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Meropenem-Vaborbactam (VABOMERE): Outcomes in Subjects with Renal Impairment in Phase 3 Studies TANGO I and II

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Abstract

Introduction

Meropenem-vaborbactam (M-V) is being developed to treat serious gram-negative infections, which often occur in patients with renal impairment. Studies of some recently approved beta-lactamase inhibitor combination products reported reduced clinical response in patients with renal impairment. The purpose of this study was to compare clinical response in patients enrolled in M-V Phase 3 studies.

Methods

TANGO I was a Phase 3, multicenter, double-blind, randomized study evaluating M-V vs. piperacillin-tazobactam (P-T) for the treatment of complicated urinary tract infection (cUTI) or acute pyelonephritis (AP). TANGO II was a randomized, open-label trial of M-V vs. Best Available Therapy (BAT) in patients with serious infections, including cUTI, AP, HABP/VABP, bacteremia, or cIAI, due to known or suspected CRE. M-V dosage was adjusted in patients with creatinine clearances <50 mL/min in both studies. Outcomes were compared according to baseline renal function calculated using the Cockcroft-Gault equation.

Results

In TANGO I, 374 subjects had a baseline pathogen and were included in the m-MITT population, and in TANGO II, 43 subjects had a baseline CRE organism and were included in the mCRE-MITT population; 43/374 (11.5%) and 9/43 (20.9%) subjects had a baseline creatinine clearance (CrCl) <50 mL/min, respectively.

Outcomes by treatment group at the End of IV Therapy (EOIVT) were assessed; overall success (clinical cure and eradication) in TANGO I and clinical outcome across all infection types in TANGO II are presented:

Table: Outcomes at EOIVT* by Baseline CrCl

	TANGO I (m-MITT)		TANGO II (mCRE-MITT)	
	Overall Success at EOIVT		Clinical Cure Across All Infection Types at EOIVT*	
Baseline CrCl	M-V	P-T	M-V	BAT
>50 mL/min	166/169 (98.2%)	148/157 (94.3%)	15/22 (68.2%)	4/9 (44.4%)
≤50 mL/min	21/21 (100%)	20/22 (90.9%)	2/5 (40%)	1/4 (25%)

*EOIVT=EOT in TANGO II because there was no oral therapy

The outcomes for P-T in TANGO I and M-V in TANGO I and TANGO II were comparable in subjects with baseline CrCl >50 mL/min and ≤50 mL/min. Outcomes with M-V were higher compared to those observed for the control regimens in each study.

Conclusions

In TANGO I and II, M-V efficacy at EOIVT was comparable in patients with baseline CrCl <50 mL/min requiring a M-V dose adjustment and those with baseline CrCl >50 mL/min.

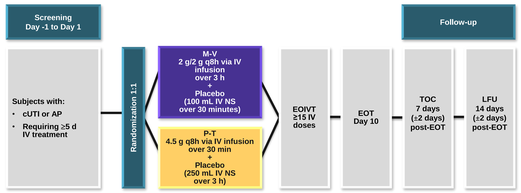
Background

- Meropenem-vaborbactam (M-V; VABOMERE) was developed to treat serious gram-negative infections, which often occur in patients with renal impairment.
- Studies of some recently approved beta-lactamase inhibitor combination products reported reduced clinical response in patients with renal impairment.
- The TANGO (Targeting Antibiotic Non-susceptible Gram-negative Organisms) trials were Phase 3 clinical trials designed to evaluate the safety and efficacy of M-V in patients with serious bacterial infections.
- Here we report clinical response of subjects with renal impairment enrolled in the TANGO trials.

Methods

- TANGO I was a Phase 3, multicenter, double-blind, randomized study evaluating M-V vs. piperacillin-tazobactam (P-T) for the treatment of complicated urinary tract infection (cUTI)/acute pyelonephritis (AP) (**Figure 1**).

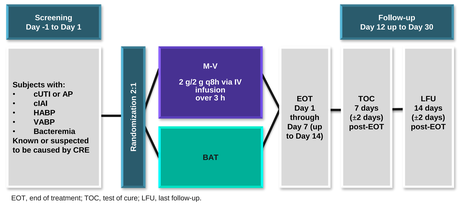
Figure 1. Study Schema for TANGO I



EOIVT, end EOT; end of treatment; TOC, test of cure; LFU, last follow-up.

- TANGO II was a randomized, open-label comparative trial with best available therapy (BAT) in subjects with cUTI, AP, hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP), bacteremia, or complicated intra-abdominal infection (cIAI) due to known or suspected CRE (**Figure 2**).

Figure 2. Study Schema for TANGO II



EOT, end of treatment; TOC, test of cure; LFU, last follow-up.

Table 1. Dose Reduction Scheme for Renal Impairment

Estimated CrCl (mL/min)	M-V
≥50	2g - 2g q8h
≥30 – 49	1g - 1g q8h
≥20 – 29	1g - 1g q12h
≥10-19	500mg - 500mg q12h
<10	500mg - 500mg q24h[a]

All doses infused over 3 hours.
[a] Subjects with an estimated CrCl <10 mL/min were required to receive dialysis at least twice per week.
q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours.
TANGO I only included patients with CrCl ≥30 mL/min.

- Overall success (clinical cure and microbiological eradication) in TANGO I and clinical outcome across all infection types in TANGO II were compared according to baseline renal function.
- Baseline renal function was calculated with the Cockcroft-Gault equation.
- In both studies, those requiring continuous renal replacement therapy were not eligible and M-V dosage was adjusted in subjects with creatinine clearance (CrCl) of <50 mL/min. Dose reduction in renal dosing of M-V is shown in **Table 1**.

Results

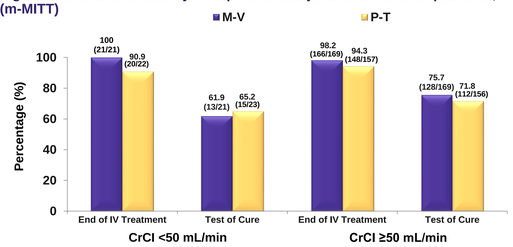
- Baseline demographics in subjects with renal impairment (CrCl <50 mL/min) from both TANGO I and II in the modified intent-to-treat (MITT) population are shown in **Table 2**.
  - In TANGO I, 67 subjects (31 M-V, 36 P-T) had renal impairment (MITT).
  - In TANGO II, 19 subjects (10 M-V, 9 BAT) had renal impairment (MITT).

Table 2. Baseline Demographics in Subjects with Renal Impairment, TANGO I and II (MITT/Safety Population)

	TANGO I			TANGO II		
Characteristic	M-V N=31 n (%)	P-T N=36 n (%)	Total N=67 n (%)	M-V N=10 n (%)	BAT N=9 n (%)	Total N=19 n (%)
cUTI/AP	31 (100)	46 (100)	67 (100)	8 (80.0)	5 (55.6)	13 (68.4)
HABP/VABP	NA	NA	NA	0 (0.0)	1 (11.1)	1 (5.3)
cIAI	NA	NA	NA	0 (0.0)	0 (0.0)	0 (0.0)
Bacteremia	NA	NA	NA	2 (20.0)	3 (33.3)	5 (26.3)
Age (y): mean (SD) > 65 years	69.7 (15.33)	68.1 (15.71)	68.9 (15.44)	74.4 (10.35)	66.4 (11.65)	70.6 (11.43)
Gender, female	22 (71.0)	21 (58.3)	43 (64.2)	5 (50.0)	1 (11.1)	6 (31.6)
Race, white	29 (93.5)	31 (86.1)	60 (89.6)	10 (100.0)	8 (88.9)	18 (94.7)
CrCl (mL/min): mean (SD) ≤50 mL/min	40.1 (6.57)	39.5 (6.86)	39.8 (6.68)	26.5 (14.82)	37.4 (10.14)	31.7 (13.68)
Diabetes mellitus	6 (19.4)	11 (30.6)	17 (25.4)	5 (50.0)	3 (33.3)	8 (42.1)
SIRS	9 (29.0)	12 (33.3)	21 (31.3)	5 (50.0)	4 (44.4)	9 (47.4)
Charlson Comorbidity Index Score ≥3	28 (90.3)	31 (86.1)	59 (88.1)	10 (100.0)	9 (100.0)	19 (100.0)

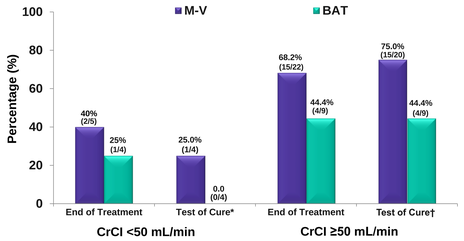
- In TANGO I and II, the efficacy population was 374 (m-MITT) and 43 (mCRE-MITT), respectively.
  - In TANGO I, 43/374 (11.5%) had a baseline CrCl of <50 mL/min.
  - In TANGO II, 9/43 (20.9%) had a baseline CrCl of <50 mL/min.
- Overall success (clinical cure+microbiological eradication) by timepoint in TANGO I subjects with renal impairment in the m-MITT population is presented in **Figure 3**. Efficacy at EOIVT among subjects with CrCl <50 mL/min requiring a dose adjustment of M-V or P-T was comparable to subjects not requiring a dosage adjustment (ie, CrCl ≥50 mL/min).
  - Success rates >90% were demonstrated across both study arms at EOIVT, regardless of presence/absence of renal impairment.

Figure 3. Overall Success by Timepoint in Subjects with Renal Impairment, TANGO I (m-MITT)



- In TANGO II, subjects with renal impairment (ie, CrCl <50 mL/min) had lower clinical cure rates across all infection types at EOT compared with subjects with normal renal function, though the number of subjects with impaired renal function was small (n=9, mCRE-MITT).
- In subjects with and without renal impairment in TANGO II, clinical cure at EOT was numerically higher among M-V-treated subjects than BAT-treated subjects (**Figure 4, Table 3**).
- Efficacy outcomes in subjects with renal impairment (CrCl <50 mL/min) in TANGO I and II are shown in **Table 3**.

Figure 4. Clinical Cure Rates Across all Infection Types by Timepoint in Subjects with Renal Impairment, TANGO II (mCRE-MITT)



* 1 subject in the M-V arm was indeterminate/not assessed at TOC.
† 2 subjects in the M-V arm were indeterminate/not assessed at TOC.

- A summary of adverse events in subjects with renal impairment (CrCl <50 mL/min) in TANGO I and II is presented in **Table 4**.

Table 4. Adverse Events in Subjects with Renal Impairment, TANGO I and II

	TANGO I		TANGO II	
Event	M-V N=31 n (%)	P-T N=36 n (%)	M-V N=10 n (%)	BAT N=9 n (%)
TEAEs	15 (48.4)	15 (41.7)	8 (80.0)	8 (88.9)
Study drug related AEs	3 (9.7)	5 (13.9)	3 (30.0)	3 (33.3)
Serious AEs	3 (9.7)	3 (8.3)	6 (60.0)	4 (44.4)
TEAE leading to drug discontinuation	1 (3.2)	4 (11.1)	3 (30.0)	1 (11.1)
Drug related deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 3. Efficacy Outcomes in Subjects with Renal Impairment, TANGO I and II

	TANGO I (m-MITT)		TANGO II (mCRE-MITT)	
Endpoint	M-V N=21 n/N' (%)	P-T N=22 n/N' (%)	M-V N=5 n/N' (%)	BAT N=4 n/N' (%)
Clinical Cure				
EOIVT/EOT	17/21 (81.0)	15/21 (71.4)	2/5 (40.0)	1/4 (25.0)
TOC	17/18* (94.4)	19/20* (95.0)	1/4* (25.0)	0/4 (0)
Microbiological Eradication/Cure†				
EOIVT/EOT	21/21 (100.0)	19/19 (100.0)	2/5 (40.0)	1/4 (25.0)
TOC	13/18* (72.2)	14/19 (73.7)	0/4* (0)	1/4 (25.0)
Overall Success (TANGO I Only)				
EOIVT	21/21 (100.0)	20/22 (90.9)		
TOC	13/21 (61.9)	14/22 (63.6)		

*'N' <N indicates subject/s was not assessed/indeterminate/censored.
† Microbiological eradication is shown for TANGO I. Microbiological cure (eradication + presumed eradication) is shown for TANGO II.

Conclusions

- Based upon observations from the TANGO studies, 11.5% of patients with cUTI have underlying renal impairment; this incidence is doubled (21%) in patients with CRE infections.
- In TANGO I, overall success at EOIVT and TOC were similar between treatment groups regardless of baseline renal function.
- In TANGO II, M-V clinical cure rates at EOT were lower in patients with renal impairment vs. those with no renal impairment but remained higher in the M-V arm than the BAT arm.
- There is no evidence of decreased safety associated with M-V in patients with renal impairment.
- M-V is a safe and effective treatment for serious gram-negative infections in renally impaired patients when the dose is adjusted as recommended in the USPI.

Disclosures

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