Hospital and ICU Length of Stay (LOS) with Meropenem-Vaborbactam (M-V) versus Piperacillin-Tazobactam (P-T) in Complicated Urinary Tract Infections (cUTI), including Acute Pyelonephritis (AP) in TANGO 1

Poster
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Abstract

Background: Meropenem-vaborbactam is a new carbapenem/beta-lactamase inhibitor combination designed to have enhanced in vitro activity against select carbapenemase-producing Enterobacteriaceae, and is a potential new option for the treatment of severe gram-negative infections. Here, we examine hospital length of stay (LOS) associated with meropenem-vaborbactam (M-V) versus piperacillin-tazobactam (P-T) as assessed in a complicated urinary tract infections (cUTI) trial.

Methods: We conducted a Phase 3, randomized, double-blind, double-dummy trial (TANGO 1) in adult patients with cUTI, including acute pyelonephritis (AP). Patients meeting the inclusion criteria for cUTI or AP 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 hrs. Enrollment was stratified by geographic region and type of infection (AP, cUTI with removable source of infection, and cUTI with a non-removable source). After a minimum of 15 doses (5 days), patients could switch to oral levofloxacin if they met pre-specified criteria, so as to complete 10 days of total treatment. Hospital ward and LOS data was collected per protocol; LOS was defined as number of days from first dose of study drug until discharge. Intensive care unit (ICU) LOS was defined as number of days from first dose of study drug until discharge from the ICU. We analyzed hospital admission, LOS, and discharge status in two populations: the microbiologic modified intent-to-treat (m-MITT) and the modified intent-to-treat (MITT).

Results: 550 patients were enrolled; 272 received M-V and 273 received P-T. Most patients in the M-V (99.0%) and P-T groups (97.8%) were already hospitalized at study enrollment; 9.9% of patients in both groups in the m-MITT population were either in or admitted to the ICU at the time of study enrollment. For patients in the ICU at study enrollment, mean ICU LOS in the M-V group vs the P-T group was 9.3 (range 1-13) vs 11.1 (range 6-16) days, respectively. Across all hospitalized patients, mean LOS in the M-V and P-T groups was 9.7 (range 1-16) vs 9.9 (range 2-40) days, respectively. In the m-MITT population, most patients in both groups were discharged home (96.9% and 94.0% for M-V and P-T, respectively). Similar results for ICU admission, LOS, and discharge status were seen in the MITT population.

Conclusions: In this Phase 3 randomized, double-blind, double-dummy trial, ICU LOS was numerically shorter in patients receiving M-V compared with P-T, which might indicate cost-saving opportunities for cUTI treatment in ICU units.

Background

Meropenem-vaborbactam (M-V) is a new carbapenem/beta-lactamase inhibitor combination designed to have enhanced in vitro activity against select carbapenemase-producing Enterobacteriaceae.

- Hospital resource use is associated with higher costs in the management of serious gram-negative infections.
- ICU stay is a major contributor to the hospital cost of care for patients with serious gram-negative infections.
- M-V is a potential new option for the treatment of severe gram-negative infections.
- Hospital length of stay (LOS), including LOS in the ICU of patients treated with M-V vs those treated with piperacillin-tazobactam (P-T) was examined in TANGO 1, a Phase 3, randomized, double-blind, double-dummy trial in adult patients with complicated urinary tract infections (cUTI) or acute pyelonephritis (AP).

Methods

TANGO 1 was a Phase 3, multicenter, double-blind, double-dummy, randomized, parallel-group study of M-V vs P-T for adults 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.

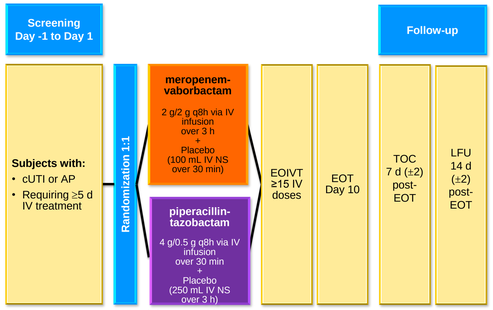
- Adult patients with documented or suspected cUTI or AP were eligible for enrollment into the study.
- After enrollment, patients were randomized 1:1 to receive either M-V (2 g/2 g; 3-hr infusion) or P-T (4 g/0.5 g; 30-min infusion) every 8 hours **(Figure 1)**.
- After 15 doses, the agent could be switched to oral levofloxacin if pre-specified criteria were met, to complete a 10-day total treatment.

Hospital ward and LOS data was collected per study protocol.

- LOS was defined as number of days from first dose of study drug until discharge.
- Intensive care unit (ICU) LOS was defined as number of days from first dose of study drug until discharge from the ICU.

Hospital admission, LOS, and discharge status were analyzed in two study populations: microbiologic modified intent-to-treat (m-MITT) and modified intent-to-treat (MITT). Definitions of the study populations are shown in **Table 1**. This analysis focuses on the m-MITT population.

Figure 1. Study Schema



EOIVT, end of IV treatment; EOT, end of treatment; TOC, test of cure; LFU, last follow-up.
Note: For subjects with cUTI, isolation of pathogens was obtained after any indwelling urinary catheter or instrumentation was removed or replaced (if removal is not clinically acceptable).

Table 1. Analysis Populations

Population	Definition
Intent-to-Treat (ITT)	All subjects screened and randomized to study drug (ie, M-V or P-T)
Modified Intent-to-Treat (MITT)	All subjects who met ITT criteria and received ≥1 dose of study drug
Microbiological Modified Intent-to-Treat (m-MITT)	All subjects who met MITT criteria plus baseline bacterial pathogens ≥10^5 CFU/mL of urine at baseline culture or same pathogen present in concurrent blood/urine cultures

Results

In total, 550 subjects were randomized, of which 545 received at least one dose of study drug: 272 received M-V and 273 received P-T.

- 374 subjects (192 for M-V; 182 for P-T) were included in the m-MITT population.
- In the m-MITT population, most patients in the M-V (99.0%) and P-T (97.8%) groups were already hospitalized at study enrollment; 19 (9.9%) patients in the M-V group and 18 (9.9%) patients in the P-T group were either in or admitted to the ICU at the time of study enrollment **(Table 2)**. One patient in the M-V treatment arm and one patient in the P-T treatment arm who were not in the ICU at study enrollment were later transferred to the ICU during the study period.
- Duration of IV therapy for all study subjects in the m-MITT population is further summarized by ICU status in **Table 3**. Duration of IV therapy was similar between the M-V and P-T groups for the entire study population, but it was slightly shorter for the M-V group when only considering patients with an ICU stay during the study period.

Total ICU LOS was recorded for patients who were either in the ICU at study enrollment or were transferred to the ICU during the study period **(Table 4)**.

- Total ICU LOS was calculated from the start of study drug administration to ICU discharge.
- On average, total ICU LOS was shorter for the M-V group by 1.8 days compared with the P-T group (*P*=0.0546).
- In the M-V group, the LOS range was 1 to 13 days. In the P-T group, the LOS range was 6 to 16 days.
- The Kaplan-Meier plot in **Figure 2** summarizes the ICU discharge rate over time for both the M-V and P-T groups.

Clinical cure rates by ICU status at the end of IV therapy (EOIVT) and test of cure (TOC) timepoints are shown in **Figures 3 and 4**, respectively.

- At both timepoints, clinical cure rates are numerically higher in the M-V group compared with the P-T group, regardless of ICU stay during the study period.
- Clinical cure rates were numerically higher for both study groups at EOIVT than at TOC, regardless of ICU status during the study period.

Safety Findings

- In this study, the safety profile for M-V was similar to that observed for P-T.
- The most frequent adverse drug reactions for M-V, including headache, diarrhea, infusion-site reaction, and hypersensitivity, were similar to those reported for meropenem alone.[1-3]
- These data support a positive benefit-risk profile for M-V and support its use in the treatment of cUTI and AP.

Figure 2. Kaplan-Meier Plot for Length of ICU Stay (m-MITT Population)

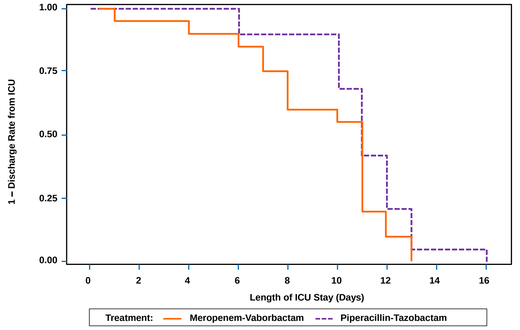


Table 2. Summary of Subject Disposition at Enrollment (m-MITT Population)

Category	M-V (N=192) n (%)	P-T (N=182) n (%)	Total (N=374) n (%)
Inpatient at Enrollment	**190 (99.0)**	**178 (97.8)**	**368 (98.4)**
Admission type: ICU	**19 (9.9)**	**18 (9.9)**	**37 (9.9)**
Admission type: non-ICU	**171 (89.1)**	**160 (87.9)**	**331(88.5)**

ICU, intensive care unit; LTAC, long-term acute care; LTCF, long-term care facility; M-V, meropenem-vaborbactam; P-T, piperacillin-tazobactam.

Table 3. Duration of IV Therapy by ICU Status (m-MITT Population)

Category	M-V (N=192) mean ± SD (days)	P-T (N=182) mean ± SD (days)	*P*-value**
All patients	**8.1 ± 2.43**	**8.2 ± 2.54**	**0.8453**
Patients with ICU stay*	**7.0 ± 1.81**	**7.6 ± 2.24**	**0.3793**
Patients with no ICU stay	**8.2 ± 2.47**	**8.2 ± 2.57**	**0.9680**

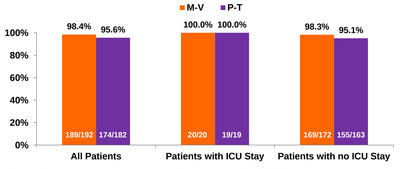
*ICU status includes ICU at baseline and non-ICU at baseline but transferred to ICU during study.
**P-value is based on Mixed Effects Model comparing mean differences of length of IV therapy in the two groups.
ICU, intensive care unit; M-V, meropenem-vaborbactam; P-T, piperacillin-tazobactam.

Table 4. Total ICU LOS for Patients with ICU Stay (m-MITT Population)

Statistics	M-V (N=192)	P-T (N=182)	*P*-value*
N	**20**	**19**	**–**
Mean (days)	**9.3**	**11.1**	**0.0546**
Standard Deviation (days)	**3.13**	**2.30**	**–**
Minimum (days)	**1**	**6**	**–**
Median (days)	**11**	**11**	**–**
Maximum (days)	**13**	**16**	**–**

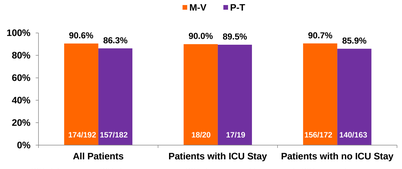
*P-value is based on Mixed Effects Model of comparing the mean difference of length of hospital stay in the two groups.
ICU status includes ICU at baseline and non-ICU at baseline but transferred to ICU during study.
LOS, length of stay; ICU, intensive care unit; M-V, meropenem-vaborbactam; P-T, piperacillin-tazobactam.

Figure 3. Clinical Cure Rates by ICU Status at EOIVT (m-MITT Population)



Clinical Cure rate includes a clinical outcome of Cure or Improvement at EOIVT.
ICU status includes ICU at baseline and non-ICU at baseline but transferred to ICU during study.
ICU, intensive care unit; EOIVT, end of IV therapy; M-V, meropenem-vaborbactam; P-T, piperacillin-tazobactam.

Figure 4. Clinical Cure Rates by ICU Status at TOC (m-MITT Population)



ICU status includes ICU at baseline and non-ICU at baseline but transferred to ICU during study.
ICU, intensive care unit; TOC, test of cure; M-V, meropenem-vaborbactam; P-T, piperacillin-tazobactam.

Conclusions

- Among patients in the m-MITT group who were in the ICU at baseline or who transferred to the ICU during the study period, ICU LOS was shorter by approximately 2 days (*P*=0.0546) for patients treated with meropenem-vaborbactam compared with those treated with piperacillin-tazobactam.
- Meropenem-vaborbactam is a promising alternative for treating serious gram-negative infections, particularly for patients in the ICU.

Disclosures

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References

1. MERREM® I.V. (meropenem for injection) USPI. Astra-Zeneca. 2016.
2. Meronem I.V. 500 mg. SmPC. Luton, UK; AstraZeneca UK Ltd. 2016.
3. Linden P. Safety profile of meropenem: an updated review of over 6,000 patients treated with meropenem. *Drug Saf*. 2007;30:657-68.

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