Meropenem/vaborbactam

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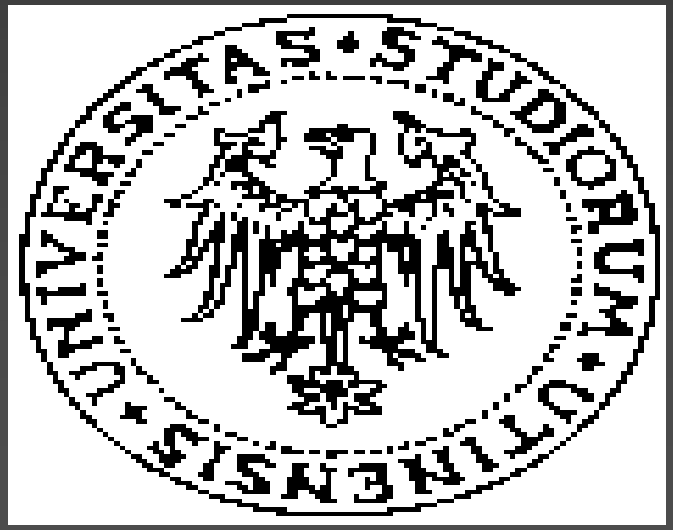

Disclosures

- Research grants
  - Astellas, Pfizer, MSD, Gilead
- Advisor/consultant
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- Speaker/chairman
  - Angelini, Astellas, AstraZeneca, Bayer, Pfizer, MSD, Gilead, Vifor, Novartis, Bayer,Tetraphase,Menarini, Cidara

Meropenem/vaborbactam clinical development program

Phase I Program

Study 402

Healthy subject PK and safety

single and multiple doses of vaborbactam alone

Study 501

Healthy subject PK and safety

single and multiple doses of meropenem-vaborbactam alone or in combination

Study 503

Healthy subject PK in epithelial lining fluid

Study 504

PK and safety of subjects with mild to severe chronic renal impairment, including subjects on hemodialysis

Phase III Program

Study 506NH (TANGO 0)

CRE target patient population retrospective study

Study 505 (TANGO I)

cUTI and AP

meropenem-vaborbactam versus piperacillin/tazobactam

(1:1 Randomization)

Study 506 (TANGO II)

Suspected or documented CRE infection

meropenem-vaborbactam versus best available therapy

(2:1 Randomization)

Why choose a carbapenem as the partner for a new beta-lactamase inhibitor combination?

MIC_{90}, µg/ml vs. bloodstream isolates of carbapenemase-negative, ESBL-producing Enterobacteriaceae from U.S. Hospitals[1]

Data are MIC_{90}	Meropenem	Imipenem	Ertapenem	Ceftazidime	Pip/Tazo	Aztreo
All strains, ESBL Phenotype (151)	0.125	0.5	0.5	>8	>64	>8
Escherichia coli (81)	0.06	0.25	0.125	>8	32	>8
Klebsiella spp (55)	0.125	0.5	0.5	>8	>64	>8
Enterobacter spp (9)	0.25	0.5	2	>8	>64	>8
Enterobacter spp (AmpC hyperproducer) (22)	0.25	1	1	>8	>64	>8
CTX-M producing Enterobacteriaceae (76)	0.125	0.25	0.5	>8	>64	>8
CMY-producers (12)	0.06	1	0.5	> 8	>64	>8

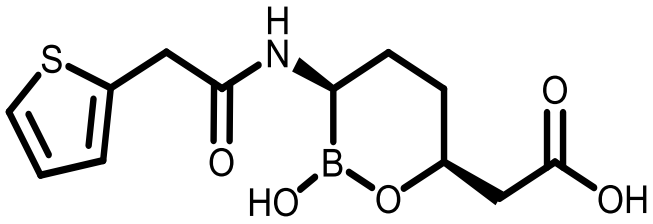
Carbapenems are more active and stable to ESBLs that have become endemic over the past 2 decades than cephalosporins, aztreonam, penicillin/BLI combobinations[2]

1. Castainheira M, et al. Poster F-855. Presented at: ICAAC; September 9-12, 2012; San Francisco, CA.
2. Castainheira M, et al. Antimicrob Agents Chemother. 2014;58(2):833-8.

Adds a novel beta-lactamase inhibitor

Vaborbactam

- Cyclic boronic acid, non-suicidal beta-lactamase inhibitor that forms covalent bonds between the boronate moiety and the serine residue of beta-lactamases
- Potent inhibitory activity against class A and C serine beta-lactamases, particularly the KPC carbapenemase
- Nearly irreversible inhibition of KPC due to very slow off-rate of dissociation of the enzyme-inhibitor complex (residence time: 16.5 hours)
- Vaborbactam inhibit**s** KPC in the presence of mutations that effect avibactam activity
- Pharmacokinetic properties that complement meropenem
- No additive toxicity to meropenem or effect the safety and tolerability of meropenem



Vaborbactam
(formerly known as RPX7009)

Hecker et. al. *J Med Chem.* 2015;58:3682-92.

Microbiology

New BL-BLI combinations

	ESBL	AmpC	KPC	OXA	MBL
Ceftolozane-tazobactam	+	+/-	-	-	-
Ceftazidime-avibactam	+	+	+	+	-
Ceftaroline-avibactam	+	+/-	+	-	-
Aztreonam-avibactam	+	+	+	+	+
Imipenem-relebactam	+	+	+	-	-
Meropenem/vaborbactam	+	+	+	-	-

Lagace-Wiens et al. Infect Drug Res 2014;9:13-25
Castanheira et al. AAC 2012;56:4779-85

Livermore et al. AAC 2011; 55:390-4
Hong et al. Infect Drug Res 2013;6:215-23

Livermore et al. JAC 2013;68:2286-90

In Vitro Activity of Meropenem – vaborbactam

- 4,500 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014

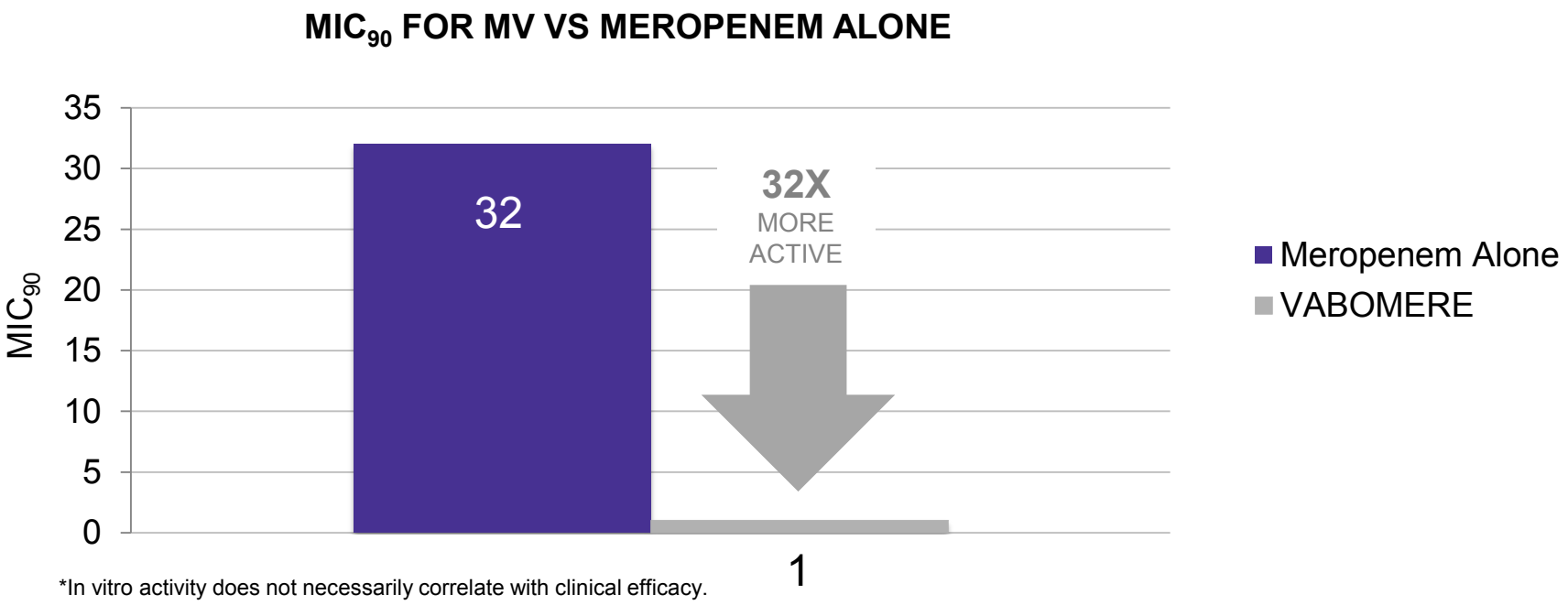
Species (n)	Meropenem		Meropenem-RPX7009		Meropenem-RPX7009	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Klebsiella pneumonia (KPC+) (121)	8	64	0.06 / 4	2 / 4	0.03 / 8	0.5 / 8
Pseudomonas aeruginosa (96)	32	64	32 / 4	64 / 4	32 / 8	64 / 8
Acinetobacter baumannii (98)	8	32	8 / 4	32 / 4	8 / 8	32 / 8

- Addition of RPX7009 resulted in a 64- to 512-fold decrease in meropenem MIC in majority of KPC-positive isolates
- All but 2 of these isolates (98.3%) were inhibited by 1 µg/mL meropenem combined with RPX7009 at 8 µg/mL

Lapuebla A, et al. *Antimicrob Agents Chemother* 2015; 59: 4856-4860

Meropenem/vaborbactam has 32 times more activity than meropenem alone evaluated against KPC-producing strains of Enterobacteriaceae*

- Adding vaborbactam significantly reduces the minimum inhibitory concentration (MIC) of meropenem alone
  - Meropenem alone and in combination with vaborbactam was evaluated against KPC-producing strains of Enterobacteriaceae involving >1900 isolates



*In vitro activity does not necessarily correlate with clinical efficacy.

Data on File. Melinta Therapeutics.

Meropenem/vaborbactam restores activity of meropenem against KPC-producing Enterobacteriaceae

Strain	Beta-Lactamases	Meropenem MIC (µg/ml)	
		Alone	w/ Vaborbactam 8 µg/ml
***E. coli* EC1007**	KPC-3	16	**≤0.06**
***E. cloacae* ECL1026**	KPC-2, TEM-1	8	**≤0.06**
***E. cloacae* ECL1055**	KPC-3, TEM	8	**≤0.06**
***E. cloacae* ECL1058**	KPC-3, SHV-11, TEM-1	32	**≤0.06**
***E. cloacae* ECL1061**	KPC-3, Hyper AmpC Expression	32	**≤0.06**
***E. cloacae* ECL1079**	KPC, TEM	>256	**4**
***K. pneumoniae* KP1008**	KPC-2, TEM SHV	4	**≤0.06**
***K. pneumoniae* KP1083**	KPC-3, TEM-1 SHV-11	16	**≤0.06**
***K. pneumoniae* KP1004**	KPC-2, TEM-1, SHV-11	32	**≤0.06**
***K. pneumoniae* KP1061**	KPC-3, SHV-11, TEM-1	16	**≤0.06**
***K. pneumoniae* KP1087**	KPC-2, CTX-M-15, SHV-11, TEM-1	32	**0.125**
***K. pneumoniae* KP1074**	KPC-3, SHV-11, TEM	128	**0.25**
***K. pneumoniae* KP1084**	KPC-3,TEM-1 SHV-11	64	**0.5**
***K. pneumoniae* KP1093**	KPC-3, SHV-11, TEM	128	**1**
***K. pneumoniae* KP1099**	KPC-2	128	**2**
***K. pneumoniae* KP1100**	KPC-3	≥256	**4**
***K. pneumoniae* KP1094**	KPC-2, TEM-1, LEN-17	512	**8**

Data on File. Melinta Therapeutics.

Pharmacokinetics

Pharmacokinetic studies: Population pharmacokinetics

Summary [Mean (SD)] of Post-Hoc Pharmacokinetic Parameters in Phase III Patients[1-3]

Parameter	Pooled (n=295)	
	Meropenem	Vaborbactam
C_{max} (µg/mL)	57.3 (23.0)	71.3 (28.6)
$AUC_{0\text{-}24\ Day\ 1}$ (µg·h/mL)	637 (295)	821 (369)
$AUC_{0\text{-}24,\ steady\ state}$ (µg·h/mL)	650 (364)[a]	835 (508)[a]
Free $AUC_{0\text{-}24,\ ss}$ (µg·h/mL)	—	559
Free AUC/MIC at 8 µg/mL	—	70
CLt (L/h)	10.5 (6.4)	7.95 (4.3)
$t_{1/2}$ (h)	2.30 (2.5)	2.25 (2.1)

SD=standard deviation; C_{max}= maximum concentration; $AUC_{0\text{-}24}$= area under the concentration-time curve from 0 to 24 hours; CLt= clearance; $t_{1/2}$,= half-life
[a] $AUC_{0\text{-}24,\ steady\ state}$ estimates were not available for two patients as they received less than 3 doses of VABOMERE

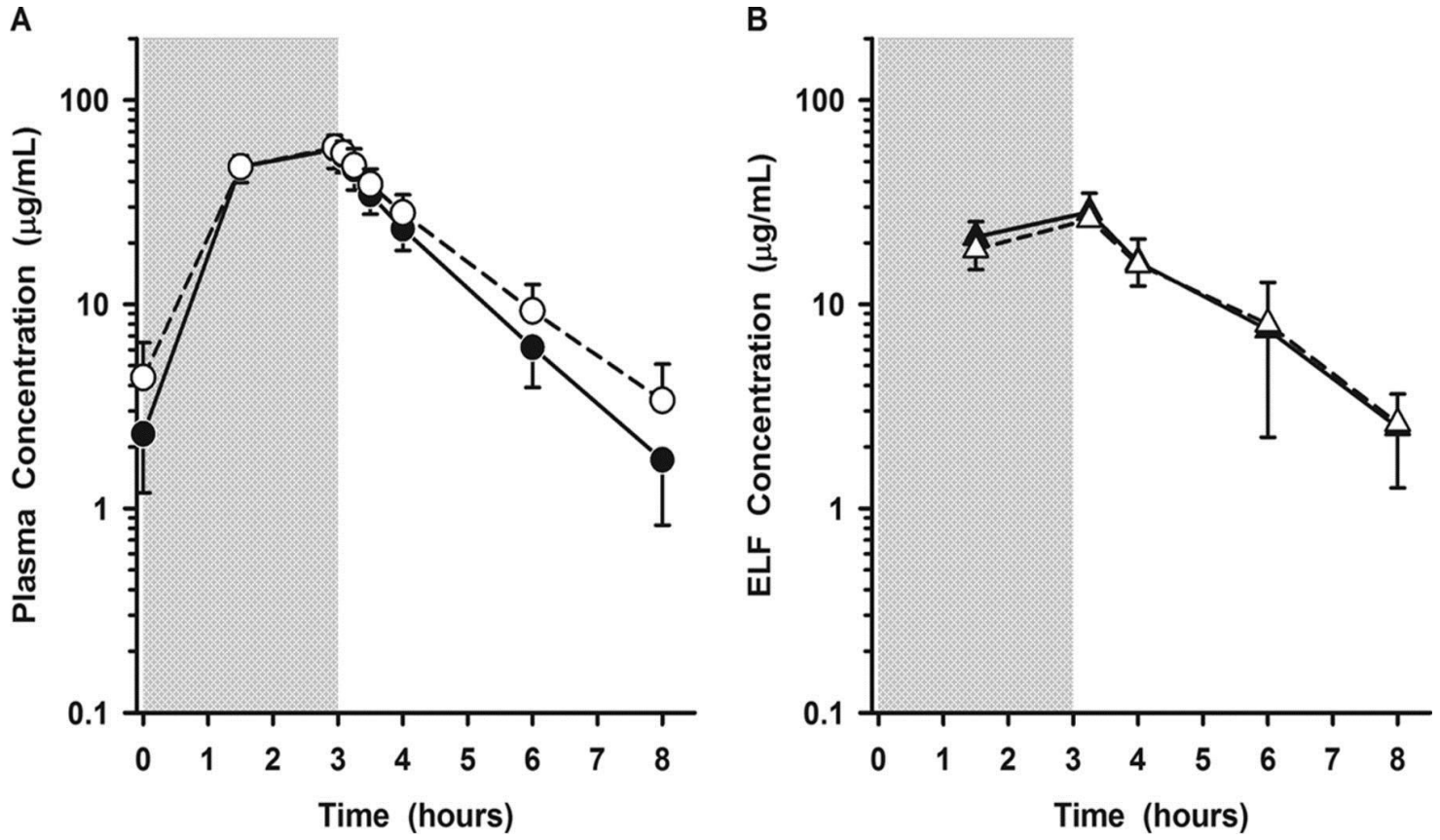
The plasma protein binding of meropenem is approximately 2%. The plasma protein binding of vaborbactam is approximately 33%.

1. Data on File. Melinta Therapeutics.
2. VABOMERE Prescribing Information.
3. Trang M, et al. Poster 341. Presented at: ASM Microbe; June 1-4, 2017; New Orleans, LA.

Meropenem-Vaborbactam: Human ELF pharmacokinetics

- Pharmacokinetics of meropenem 2g – vaborbactam 2g administered by 3 hour infusion in plasma and ELF
- ELF Penetration (based on Free Drug) of 65% for meropenem and 79% for vaborbactam

Filled circles and triangles are meropenem; open are vaborbactam

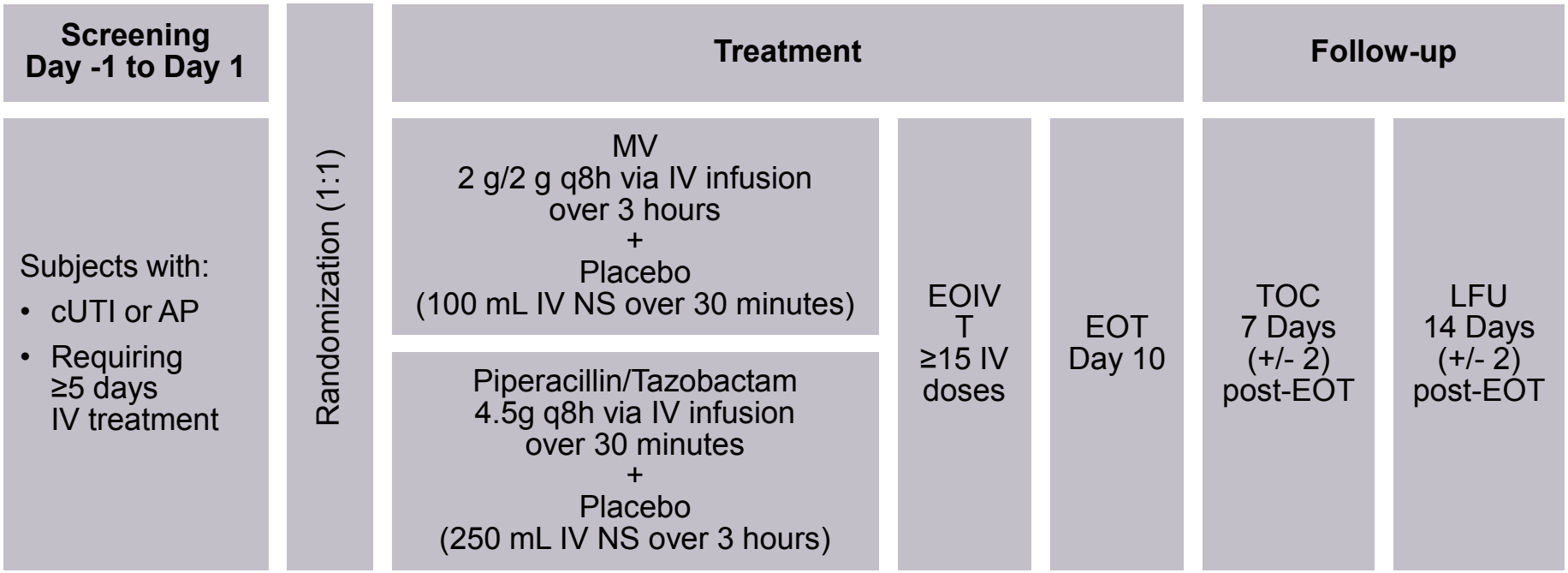


Wenzler E, et al. Antimicrob Agents Chemother. 2015.59(12):7232–7239.

Clinical Data

TANGO I study design

- Randomized, double-blind, double-dummy, active control, non-inferiority study
- Subject with complicated urinary tract infections (cUTI), including acute pyelonephritis (AP), randomized 1:1 ratio to receive either VABOMERE or piperacillin/tazobactam
- After a minimum of 15 doses (5 days) of IV therapy, subjects could be switched to oral therapy (levofloxacin) provided they met pre-specified criteria, including improvement in symptoms, afebrile, leukocytosis improved and a negative culture
- Treatment duration (IV +/- oral) 10 days



TEAE=treatment emergent adverse events; AE=adverse event; SAE=serious adverse event

Kaye KS, et al. *JAMA*. 2018;319(8):788-799.

TANGO I efficacy results

Primary Efficacy Endpoint:
Microbial eradication (baseline pathogens reduced to $<10^3$ CFU/mL urine) at the test-of-cure visit for the microbiologic modified ITT and microbiologic evaluable populations.

Microbial Eradication at Test of Cure (TOC) Visit

Primary Endpoint	MV (n=192) n (%)	Piperacillin/Tazobactam (n=182) n (%)	Difference (95% CI)
Microbiologic MITT analysis	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)

CI=confidence interval; TOC=test of cure; m-MITT=Microbiological Modified Intent-to-Treat

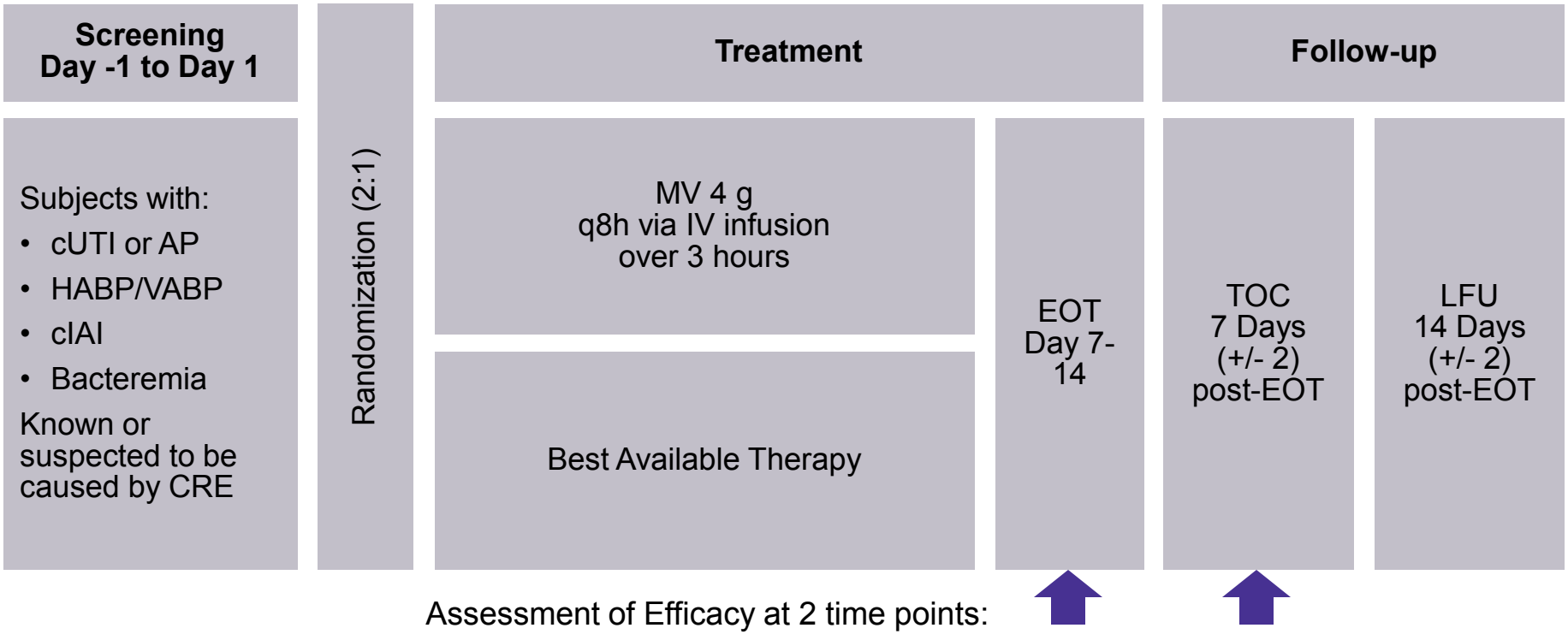
Kaye KS, et al. *JAMA*. 2018;319(8):788-799.

TANGO II study design

Phase 3, multicenter, randomized, open-Label, active comparator study

Randomized 2:1 MV vs. Best Available Therapy (BAT)

Known or suspected CRE (defined as suspected CRE was based on evidence from CRE culture, or other phenotypic or molecular testing within 90 days of Day 1) infections including bacteremia, hospital-acquired bacterial pneumonia (HABP), ventilator-acquired bacterial pneumonia (VABP), complicated urinary tract infection (cUTI), acute pyelonephritis (AP), and complicated intra-abdominal infections (cIAI)



Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

TANGO II
Baseline demographics (mCRE-MITT)

Subject Baseline Characteristics	VABOMERE N=32 n (%)	Best Available Therapy N=15 n (%)	Total N=47 n (%)
Age-years: mean (± SD) > 65 years	63.5 (± 14.1) 15 (46.9)	60.2 (± 13.0) 6 (40.0)	62.5 (± 13.7) 21 (44.7)
> 75 years	7 (21.9)	3 (20.0)	10 (21.3)
CrCl ≥50 mL/min	24 (75.0)	9 (60.0)	33 (70.2)
30-49 mL/min	4 (12.5)	2 (13.3)	6 (12.8)
20-29 mL/min	1 (3.1)	2 (13.3)	3 (6.4)
< 20mL/min	2 (6.3)	0 (0)	2 (4.3)
Diabetes mellitus	12 (37.5)	7 (46.7)	19 (40.4)
Systemic Inflammatory Response Syndrome	15 (46.9)	6 (40.0)	19 (40.4)
Charlson Comorbidity Index Score ≥5	25 (78.1)	12 (80.0)	37 (78.7)
Immunocompromised*	11 (34.4)	8 (53.3)	19 (40.4)
Prior Treatment Failure	**9 (28.1)**	**0/15 (0)**	**9 (19.1)**

* Immunocompromised subjects were defined as any subject with an underlying active leukemia, lymphoma, prior transplant or splenectomy on medical history; any active receipt of immunosuppressive drugs including selective immunosuppressants, calcineurin inhibitors, or high-dose systemic steroids (equivalent to ≥20mg/day of prednisone for ≥2 weeks); or neutropenia (ANC <1000cells/mm^3) at any point during the study period.

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

TANGO II
BAT antibiotic regimens

Antibiotic Regimens in Best Available Therapy (mCRE-MITT)

BAT Regimen	All (N=15*) n (%)
Monotherapy	**4 (26.7)**
Aminoglycoside	1 (6.7)
Carbapenem	1 (6.7)
Ceftazidime-Avibactam	1 (6.7)
Polymyxin B/Colistin	1 (6.7)
Dual Therapy	**7 (46.7)**
Carbapenem + Aminoglycoside	1 (6.7)
Carbapenem + PolymyxinB/Colistin	1 (6.7)
Carbapenem + Tigecycline	2 (13.3)
PolymyxinB/Colistin + Aminoglycoside	3 (20.0)
Triple Therapy	**1 (6.7)**
Carbapenem + Polymyxin/Colistin+Tigecycline	1 (6.7)
4 or More Drugs	**2 (13.3)**
Carbapenem+Polymyxin/Colistin+Tigecycline+Aminoglycoside	2 (13.3)

*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.

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

TANGO II
Clinical outcome by visit across all indications (mCRE-MITT)

Time Point Clinical Response	MV N=32 N (%)	Best Available Therapy N=15 N (%)	Absolute Percent Difference (VABOMERE-BAT) 95% CI	P Value	Relative Percent Difference [(VABOMERE-BAT)/BAT]
End of Therapy					
Cure	**21 (65.6)**	**5 (33.3)**	**32.3** (3.3 to 61.37)	**0.03**	**97.0**
Test of Cure					
Cure	**19 (59.4)**	**4 (26.7)**	**32.7** (4.6 to 60.8)	**0.02**	**122.5**

Similar Difference in Clinical Outcomes Favoring VABOMERE seen at EOT, TOC in micro-MITT and MITT Populations

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

TANGO II
Day 28 All-Cause Mortality
All Infection Types (mCRE-MITT)

Endpoint/Statistics	MV N=32 n, (%)	Best Available Therapy N=15 n, (%)	Absolute Percent Difference (MV-BAT)	Relative Percent Difference [(MV-BAT)/BAT]
All-Cause Mortality Rate Day 28	5 (15.6)	5 (33.3)	-17.7	-53.2
Subjects Censored*	27 (84.4)	10 (66.7)		
Kaplan-Meier Estimate (95%CI)	15.6 (6.8 to 33.5)	33.3 (15.4 to 62.5)		

*Subjects whose survival status is unknown due to early termination or lost to follow up will be censored at the last day the subject was known to be alive.

Similar Difference in All-Cause Mortality Favoring VABOMERE also seen in micro-MITT (RRR 45.6%) Population

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

TANGO II
Day 28 All-Cause Mortality
All Infection Types (mCRE-MITT)
Sensitivity analysis – Eliminate prior treatment failures

Endpoint/Statistics	MV N=23 n (%)	Best Available Therapy N=15 n (%)	Absolute Percent Difference (MV-BAT)	Relative Percent Difference [(MV-BAT)/BAT]
All-Cause Mortality Rate Day 28*	1 (4.3)	5 (33.3)	-29.0.1	-87.1

*An ad hoc sensitivity analysis was conducted for all-cause mortality at Day 28 in which subjects in the mCRE-MITT Population who were prior antibiotic treatment failures (VABOMERE, 9 subjects; BAT, no subjects) were excluded from analysis

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

TANGO II
Subjects with Poor Outcomes (mCRE-MITT)

Exploratory Analysis of Risk-Benefit Profile of VABOMERE compared to Best Available Therapy[a]

	MV (n = 32) n (%)	BAT (n = 15) n (%)	Absolute Difference (95% CI)	P value	Relative Difference
Day-28 All-Cause Mortality or Nephrotoxicity[b]	8 (25.0)	6 (40.0)	-15.0 (-44.0 to14.0)	0.31	-37.5
Clinical Failure or Nephrotoxicity[c]	10 (31.3)	12 (80.0)	-48.7 (-74.6 to -22.9)	<0.001	-60.9
Day-28 All-Cause Mortality or Renal AEs[d]	6 (18.8)	9 (60.0)	-41.2 (-69.5 to -13.0)	0.004	-68.7
Clinical Failure or Renal AEs[e]	9 (28.1)	12 (80.0)	- 51.9 (-77.4 to -26.3)	<0.001	-64.9

AE=adverse event; BAT=best available therapy; CI=confidence interval; cUTI/AP=complicated urinary tract infection/acute pyelonephritis; EOT=end of treatment; mCRE-MITT=microbiologic carbapenem-resistant Enterobacteriaceae modified intent to treat; TOC=test of cure.

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

[b] Composite outcome of either Day 28 all-cause mortality or a post-baseline increase in serum creatinine ≥1mg/dL

[c] Composite outcome of either clinical failure at test of cure or a post-baseline increase in serum creatinine ≥1mg/dL.

[d] Composite outcome of either Day 28 all-cause mortality or adverse event of renal failure, renal failure acute or renal impairment.

[e] Composite outcome of either clinical failure at test of cure or adverse event of renal failure, renal failure acute or renal impairment.

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

TANGO II

Number (%) of subjects with renal related events — kidney injury defined by RIFLE criteria or renal TRAEs (Safety Population/ MITT Population)

Time Point/ RIFLE Criteria	MV N=50 n (%)	Best Available Therapy N=25 n (%)	Total N=75 N (%)
Any Post-Baseline Maximum RIFLE Class	**1/48 (2.1)**	**2/24 (8.3)**	**3/72 (4.2)**
R	0/48 (0)	1/24 (4.2)	1/72 (1.4)
I	1/48 (2.1)	1/24 (4.2)	2/72 (2.8)
F	0/48 (0)	0/24 (0)	0/72 (0)
Renal Related TRAEs by Preferred Term			
Renal Failure Acute	1 (2.0)	3 (12.0)	4 (5.3)
Renal Impairment	1 (2.0)	2 (8.0)	3 (4.0)
Renal Failure	0 (0)	1 (4.0)	1 (1.3)
TOTAL	**2 (4.0)**	**6 (24)**	**8 (10.6)**

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

Summary

Unlike cephalosporin antibiotics, meropenem is stable against narrow-spectrum class A beta-lactamases as well as ESBLs, but labile to carbapenemases.

MV combines the trusted power of meropenem with vaborbactam (a novel, boronic acid BLI) specifically designed to restore the power of meropenem against KPC-producing Enterobacteriaceae.

Vaborbactam restores meropenem potency against *Klebsiella pneumoniae* carbapenemase (KPC)-producing carbapenem-resistant Enterobacteriaceae (CRE). Against KPC, meropenem minimum inhibitory concentrations (MICs) were reduced by ≥32-fold with the addition of vaborbactam at a fixed concentration of 8 mcg/mL.

MV is safe and effective for the treatment of serious infections due to KPC-producing Enterobacteriaceae.