Meropenem-Vaborbactam (M-V): Clinical Outcomes by Bacteremia Status in a Phase 3 Randomized, Double-blind Trial in cUTIs (TANGO 1)

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Abstract

Background: Meropenem-vaborbactam (M-V) is a new beta-lactam/beta-lactamase inhibitor combination being developed to treat serious gram-negative infections such as complicated urinary tract infection (cUTI) or acute pyelonephritis (AP), including cases with concomitant bacteremia.

Methods: TANGO 1 was a Phase 3 randomized trial of M-V vs piperacillin-tazobactam (P-T) in the treatment of adults with cUTI/AP. Subjects with cUTI/AP, with or without bacteremia requiring at least 5 days of IV treatment were randomized 1:1 to receive M-V (2 g/2 g via 3-hr infusion) or P-T (4 g/0.5 g via 30-min infusion) every 8 h. After 15 doses, the agent could be switched to oral levofloxacin, to complete 10-day total treatment (up to 14 days if clinically indicated in those with concurrent bacteremia). Overall success (composite of clinical cure and microbial eradication) rates for cUTI/AP were assessed at End of IV Treatment (EOIVT) and Test of Cure (TOC) visits by bacteremia status at baseline.

Results: Of 550 subjects randomized, 374 (192 for M-V; 182 for P-T) were included in the microbiological modified intent-to-treat population (m-MITT popn). Five percent of subjects had concurrent bacteremia at baseline. The proportion of M-V and P-T subjects at baseline who had concurrent bacteremia (6.3% [12/192]; 8.2% [15/182]) or had unknown bacteremia status (2.6% [5/192]; 1.6% [3/182]) was similar. Most subjects with bacteremia had AP (92% [11/12] for M-V; 60% [9/15] for P-T). Overall success rates by bacteremia status at EOIVT and TOC are presented.

Overall Success by Timepoint (m-MITT population)

	EOIVT		TOC	
	M-V (N=192)	P-T (N=182)	M-V (N=192)	P-T (N=182)
Presence of Bacteremia	10/12, 83.3%	15/15, 100%	9/12, 75.0%	9/15, 60.0%
Absence of Bacteremia	174/175, 99.4%	153/164, 93.3%	131/175, 74.9%	118/164, 72.0%

At EOIVT, the 2 subjects with bacteremia in the M-V group who did not achieve overall success were classified as failures because study drug was prematurely discontinued due to an AE (tremor in one; infusion-related reaction in the other). The bloodstream was cleared of bacteria in all subjects with bacteremia.

Conclusions: In this post hoc analysis, the overall success rates in the M-V group vs the P-T group at the TOC visit for patients with bacteremia and cUTI/AP were 75% and 60%, respectively. All organisms in the bloodstream were eradicated in all subjects with bacteremia. Findings suggest that M-V is able to effectively treat subjects with concurrent bacteremia associated with cUTI/AP.

Background

Meropenem-vaborbactam (M-V) is a new beta-lactam/beta-lactamase inhibitor combination being developed to treat serious gram-negative infections, such as complicated urinary tract infection (cUTI) or acute pyelonephritis (AP), including cases with concomitant bacteremia.

Methods

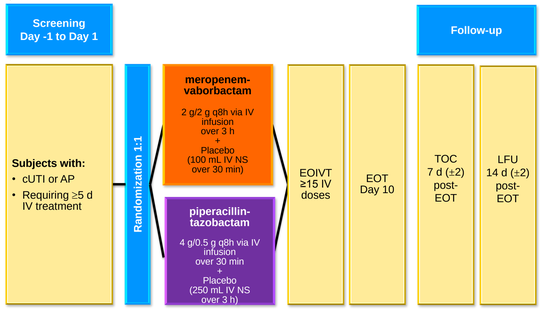
TANGO 1 was a Phase 3, multicenter, double-blind, double-dummy, randomized, parallel-group trial of M-V vs piperacillin-tazobactam (P-T) in the treatment of adults (>18 y) with cUTI or AP. The objective of the study was to assess the efficacy, safety, and tolerability of M-V administered by IV infusion in subjects with cUTI or AP.

The study design is outlined in **Figure 1**.

- Patients meeting inclusion criteria for cUTI or AP, with or without bacteremia, requiring at least 5 days of IV treatment were randomized 1:1 to receive either M-V or P-T every 8 hours to complete a total of 10 days of treatment. Treatment was up to 14 days if clinically indicated in subjects with concurrent bacteremia.
- If a patient met specific step-down criteria for oral therapy and had received a minimum of 15 doses of study drug, the antimicrobial agent could be switched to oral levofloxacin to complete the 10-day total treatment.
- Within this study design, the modified intent-to-treat (MITT) population included all subjects who were screened and randomized who received ≥1 dose of study drug (ie, M-V or P-T).

The microbiological modified intent-to-treat (m-MITT) population included all subjects who met the MITT criteria and had baseline bacterial pathogens of ≥10^5 CFU/mL of urine at baseline culture or the same pathogen present in concurrent blood and urine cultures.

Figure 1. Study Schema



EOIVT, end of IV treatment; EOT, end of treatment; TOC, test of cure; LFU, last follow-up.
Note: Subjects with bacteremia may receive treatment up to 14 days. For subjects with bacteremia, the visit window for the TOC visit is Day 15 to Day 23 and the visit window for the LFU visit is Day 22 to Day 30.

Concurrent bacteremia was defined as having the same pathogen in blood and urine cultures.

- Blood and urine cultures were collected prior to randomization in order to assess concurrent bacteremia in study subjects.
- If a blood culture was positive at baseline for an organism obtained in a concurrently collected urine sample, daily blood cultures were collected until the first negative blood culture (culture reading at 24 h or more). Additional blood cultures were collected at the investigator's discretion.
- Minimum inhibitory concentration (MIC) values were assessed for M-V and P-T using blood isolates from subjects with concurrent bacteremia.

The primary efficacy endpoint was the proportion of subjects in the m-MITT population who achieved overall success at the end of IV therapy (EOIVT) visit.

- Overall success was defined as a composite endpoint that required a clinical outcome of Cure or Improvement and a microbiologic outcome of Eradication.
- A clinical outcome of Cure at EOIVT was defined as the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP. Improvement was defined as the lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms of cUTI or AP, but continued IV therapy was warranted.
- A microbiologic outcome of Eradication was defined as a reduction in baseline bacterial pathogen(s) to <10^4 CFU/mL (FDA criteria).
- A key secondary endpoint was overall success at the test of cure (TOC) timepoint.

This post hoc analysis assessed overall success rates for cUTI/AP at EOIVT and TOC visits by bacteremia status at baseline.

Results

550 subjects were randomized, of which 545 received at least one dose of study drug (272 in M-V group and 273 in P-T group).

- 374 subjects (192 for M-V; 182 for P-T) were included in the m-MITT population.
- Study drug exposure for subjects with baseline bacteremia is summarized in **Table 1**.

Disease status, age, gender, race, renal function, diabetes status, systemic inflammatory response (SIRS) status, Charlson comorbidity score, and bacteremia status were summarized at baseline. The baseline characteristics of subjects with bacteremia in the m-MITT population are listed in **Table 2**.

- In the m-MITT group, the bacteremia status of M-V and P-T subjects at baseline was similar:
  - Concurrent bacteremia: M-V 6.3% (12/192); P-T 8.2% (15/182)
- Most subjects with bacteremia had AP (92% [11/12] in the M-V group; 60% [9/15] in the P-T group) **(Table 2)**.
- *Escherichia coli* was the most common baseline pathogen found in blood and urine cultures in subjects with bacteremia **(Figure 2)**.
- MIC values for baseline pathogens in subjects with bacteremia at baseline are summarized in **Table 3**.

Table 1. Study Drug Exposure in Subjects with Baseline Bacteremia (m-MITT Population)

Category	M-V (N=12)	P-T (N=15)	Total (N=27)
Patients Receiving only IV therapy			
N	4	8	12
Mean ± SD (days)	7.8 (6.40)	10.6 (3.02)	9.7 (4.36)
Patients Receiving IV and Oral Step-Down Therapy			
N	8	7	15
Total (Mean ± SD (days))	10.5 (0.76)	10.7 (1.11)	10.6 (0.91)
IV (Mean ± SD (days))	6.9 (1.13)	7.0 (1.41)	6.9 (1.22)
PO (Mean ± SD (days))	4.4 (1.06)	4.6 (1.13)	4.5 (1.06)

Exposure = last dose date of study drug – first dose date of study drug + 1, using calendar days.
Note: IV dose may be taken in 11 calendar days.
M-V, meropenem-vaborbactam; P-T, piperacillin-tazobactam.

Table 2. Baseline Characteristics of Subjects with Bacteremia (m-MITT Population)

Characteristic	M-V (N=12) n (%)	P-T (N=15) n (%)	Total (N=27) n (%)
AP	11 (91.7)	9 (60.0)	20 (74.1)
cUTI	1 (8.3)	6 (40.0)	7 (25.9)
With removable source of infection	0 (0.0)	3 (20.0)	3 (11.1)
With non-removable source of infection	1 (8.3)	3 (20.0)	4 (14.8)
Age (y): mean (SD)	55.3 (20.7)	58.7 (15.9)	57.2 (17.9)
No. ≥65 y	5 (41.7)	5 (33.3)	10 (37.0)
Gender, female	10 (83.3)	12 (80.0)	22 (81.5)
Race, white	9 (75.0)	14 (93.3)	23 (85.2)
Creatinine clearance (mL/min): mean (SD)	68.1 (26.6)	73.3 (24.8)	71.0 (25.3)
No. with ≤50 mL/min	4 (33.3)	3 (20.0)	7 (25.9)
Diabetes mellitus	1 (8.3)	6 (40.0)	7 (25.9)
SIRS	8 (66.7)	7 (46.7)	15 (55.6)
Charlson comorbidity score ≥3	9 (75.0)	11 (73.3)	20 (74.1)

Figure 2. Baseline Pathogens Present in Subjects with Concurrent Bacteremia at Baseline (m-MITT Population)

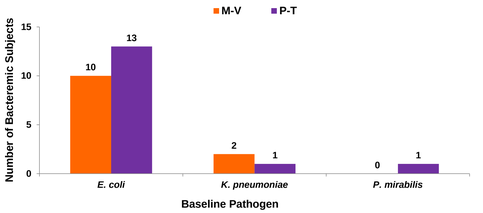


Figure 3 outlines overall success rates in baseline bacteremic subjects at both the EOIVT and TOC timepoints.

- In bacteremic subjects, the overall success rates at EOIVT were lower in the M-V group than in the P-T group (83.3% vs 100%).
- At EOIVT, the 2 subjects with bacteremia in the M-V group who did not achieve overall success were classified as failures because study drug was prematurely discontinued due to an AE (tremor in one; infusion-related reaction in the other). In both cases, the bloodstream was cleared of bacteria.
- At EOIVT, the bloodstream was cleared of bacteria in all subjects with bacteremia.
- Overall success rates at TOC were higher in the M-V group compared with the P-T group (75% vs 60%).
- Lower overall success rates at the TOC timepoint vs the EOIVT timepoint were driven by recurrence of baseline organisms in the urine.

Figure 3. Overall Success Rates by Bacteremia Status at EOIVT and TOC (m-MITT Population)

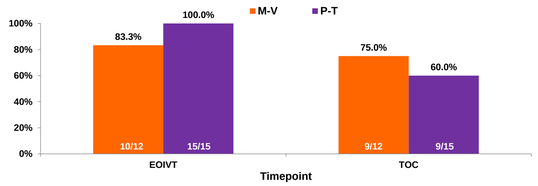


Table 3. MIC Per Baseline Pathogen in Subjects with Baseline Bacteremia (m-MITT Population)

Antimicrobial Agent Baseline Pathogen	MIC (μg/mL) of Antimicrobial Agent	
	Median* (μg/mL)	Range**
Meropenem-vaborbactam		
E. coli (N=9)	≤0.06	NA
K. pneumoniae (N=2)	≤0.06	NA
Piperacillin-tazobactam		
E. coli (N=13)	2	1 – 32
K. pneumoniae (N=1)	2	NA
P. mirabilis (N=1)	≤0.05	NA

Note: Only data from blood cultures are included. N refers to the number of isolates recovered in subjects with baseline bacteremia treated with the specified antimicrobial agent.
*Where the number of isolates equals 1 (N=1), the individual MIC value is provided. Where N=2, the median MIC value is provided.
**Range is provided for baseline pathogens with ≥2 isolates.
MIC, minimum inhibitory concentration.

Conclusions

- In the TANGO I clinical trial, *E. coli* was the most common baseline pathogen in concurrent blood and urine cultures in subjects with bacteremia.
- All organisms in the bloodstream were eradicated in all subjects with bacteremia.
- In this post hoc analysis, the overall success rates in the M-V group vs the P-T group at the TOC visit for patients with bacteremia and cUTI or AP were 75% and 60%, respectively.
- Findings suggest that meropenem-vaborbactam is able to effectively treat subjects with concurrent bacteremia associated with cUTI or AP, which occurred in 7% of study subjects with a baseline urinary pathogen.

Disclosures

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