Manuscript Title:

Effect and Safety of Meropenem-Vaborbactam vs Best Available Therapy in Patients with Carbapenem-resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

eTables

eTable 1. Eligibility Criteria for Each Infection Type

cUTI

Expectation, in the judgment of the investigator, that any indwelling urinary catheter or instrumentation (including nephrostomy tubes and/or indwelling stents) would be removed or replaced (if removal was not clinically acceptable) before or as soon as possible, but not longer than 12 hours, after randomization, AND:

Indication	At least ONE of the following:	AND at least TWO of the following signs or symptoms:	AND at least ONE of the following:
cUTI	• Indwelling urinary catheter • Neurogenic bladder with presence or history of urine residual volume of ≥100 mL • Obstructive uropathy (eg, nephrolithiasis, tumor, fibrosis) that was expected to be medically or surgically treated within 48 hours after randomization • Azotemia due to intrinsic renal disease • Urinary retention in men due to previously diagnosed benign prostatic hypertrophy	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) • Elevated WBC count (>10,000 cells/μL) or left shift (>15% immature PMNs) • Nausea or vomiting • Dysuria, increased urinary frequency, or urinary urgency • Lower abdominal pain or pelvic pain	• Positive LCE on urinalysis • WBC count ≥10 cells/μL in unspun urine • WBC count ≥10 cells/hpf in urine sediment

AP

Expectation, in the judgment of the investigator, that any indwelling urinary catheter or instrumentation (including nephrostomy tubes and/or indwelling stents) would be removed or replaced (if removal was not clinically acceptable) before or as soon as possible, but not longer than 12 hours, after randomization, AND:

Indication	Presence of an ascending tract infection including at least TWO of the following signs or symptoms:	AND at least ONE of the following:
AP	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) • Elevated WBC count (>10,000/μL), or left shift (>15% immature PMNs) • Nausea or vomiting • Dysuria, increased urinary frequency, or urinary urgency • Flank pain • Costo-vertebral angle tenderness on physical examination	• Positive LCE on urinalysis • WBC count ≥10 cells/μL in unspun urine • WBC count ≥10 cells/hpf in urine sediment

cIAI

Subjects were enrolled approximately 24 hours before or 96 hours after the surgical procedure when the following conditions were met:

- Expectation, in the judgment of the investigator, that operative drainage/debridement/removal (including open laparotomy, percutaneous drainage, or laparoscopic surgery) of any intra-abdominal collection or other potential source of intra-abdominal infection would be performed
- Expectation that cultures from the aforementioned procedure (including open laparotomy, percutaneous drainage, or laparoscopic surgery) would be sent for microbiological evaluation, including gram stain, culture and susceptibility testing, and meropenem 2 g-vaborbactam 2 g susceptibility testing

AND:

Indication	At least ONE of the following, either on intra-operative visualization of infection (eg, pus within the abdominal cavity) OR supportive radiographic imaging :	AND at least ONE of the following:
cIAI	• Intra-abdominal abscess, including splenic or hepatic abscess • Appendicitis or diverticulitis with peritonitis, perforation, or abscess • Perforation of stomach or intestine, associated with peritonitis, abscess, or fecal contamination • Cholecystitis or cholangitis with perforation, abscess, or progression beyond the gallbladder wall or biliary tract	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C • Hypotension, systolic BP <90 mmHg • Abdominal pain or tenderness • Nausea or vomiting • Abdominal mass on clinical examination • Altered mental status

HABP

Indication	All of the following:	AND signs or symptoms evidenced by at least TWO of the following:	AND at least ONE of the following:
HABP	• The onset of symptoms >48 hours after admission or ≤7 days after discharge from an insubject acute or chronic care facility (eg, LTAC, rehabilitation center, hospital, or skilled nursing home) OR • Admission from LTAC or rehabilitation center or admission from home <7 days after discharge from an LTAC or rehabilitation center • New or evolving infiltrate on chest X-ray obtained within 48 hours prior to randomization and >48 hours after hospitalization	• A new onset of cough (or worsening of baseline cough) • Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, dullness on percussion, bronchial breath sounds, or egophony) • Dyspnea, tachypnea, or respiratory rate >25/min • Hypoxemia (O_2 saturation <90% or pO_2 <60 mmHg while breathing room air, or worsening of the O_2 saturation/FiO_2) OR the following criterion ALONE: • New onset need for mechanical ventilation	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]) • Elevated total peripheral WBC count (>10,000/μL) • >15% immature neutrophils (bands) regardless of total peripheral WBC count • Leukopenia (total WBC count <4,500/μL) • Procalcitonin >0.25 μg/mL

VABP

Indication	All of the following:	AND signs or symptoms evidenced by at least TWO of the following:	AND at least ONE of the following:
VABP	• The onset of symptoms >48 hours after receiving ventilatory support via an endotracheal (or nasotracheal) tube • Required ventilatory support • New or evolving infiltrate on chest x-ray obtained within 48 hours prior to randomization and >48 hours after intubation	• Auscultatory findings consistent with pneumonia/ pulmonary consolidation (eg, rales, dullness on percussion, bronchial breath sounds, or egophony) • An acute change in the ventilator support system to enhance oxygenation, as determined by a worsening O_2 sat/FiO_2 ratio • Increased suctioning • Tracheal aspirate change to purulence	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]) • Elevated total peripheral WBC count (>10,000 cells/µL) • >15% immature neutrophils (bands) regardless of total peripheral WBC count • Leukopenia (total WBC count <4,500 cells/µL) • Procalcitonin >0.25 µg/mL

Bacteremia

Subjects with bacteremia unrelated to cUTI or AP, cIAI, HABP, or VABP were enrolled when the following conditions were met:

Indication	All of the following:	AND at least ONE of the following:
Bacteremia	• Isolation of a CRE from at least 1 blood culture	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]) • Elevated total peripheral WBC count (>10,000 cells/µL) • >15% immature neutrophils (bands) regardless of total peripheral WBC count (>10,000 cells/µL) • Leukopenia (total WBC <4,500 cells/µL) • Tachycardia >100 bpm • Tachypnea >20 breaths/min • Hypotension, systolic blood pressure <90 mmHg

Abbreviations: cUTI = complicated urinary tract infection; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell; AP = acute pyelonephritis; BP = blood pressure; cIAI = complicated intra-abdominal infection; FiO_2 = fraction of inspired oxygen; HABP = hospital-acquired bacterial pneumonia; LTAC = long-term acute care; O_2 = oxygen; pO_2 = partial pressure of oxygen; VABP = ventilator-associated bacterial pneumonia; bpm = beats per minute; CRE = carbapenem-resistant Enterobacteriaceae; mmHg = millimeter of mercury.

*Evidence of fever within 24 hours of the screening visit was acceptable if observed and documented by a health care provider.

eTable 2. Baseline Demographic and Clinical Characteristics (MITT)			
Characteristic	**M-V (n = 50)**	**BAT (n = 25)**	**Total (N = 75)**
Age, mean (SD), y	63.6 (15.3)	63.2 (13.1)	63.5 (14.5)
Age cohort, n (%)			
<65 y	26 (52.0)	14 (56.0)	40 (53.3)
≥65 y	11 (22.0)	4 (16.0)	15 (20.0)
≥75 y	13 (26.0)	7 (28.0)	20 (26.7)
Female gender, n (%)	25 (50.0)	7 (28.0)	32 (42.7)
White race, n (%)	43 (86.0)	22 (88.0)	65 (86.7)
Region, n (%)			
North America	13 (26.0)	10 (40.0)	23 (30.7)
Europe	29 (58.0)	13 (52.0)	42 (56.0)
Rest of World[a]	8 (16.0)	2 (8.0)	10 (13.3)
BMI, mean (SD)	27.9 (8.3)	27.1 (7.5)	27.6 (8.0)
Infection type, n (%)			
Bacteremia	18 (36.0)	9 (36.0)	27 (36.0)
cUTI/AP	23 (46.0)	11 (44.0)	34 (45.3)
HABP/VABP	5 (10.0)	2 (8.0)	7 (9.3)
cIAI	4 (8.0)	3 (12.0)	7 (9.3)
Baseline pathogen, n (%)[b]			
Klebsiella pneumoniae	30 (60.0)	14 (56.0)	44 (58.7)
Escherichia coli	3 (6.0)	4 (16.0)	7 (9.3)
Enterobacter cloacae species	1 (2.0)	2 (8.0)	3 (4.0)
Proteus mirabilis	0 (0.0)	2 (8.0)	2 (2.7)
Serratia marcescens	1 (2.0)	1 (4.0)	2 (2.7)
Enrolled as confirmed CRE, n (%)	26 (52.0)	17 (68.0)	43 (57.3)
Enrolled as suspected CRE, n (%)	24 (48.0)	8 (32.0)	32 (42.7)
Creatinine clearance, mL/min, n (%)			
≥50	36 (72.0)	14 (56.0)	50 (66.7)
30–49	6 (12.0)	7 (28.0)	13 (17.3)
20–29	1 (2.0)	2 (8.0)	3 (4.0)
<20	5 (10.0)	0 (0)	5 (6.6)
Missing	2 (4.0)	2 (8.0)	4 (5.3)
Charlson Comorbidity Index, n (%)			
≤2	8 (16.0)	2 (8.0)	10 (13.3)
3–4	6 (12.0)	4 (16.0)	10 (13.3)
5	12 (24.0)	4 (16.0)	16 (21.3)
≥6	24 (48.0)	15 (60.0)	39 (52.0)
Diabetes mellitus, n (%)	18 (36.0)	10 (40.0)	28 (37.3)
SIRS, n (%)	22 (44.0)	10 (40.0)	32 (42.7)
ICU admission, n (%)	8 (16.0)	6 (24.0)	14 (18.7)
Immunocompromised[c], n (%)	14 (28.0)	10 (40.0)	24 (32.0)
Prior antibiotic failure[d], n (%)	10 (20.0)	0 (0)	10 (13.3)

Abbreviations: BAT, best available therapy; BMI, body mass index; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant Enterobacteriaceae; cUTI/AP, complicated urinary tract infection/acute pyelonephritis; HABP/VABP, hospital-acquired bacterial

pneumonia/ventilator-associated bacterial pneumonia; ICU, intensive care unit; mCRE-MITT, microbiologic carbapenem-resistant Enterobacteriaceae modified intent to treat; M-V, meropenem-vaborbactam; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

[a] Israel, Latin America (Colombia, Brazil, Argentina)

[b] Baseline pathogens listed occurred in 2 or more patients.

[c] Receipt of immunosuppressive medications or bone marrow ablative chemotherapy, underlying lymphoma or leukemia (not in remission), previous transplantation, splenectomy, or presence of neutropenia.

[d] Clinical evidence of prior antimicrobial failure as ascertained by the study investigator at screening and randomization.

eTable 3. Microbiology and MIC distributions of Baseline Pathogens (mCRE-MITT)

	M-V (n=32)		BAT (n=15)		All (N=47)	
Baseline Pathogen[a]	**Meropenem MIC_{50} (MIC_{90}) (µg/mL)**	**n (%)**	**Meropenem MIC_{50} (MIC_{90}) (µg/mL)**	**n (%)**	**Meropenem MIC_{50} (MIC_{90}) (µg/mL)**	**n (%)**
Klebsiella pneumoniae	32 (>64)	29 (90.6)	>32 (>64)	12 (80.0)	32 (>64)	41 (87.2)
Enterobacter cloacae species	>8 (—[b])	1 (3.1)	>8 (—)	2 (13.3)	>8 (—)	3 (6.4)
Escherichia coli	4 (—)	3 (9.4)	>16 (—)	1 (6.7)	4(—)	4 (8.5)
Proteus mirabilis	—	0 (0.0)	—	2 (13.3)	—	2 (4.3)
Serratia marcescens	—	1 (3.1)	—	1 (6.7)	—	2 (4.3)
Elizabethkingia species	—	1 (3.1)	—	0 (0.0)	—	1 (2.1)

Abbreviations: BAT, best available therapy; M-V, meropenem-vaborbactam; mCRE-MITT, microbiologic carbapenem-resistant Enterobacteriaceae modified intent to treat; MIC, minimum inhibitory concentration.

[a] 5 patients in the meropenem-vaborbactam group and 4 patients in the BAT group had polymicrobial infections (ie, more than 1 species at baseline).

[b] —, not calculated

eTable 4. Antibiotic Regimens in BAT Group (N = 15[a]; mCRE-MITT)	
	n, (%)
Monotherapy	**4 (26.7)**
Aminoglycoside	1 (6.7)
Carbapenem	1 (6.7)
Ceftazidime-Avibactam	1 (6.7)
Polymyxin	1 (6.7)
Dual Therapy	**7 (46.7)**
Carbapenem + Aminoglycoside	1 (6.7)
Carbapenem + Polymyxin	1 (6.7)
Carbapenem + Tigecycline	2 (13.3)
Polymyxin + Aminoglycoside	3 (20.0)
Triple Therapy	**1 (6.7)**
Carbapenem + Polymyxin + Tigecycline	1 (6.7)
≥4 Drugs	**2 (13.3)**
Carbapenem + Polymyxin + Tigecycline + Aminoglycoside	2 (13.3)

Abbreviations: BAT, best available therapy; mCRE-MITT, microbiologic carbapenem-resistant Enterobacteriaceae modified intent to treat.

[a] 1 patient received ceftazidime-avibactam (which was only permitted per protocol as monotherapy) in combination with other antimicrobial agents and is therefore not reflected in this table.

eTable 5. Primary Infection Type, Initial BAT Regimen, Baseline Pathogen, and MICs for BAT for Subjects in BAT Group (mCRE-MITT Population)

Subject	Primary Infection Type	Initial BAT Regimen	Pathogen[a]	BAT Agent(s) MIC (µg/mL)
1	AP	Amikacin 250mg QD; Colistin 2MU q8h	*K. pneumoniae*	Colistin >4 Amikacin 16
			P. stuartii	Colistin >4 Amikacin >32
2	AP	Polymyxin B 850,000 q12h	*K. pneumoniae*	NA
3	cUTI	Gentamicin 360mg IV q24h	*E. cloacae*	Gentamicin 4
4	cUTI	Meropenem 1g IV q8h; Gentamicin 150 mg IV q24h	*E. cloacae*	Meropenem 8 Gentamicin 0.5
			K. pneumoniae	Meropenem ≤0.03 gentamicin 0.5
5	Bacteremia	Meropenem 1g q8h; Tigecycline 50mg q12h	*P. mirablis* (screen)*	NA
			P. mirablis (Day1)	Tigecycline > 4
6	Bacteremia	Amikacin 500mg QD; Colistin 9MU 4.5MU q12h	*K. pneumoniae**	NA

7	Bacteremia	Colistin 4.5MU q12h; Meropenem 2g q8h; Tigecycline 100mg q12h	*K. pneumoniae*	Meropenem >64 Colistin >4 Tigecycline 1
8	Bacteremia	Gentamicin 160 mg QD; Meropenem 1 g q8h	*K. pneumoniae*	Gentamicin 1.0 Meropenem 64
9	Bacteremia	Meropenem 1.5 g q6h; Colistin 4.5 MU q12h; Ertapenem 1g q24h	*K. pneumoniae*	Colistin >4 Ertapenem >16
10	Bacteremia	Colistin 4.5 MU q12h; Tigecycline 100 mg q12h; Meropenem 2 g q8h; Gentamicin 240 mg q24h	*K. pneumoniae*	Colistin 0.25 Tigecycline 2 Meropenem 64 Gentamicin 2
11	Bacteremia	Ceftazidime-Avibactam 2.5 g q8h	*K. pneumoniae*	Ceftazidime >64; Ceftazidime-Avibactam 2
12	Bacteremia	Meropenem 1 g IV q8h; Ertapenem 1 g IV q24h	*S. marcescens*	Meropenem 0.5 Ertapenem 1
			*S. marcescens**	Meropenem > 16 Ertapenem >8
13	VABP	Colistin 150 mg q12h; Gentamicin 500mg q12h	*K. pneumoniae*	Colistin 0.5 Gentamicin 1
14	cIAI	Meropenem 1 g IV q8h; Tigecycline 50 mg q12h	*E. coli**	Meropenem >16 Tigecycline NA
			*K. pneumoniae**	Meropenem >16 Tigecycline NA
16	cIAI	Ceftazidime-Avibactam 2.5g q8h	*K. pneumoniae*	Ceftazidime >64 Ceftazidime-Avibactam 8
			K. pneumoniae	Ceftazidime >64 Ceftazidime-Avibactam 2
			*E.coli**	NA

Abbreviations: AP = acute pyelonephritis; BAT = best available therapy; BID = twice daily; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; *E. cloacae* = *Enterobacter cloacae*; *E. coli* = *Escherichia coli*; ESBL = extended-spectrum beta-lactamase; g = grams; mCRE-MITT = Microbiological carbapenem-resistant Enterobacteriaceae Modified Intent-to-Treat; mg = milligrams; MIC = minimum inhibitory concentration; m-MITT = microbiological Modified Intent-to-Treat; MU = million units; NA = not available; ND = not determined; q6h = every 6 hours; q8h = every 8 hours; *P. mirabilis* = *Proteus mirabilis*; *P. stuartii* = *Providencia stuartii*; q12h = every 12 hours; q24h = every 24 hours; QD = once daily; *S. marcescens* = *Serratia marcescens*; VABP = ventilator-acquired bacterial pneumonia.

[a]Taken from data from central lab, in cases where isolate not sent to central lab (*), data obtained from local lab

eTable 6. TEAEs Associated with Day-28 All-Cause Mortality (mCRE-MITT)

M-V (n = 32)			BAT (n = 15)		
Day	**Infection Type**	**AE Preferred Term**	**Day**	**Infection Type**	**AE Preferred Term**
2	Bacteremia	Cardiac arrest	3	Bacteremia	Sepsis
3	Bacteremia	General physical health deterioration	11	cIAI	Septic shock
4	Bacteremia	Cardiac arrest	11	Bacteremia	Septic shock
4	Acute pyelonephritis	Sepsis	12	VABP	Septic shock
5	Bacteremia	Shock hemorrhagic	16	Bacteremia	Cerebral hemorrhage

Abbreviations: AE, adverse event; BAT, best available therapy; cIAI, complicated intra-abdominal infection; M-V, meropenem-vaborbactam; TEAE, treatment-emergent adverse event; VABP, ventilator-associated bacterial pneumonia.

eTable 7. Efficacy Outcomes by Infection Type (mCRE- MITT)

Outcome	M-V n/N' (%)	BAT n/N' (%)	Difference[a]	Relative Difference[b]
Day-28 All-Cause Mortality[c]				
Patients with HABP/VABP and Bacteremia, combined	4/20 (22.2)	4/9 (44.4)	-22.2	-50.0
Patients with Bacteremia	4/14 (28.6)	3/8 (37.5)	-8.9	-23.7
Patients with HABP/VABP	0/4 (0)	1/1 (100)	-100.0	NA
Overall Success[d] at EOT				
Patients with cUTI/AP	9/12 (75.0)	2/4 (50.0)	25.0	50.0
Overall Success[c,d,e] at TOC (EOT + 7d)				
Patients with cUTI/AP	4/12 (33.3)	2/4 (50.0)	-16.7	-33.4
Clinical Cure at TOC[c]				
Patients with cIAI	2/2 (100)	0/2 (0.0)	100	NA

Abbreviations: BAT, best available therapy; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; EOT, end of treatment; M-V, meropenem-vaborbactam; mCRE-MITT, microbiologic carbapenem-resistant Enterobacteriaceae modified intent to treat; MIC, minimum inhibitory concentration; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia.

[a] Data represent the difference in percentages for meropenem-vaborbactam and BAT.

[b] Data represent (difference in percentage for meropenem-vaborbactam and BAT)/BAT.

[c] Represents regulatory guidance-based primary endpoint for specified infection type/s.

[d] Composite outcome of clinical cure and microbiologic eradication at respective visit.

[e] 4 M-V-treated patients were indeterminate/not assessed at TOC.

eTable 8. Efficacy Endpoints Among All Patients who Received ≥1 Dose of Study Drug MITT)

	M-V (n = 50) n (%)	BAT (n = 25) n (%)	Difference[a] (95% CI)	*P* value
Patients with All Infection Types				
Clinical Cure at EOT	32 (64.0)	11 (44.0)	20.0 (-3.6 to 43.6)	.10
Clinical Cure at TOC	29 (58.0)	9 (36.0)	22.0 (-1.3 to 45.3)	.06
Day-28 Mortality	7 (14.0)	5 (20.0)	-6.0 (-24.4 to 12.4)	.52

Abbreviations: BAT, best available therapy; CI, confidence interval; EOT, end of treatment; MITT, modified intent to treat; M-V, meropenem-vaborbactam; TOC, test of cure.

[a] Data represent the difference in percentages for meropenem-vaborbactam and BAT (95% CI for that difference).

eTable 9. Efficacy Endpoints Among All Patients with a Confirmed Pathogen (m-MITT)

	M-V (n = 35) n (%)	BAT (n = 19) n (%)	Difference[a] (95% CI)	*P* value
Patients with All Infection Types				
Clinical Cure at EOT	24 (68.6)	7 (36.8)	31.7 (5.1 to 58.3)	.02
Clinical Cure at TOC	21 (60.0)	6 (31.6)	28.4 (2.0 to 54.9)	.04
Microbiologic Cure[b] at EOT	23 (65.7)	8 (42.1)	23.6 (-3.6 to 50.8)	.09
Microbiologic Cure[b] at TOC	17 (48.6)	7 (36.8)	11.7 (-15.6 to 39.0)	.40
Day-28 Mortality	5 (14.3)	5 (26.3)	-12.0 (-35.0 to 10.9)	.30

Abbreviations: AE, adverse event; BAT, best available therapy; CI, confidence interval; EOT, end of treatment; m-MITT, microbiologic modified intent to treat; M-V, meropenem-vaborbactam; TOC, test of cure.

[a] Data represent the difference in percentages for meropenem-vaborbactam and BAT (95% CI for that difference).

[b] Composite of either microbiologic eradication or presumed eradication at respective visit.