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Targeting Antibiotic Non-susceptible Gram-negative Organisms

Meropenem-Vaborbactam (M-V) versus Piperacillin-Tazobactam (P-T) in the Treatment of Adults with Complicated Urinary Tract Infections (cUTI), including Acute Pyelonephritis (AP) in TANGO I, a Phase 3 Randomized, Double-blind, Double-dummy Trial

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Disclosure

Dr. Loutit is an employee and shareholder of The Medicines Company.

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Background on Meropenem-Vaborbactam

- Vaborbactam (formerly RPX7009) is the first in class of cyclic boronic acid based beta-lactamase inhibitor
- Optimized for inhibition of the serine carbapenemase *KPC,* common in carbapenemase-producing Enterobacteriaceae
- Potential new option for the treatment of severe gram-negative infections, including carbapenem-resistant Enterobacteriaceae
- Efficacy and safety of meropenem-vaborbactam was assessed in 2 Phase 3 randomized trials

KPC, *Klebsiella pneumoniae* carbapenemase; cUTI, complicated urinary tract infections; AP, acute pyelonephritis.

Meropenem-Vaborbactam Phase 3 Clinical Program

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	TANGO I	TANGO II
Features	*Site/Indication Focus*	*Pathogen-Focused*
Patients	Complicated UTI/AP (n=550)	cUTI/AP, cIAI, HABP, VABP and/or bacteremia known or suspected to be due to CRE
Design	Randomized 1:1 Double-blind	Randomized 2:1 Open-label
Comparator	Piperacillin-tazobactam	“Best available therapy”
Status	*Completed* (this presentation)	*Ongoing*

Methods:
Study Overview

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Design	• Randomized, double-blind, double-dummy, active control, non-inferiority	
Randomization	• Subjects randomized 1:1 to receive M-V or P-T for 10 days total for the treatment of cUTI, including subjects with AP	

Stratification	• Stratified by region
	  • North America
	  • Europe
	  • Asia Pacific
	  • Remaining countries with sites
		• Stratified by type of infection
		  • AP
		  • cUTI with removable source
		  • cUTI with non-removable source

Study Drug Plan	• After a minimum of 15 doses (5 days) of IV therapy, subjects could be switched to oral levofloxacin therapy if pre-specified criteria met	

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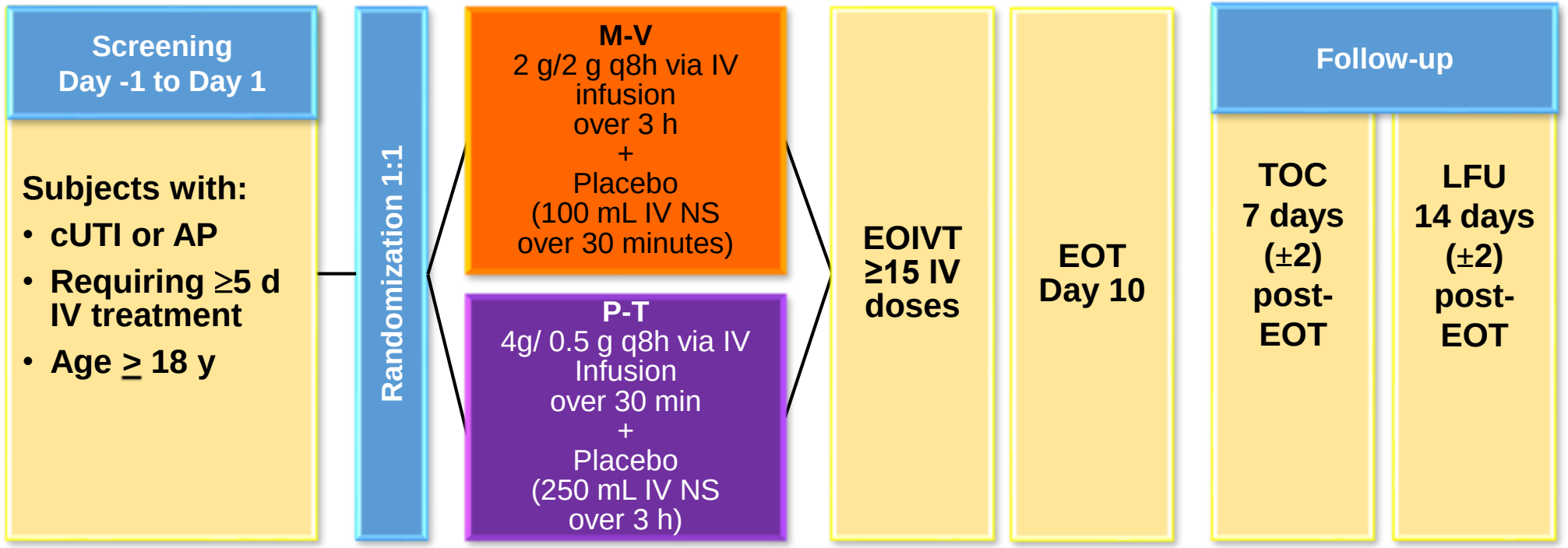
Study Schema



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).

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

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Key Inclusion/Exclusion Criteria

- **Key Inclusion**
  - Criteria for cUTI or AP as per FDA guidance
  - Require at least 5 days of study IV antibiotics
  - Any indwelling urinary catheter or instrumentation (including nephrostomy tubes and/or indwelling stents) will be removed or replaced before or as soon as possible, but not longer than 12 hours, after randomization
- **Key Exclusion**
  - Creatinine clearance <30 mL/min using the Cockcroft-Gault formula
  - Receipt of any potentially therapeutic antibiotic agent within 48 hours before randomization.
    - Exceptions
      - A single dose of a short-acting oral or IV antibiotic (No more than 25% of subjects will be enrolled who meet this criterion)
      - Subjects with unequivocal clinical evidence of treatment failure (i.e., worsening signs and symptoms).
      - Subjects who develop signs and symptoms of cUTI or AP while on antibiotics for another indication

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Primary Endpoints

Criteria	Population	Achieved:	At:	Defined as:
FDA	m-MITT	Overall Success	EOIVT visit	Clinical cure or improvement, and eradication of baseline pathogen to $<10^4$ CFU/mL
EMA	Co-primary: • m-MITT • ME	Microbiologic outcome of Eradication	TOC visit	Baseline pathogen(s) reduced to $<10^3$ CFU/mL of urine

- The pre-specified non-inferiority (NI) margin was 15% for the FDA and EMA endpoints
- If NI is demonstrated, an assessment for superiority will be performed

Results:
Study Populations

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Populations	M-V N = 274 n (%)	P-T N = 276 n (%)	Total N = 550 n (%)
Intention to Treat (ITT)	274 (100)	276 (100)	550 (100)
Modified Intention to Treat (MITT)/Safety	272 (99.3)	273 (98.9)	545 (99.1)
Microbiologic Modified Intention to Treat (m-MITT)	192 (70.1)	182 (65.9)	374 (68.0)
Microbiologic Evaluable (ME)	178 (65.0)	169 (61.2)	347 (63.1)

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Baseline Characteristics (MITT/Safety)

Subject Baseline Characteristics	M-V N = 272 n (%)	P-T N =273 n (%)	Total N = 545 n (%)
Acute pyelonephritis	161 (59.2)	161 (59.0)	322 (59.1)
Complicated UTI	111 (40.8)	112 (41.0)	233 (40.9)
w/ removable source of infection	53 (19.5)	51 (18.7)	104 (19.1)
w/ nonremovable source of infection	58 (21.3)	61 (22.3)	119 (21.8)
Age-years: mean (SD)	53 (19.4)	52.6 (20.9)	52.8 (20.2)
No. > 65 years	87 (32.0)	103 (37.7)	190 (34.9)
No. women	181 (66.5)	180 (65.9)	361 (66.2)
Creatinine clearance, mL/min: mean (SD)	93.5 (34.4)	89.2 (36.4)	91.3 (35.4)
No. with ≤ 50 mL/min	31 (11.4)	37 (13.5)	68 (12.4)
Diabetes mellitus	42 (15.4)	44 (16.1)	86 (15.8)
Systemic Inflammatory Response Syndrome	77 (28.3)	90 (33.0)	167 (30.6)
Charlson Comorbidity Index Score ≥ 3	143 (52.6)	147 (53.8)	290 (53.2)

Baseline Pathogens in at Least 15 Subjects (mMITT)

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Baseline Pathogens	M-V N = 192 n (%)	P-T N = 182 n (%)	Total N = 374 n (%)
E. coli	125 (65.1)	117 (64.3)	242 (64.7)
K. pneumoniae	30 (15.6)	28 (15.4)	58 (15.5)
Enterococcus faecalis	13 (6.8)	14 (7.7)	27 (7.2)
Proteus mirabilis	6 (3.1)	12 (6.6)	18 (4.8)
Enterobacter cloacae species complex	10 (5.2)	5 (2.7)	15 (4.0)
P. aeruginosa	5 (2.6)	10 (5.5)	15 (4.0)

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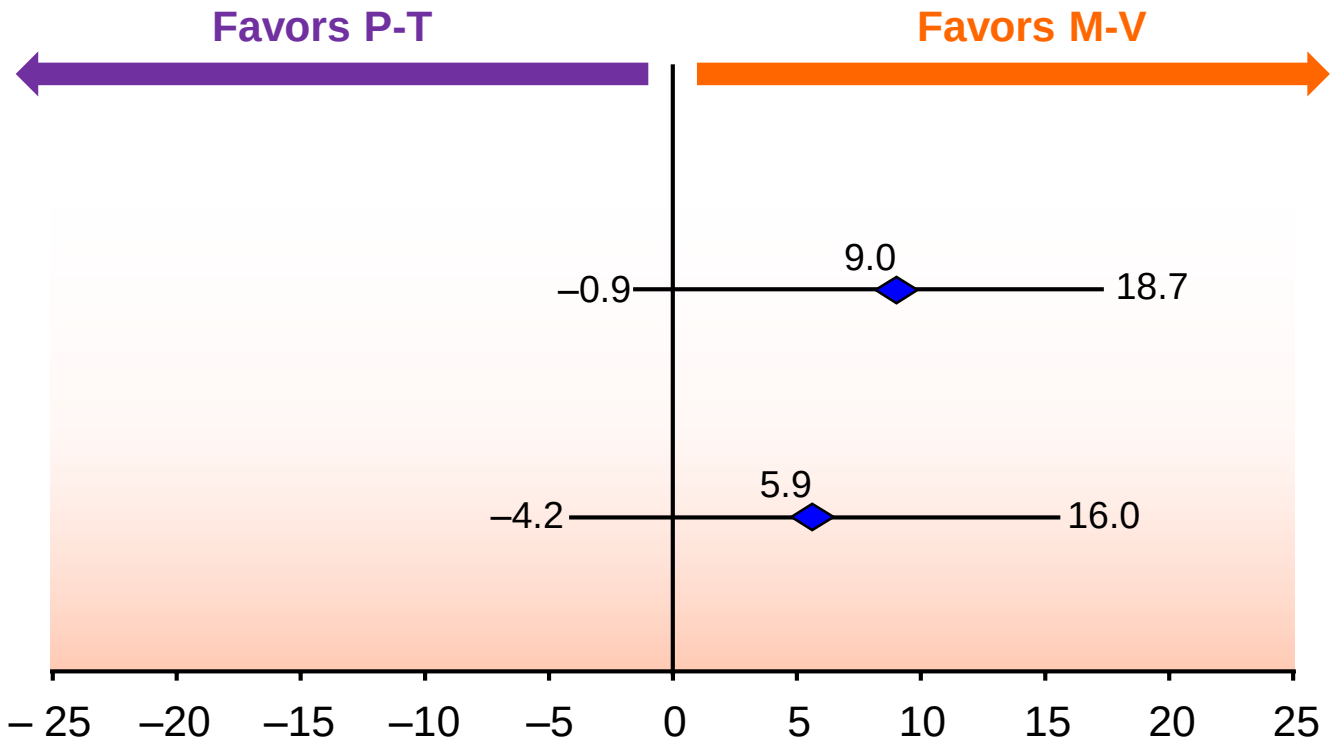
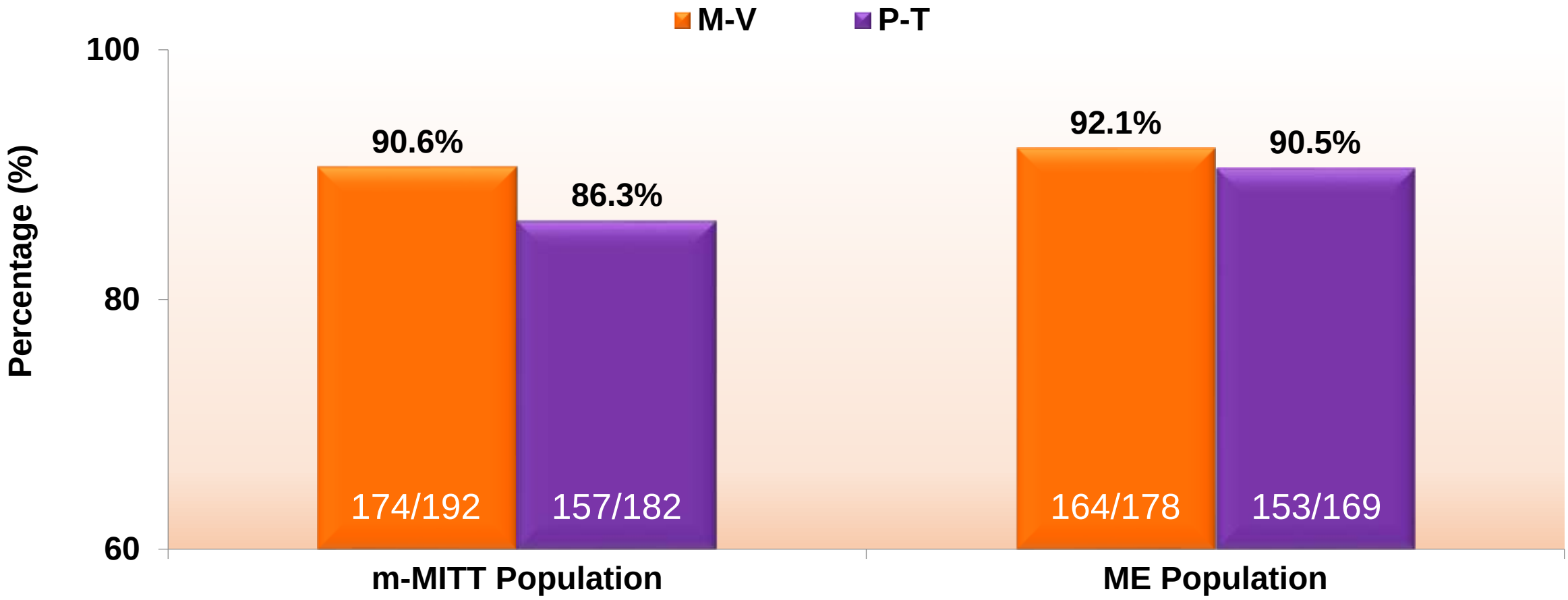
EMA Co-Primary Endpoint at TOC



	Microbial Eradication at TOC	
	M-V	P-T
m-MITT	128/192 (66.7%)	105/182 (57.7%)
ME	118/178 (66.3%)	102/169 (60.4%)

Non-inferiority met for both co-primary populations

Clinical Cure at TOC



Difference (95% CI): 4.5 (0.7, 9.1)

Difference (95% CI): 1.6 (-4.5, 7.9)

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FDA Primary Endpoint (mMITT)

	M-V N = 192	P-T N = 182
Overall Success at EOIVT	189/192 (98.4%)	171/182 (94.0%)
Difference (95% CI)	4.5 (0.7, 9.1)	

Non-inferiority met
Statistical superiority demonstrated for meropenem-vaborbactam

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Overall Safety

Preferred Term	M-V (N=272) n (%)	P-T (N=273) n (%)
Treatment-emergent adverse events (TEAEs)	106 (39.0)	97 (35.5)
Drug-related TEAEs	41 (15.1)	35 (12.8)
Discontinuation of study drug due to AE	7 (2.6)	14 (5.1)
Serious adverse events (SAEs)	11 (4.0)	12 (4.4)
Deaths	2 (0.7)	2 (0.7)

- Seizure not observed with M-V
- Incidence of Hypersensitivity and GI events (nausea, vomiting, diarrhea) was similar to P/T and reported rates for meropenem
- No evidence of renal toxicity with either M-V or P/T

Adverse Events Occurring in ≥1.5% of Subjects

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Adverse Event, n (%)	M-V (n=272)	P-T (n=273)	Total (n=545)
Headache	24 (8.8)	12 (4.4)	36 (6.6)
Diarrhea	9 (3.3)	12 (4.4)	21 (3.9)
Nausea	5 (1.8)	4 (1.5)	9 (1.7)
Asymptomatic bacteriuria	4 (1.5)	4 (1.5)	8 (1.5)
Catheter site phlebitis*	5 (1.8)	3 (1.1)	8 (1.5)
Infusion site phlebitis	6 (2.2)	2 (0.7)	8 (1.5)
Urinary tract infection	4 (1.5)	4 (1.5)	8 (1.5)
Hypokalemia	3 (1.1)	4 (1.5)	7 (1.3)
Vaginal infection	1 (0.4)	6 (2.2)	7 (1.3)
ALT increased	5 (1.8)	1 (0.4)	6 (1.1)
Anemia	2 (0.7)	4 (1.5)	6 (1.1)
AST increased	4 (1.5)	2 (0.7)	6 (1.1)
Pyrexia	4 (1.5)	2 (0.7)	5 (0.9)
Dyspnea	0 (0.0)	5 (1.8)	5 (0.9)

*Catheter site phlebitis was phlebitis not associated with IV infusion of study drug.
Percentage is calculated using the number of subjects in the column heading as the denominator.
Treatment-emergent AEs are AEs with a start date and time on or after the first dose of study drug.

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Conclusions

Meropenem-vaborbactam:
Non-inferior to piperacillin-tazobactam for the EMA primary endpoint of microbial eradication at the TOC visit in the treatment of patients with cUTI/AP
Non-inferior and statistically superior to piperacillin-tazobactam in the FDA primary endpoint of overall success at EOIVT in patients with cUTI/AP
Well tolerated, with an adverse event profile similar to piperacillin-tazobactam
Safe and efficacious treatment for cUTI/AP

TANGO 1 Investigators
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