4	73.7%, 84.0%, 86.1%, 89.2%	0.0%	100.0%
≤8	%fT>MIC of 99.0%	182		13.7%	67.6%
	%fT>MIC <99.0%	6	63.3%, 68.5%, 73.7%, 84.0%, 86.1%, 89.2%	0.0%	83.3%

%fT>MIC, percentage of time the concentration of free ceftolozane in plasma exceeded the MIC; MIC, minimum inhibitory concentration; TOC, test of cure.

Tazobactam

- All patients achieved a tazobactam PK/pharmacodynamic (PD) target of %fT>C_T >20%
- There was no exposure–response relationship for tazobactam
  - Day 28 all-cause mortality rates increased with increasing %fT>C_T (**Figure 2A**)
  - Clinical cure rates decreased with increasing tazobactam %fT>C_T (**Figure 2B**)
- Because tazobactam is not expected to have antibacterial pharmacologic activity, the lack of an exposure–response relationship is not unexpected

Figure 2. Frequency Distributions of Exposure Measures for Tazobactam (%fT>C_T) by (A) Day 28 All-Cause Mortality and (B) Clinical Response at TOC



%fT>CT, percentage of time the concentration of free tazobactam in plasma exceeded the threshold concentration; TOC, test of cure.
The number under each bar represents the median of the range of values for that bar. The ratio of numbers represents the number of deaths/total number of patients in each bar (panel A) or number of clinical cures/total number of patients in each bar (panel B). The number in parentheses is the percentage of patients who died (panel A) or who were clinically cured (panel B).

- Tazobactam exposure–response was analyzed in patients whose baseline lower respiratory tract isolate was at or below various ceftolozane/tazobactam MIC values (1, 2, 4, and 8 μg/mL; **Table 6**)
  - No exposure–response trend was observed for tazobactam at any MIC cutoff

Table 6. Summary of PK and Efficacy Response by Ceftolozane MIC Cutoff Values

Variable	Statistic	MIC ≤1 μg/mL (n=142)	MIC >1 μg/mL (n=89)	Overall (N=231)
%fT>C_T>1 μg/mL for tazobactam	Mean (SD)	72.6 (24.8)	83.9 (22.1)	77.0 (24.4)
	Median (min–max)	74.7 (22.8–99.0)	99.0 (36.3–99.0)	89.2 (22.8–99.0)
%fT>MIC for ceftolozane	Mean (SD)	98.9 (1.1)	67.3 (41.7)	86.7 (30.1)
	Median (min–max)	99.0 (86.1–99.0)	99.0 (0.0–99.0)	99.0 (0.0–99.0)
Ceftolozane MIC, μg/mL	Mean (SD)	0.5 (0.3)	54.1 (83.9)	21.1 (58.1)
	Median (min–max)	0.5 (0.1–1.0)	8.0 (2.0–256.0)	1.0 (0.1–256.0)
Day 28 all-cause mortality,[a] n (%)	Death	19 (13.4)	17 (19.1)	36 (15.6)
Clinical response at TOC visit,[b] n (%)	Cure	102 (71.8)	49 (55.1)	151 (65.4)
Variable	**Statistic**	**MIC ≤2 μg/mL (n=161)**	**MIC >2 μg/mL (n=70)**	**Overall (N=231)**
%fT>C_T>1 μg/mL for tazobactam	Mean (SD)	73.5 (24.8)	84.8 (21.6)	77.0 (24.4)
	Median (min–max)	76.8 (22.8–99.0)	99.0 (36.3–99.0)	89.2 (22.8–99.0)
%fT>MIC for ceftolozane	Mean (SD)	98.9 (1.0)	58.7 (43.2)	86.7 (30.1)
	Median (min–max)	99.0 (86.1–99.0)	75.2 (0.0–99.0)	99.0 (0.0–99.0)
Ceftolozane MIC, μg/mL	Mean (SD)	0.7 (0.6)	68.2 (89.6)	21.1 (58.1)
	Median (min–max)	0.5 (0.1–2.0)	16.0 (4.0–256.0)	1.0 (0.1–256.0)
Day 28 all-cause mortality,[a] n (%)	Death	22 (13.7)	14 (20.0)	36 (15.6)
Clinical response at TOC visit,[b] n (%)	Cure	113 (70.2)	38 (54.3)	151 (65.4)
Variable	**Statistic**	**MIC ≤4 μg/mL (n=177)**	**MIC >4 μg/mL (n=54)**	**Overall (N=231)**
%fT>C_T>1 μg/mL for tazobactam	Mean (SD)	74.4 (24.7)	85.3 (21.6)	77.0 (24.4)
	Median (min–max)	78.9 (22.8–99.0)	99.0 (36.3–99.0)	89.2 (22.8–99.0)
%fT>MIC for ceftolozane	Mean (SD)	98.6 (2.5)	47.7 (43.3)	86.7 (30.1)
	Median (min–max)	99.0 (73.7–99.0)	45.2 (0.0–99.0)	99.0 (0.0–99.0)
Ceftolozane MIC, μg/mL	Mean (SD)	1.0 (1.1)	87.3 (94.0)	21.1 (58.1)
	Median (min–max)	0.5 (0.1–4.0)	32.0 (8.0–256.0)	1.0 (0.1–256.0)
Day 28 all-cause mortality,[a] n (%)	Death	23 (13.0)	13 (24.1)	36 (15.6)
Clinical response at TOC visit,[b] n (%)	Cure	125 (70.6)	26 (48.1)	151 (65.4)
Variable	**Statistic**	**MIC ≤8 μg/mL (n=188)**	**MIC >8 μg/mL (n=43)**	**Overall (N=231)**
%fT>C_T>1 μg/mL for tazobactam	Mean (SD)	75.2 (24.8)	84.7 (21.3)	77.0 (24.4)
	Median (min–max)	81.0 (22.8–99.0)	99.0 (37.4–99.0)	89.2 (22.8–99.0)
%fT>MIC for ceftolozane	Mean (SD)	98.3 (4.2)	36.1 (40.7)	86.7 (30.1)
	Median (min–max)	99.0 (63.3–99.0)	16.6 (0.0–99.0)	99.0 (0.0–99.0)
Ceftolozane MIC, μg/mL	Mean (SD)	1.4 (2.0)	107.5 (95.3)	21.1 (58.1)
	Median (min–max)	0.5 (0.1–8.0)	64.0 (16.0–256.0)	1.0 (0.1–256.0)
Day 28 all-cause mortality,[a] n (%)	Death	25 (13.3)	11 (25.6)	36 (15.6)
Clinical response at TOC visit,[b] n (%)	Cure	128 (68.1)	23 (53.5)	151 (65.4)

%fT>C_T>1 μg/mL, percentage of time the concentration of free tazobactam in plasma exceeded the threshold concentration of 1 μg/mL; %fT>MIC, percentage of time the concentration of free ceftolozane in plasma exceeded the MIC; EOT, end of treatment; MIC, minimum inhibitory concentration; PK, pharmacokinetic; TOC, test of cure.
[a]Mortality was assessed on Days 14 and 28; the Day 28 all-cause mortality end point accounted for deaths on or before Day 28.
[b]Clinical response assessments were performed at the EOT, TOC, and late follow-up visits. Determination of clinical response was based on an overall assessment of clinical status based on signs, symptoms, and available laboratory data. Clinical responses at EOT and TOC visits were classified as cure, failure, or indeterminate. "Clinical cure" was a favorable clinical response.

CONCLUSIONS

- All patients with a baseline lower respiratory tract pathogen with an MIC ≤4 μg/mL achieved exposures above the PK/PD targets for both drugs
- No exposure–response trend was observed for ceftolozane or tazobactam
- These results support the appropriateness of the 3-g C/T dose (2-g ceftolozane and 1-g tazobactam), adjusted based on renal function, in adult patients with ventilated nosocomial pneumonia

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WG, ZZ, GL, CJB, ER, CDA, and H-PF are employees of MSD. JP, YTP, and JF-K are employees of Cognigen Corporation, a Simulations Plus company, which provides consulting services to MSD.

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