Meropenem-Vaborbactam Pharmacokinetic-Pharmacodynamic Target Attainment Analyses as Support for Dose Selection in Patients with Normal Renal Function and Varying Degrees of Renal Impairment

S.M. Bhavnani[1], M. Trang[1], D.C. Griffith[2], O. Lomovskaya[2], J.P. Hammel[1], J.S. Loutit[2], M.N. Dudley[2], P.G. Ambrose[1], C.M. Rubino[1]
[1]Institute for Clinical Pharmacodynamics, Inc., Schenectady, NY, USA; [2]The Medicines Company, San Diego, CA, USA

ICPD INSTITUTE for CLINICAL PHARMACODYNAMICS

Sujata M. Bhavnani, Pharm.D., M.S.
Institute for Clinical Pharmacodynamics, Inc.
242 Broadway
Schenectady, NY 12305
Telephone: (518) 631-8100
Fax: (518) 631-8199
E-mail: sbhavnani@ICPD.com

INTRODUCTION

- Meropenem-vaborbactam is a broad-spectrum carbapenem-β-lactamase inhibitor combination which was recently approved by the United States (US) food and drug administration (FDA) to treat patients with complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae carbapenemase* (KPC), and *Enterobacter cloacae* species complex [1].
- As part of the drug development program, two Phase 3 clinical trials were completed in patients with cUTI and patients with serious infections known or suspected to be caused by carbapenem-resistant Enterobacteriaceae (CRE) [2, 3]. Pharmacokinetic (PK) data from the above-described two trials were collected, and provided the opportunity to refine population PK models for meropenem and vaborbactam [4].
- As described herein, the above-described population PK model allowed for the evaluation of meropenem-vaborbactam dosing regimens for patients with normal renal function and renal impairment using Monte Carlo simulation and pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses.

OBJECTIVE

- To conduct PK-PD target attainment analyses using Monte Carlo simulation, population PK models, non-clinical PK-PD targets for efficacy, and *in vitro* surveillance data to provide support for meropenem-vaborbactam dose selection for patients with normal renal function and varying degrees of renal impairment.

METHODS

- Using R version 3.3.1, four simulated patient populations (n=1000 each) varying by estimated glomerular filtration rate (eGFR) were generated using a uniform probability distribution for the following groups: ≥50, ≥30-49, ≥15-29, and <15 mL/min/1.73 m^2.
- Using meropenem and vaborbactam population pharmacokinetic PK models [4], individual post-hoc parameter estimates were generated. Using these estimates, total-drug concentration-time profiles were generated for simulated patients who received meropenem-vaborbactam dosing regimens according to eGFR as described in **Table 1**.

Table 1. Merepenem-vaborbactam dosing regimens evaluated by renal function groups as defined by eGFR range

Renal function group (eGFR range in mL/min/1.73m^2)[a]	Meropenem- vaborbactam dosing regimens[b,c]
≥50	meropenem 2 g - vaborbactam 2 g q8h
≥30-49	meropenem 1 g - vaborbactam 1 g q8h
≥15-29	meropenem 1 g - vaborbactam 1 g q12h
<15	meropenem 0.5 g - vaborbactam 0.5 g q12h

a. Calculated using MDRD formula.
b. All doses were administered intravenously over 3 hours.
c. Meropenem-vaborbactam dosing regimens represent those that are recommended in the package insert [1].

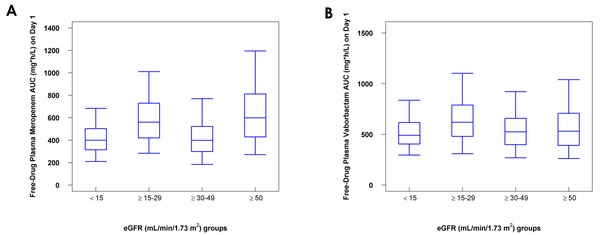
METHODS

- Protein binding estimates were used to determine free-drug concentration-time profiles for meropenem and vaborbactam (2 and 33%, respectively).
- The Day 1 percentage of time during the dosing interval that free-drug meropenem concentrations were above the MIC (%T>MIC), for MIC values as described below, and the ratio of the vaborbactam free-drug area under the concentration-time curve from 0 to 24 hours to the meropenem-vaborbactam MIC (AUC:MIC ratio), the MIC for which was assessed as the meropenem MIC with vaborbactam fixed at 8 mg/L, were determined.
- Percent probabilities of achieving meropenem %T>MIC targets of 30, 35 and 45% associated with net bacterial stasis, and 1- and 2-log$_{10}$ colony forming unit reductions from baseline, respectively, and the vaborbactam AUC:MIC ratio target associated with net bacterial stasis of 12 [5] were evaluated.
- An algorithm to assess PK-PD target attainment at meropenem and corresponding meropenem-vaborbactam MIC values based on worldwide *in vitro* surveillance data for Enterobacteriaceae and KPC-producing Enterobacteriaceae was followed. For *Pseudomonas aeruginosa*, meropenem %T>MIC targets alone were assessed relative to meropenem-vaborbactam MIC values.

RESULTS

- As shown by **Figure 1**, boxplots of Day 1 free-drug plasma meropenem and vaborbactam AUC$_{0\text{-}24}$ values, respectively, demonstrated distributions of exposures for each drug that generally overlapped across renal function group.

Figure 1. Boxplots showing the distributions of free-drug plasma meropenem (A) and vaborbactam (B) AUC$_{0\text{-}24}$ values on Day 1 among simulated patients by renal function group



- As shown in **Table 2** and **Figure 2**, percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall on Day 1, based on the assessment of three free-drug plasma meropenem %T > MIC targets and MIC distributions for each isolate collection, were similar across renal function groups.
- At the meropenem-vaborbactam MIC value of 4 and 8 µg/mL, percent probabilities of PK-PD target attainment based on all free-drug plasma meropenem %T>MIC targets and pathogen MIC distributions evaluated were ≥98.5 and ≥90.9, respectively, among simulated patients by renal function group.

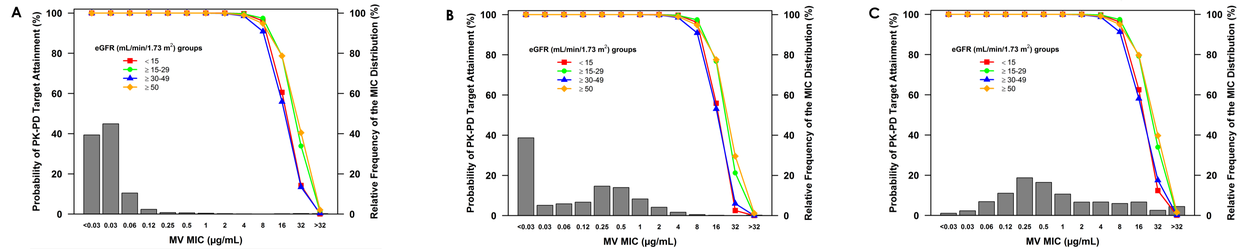
RESULTS

Table 2. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall on Day 1 for meropenem-vaborbactam dosing regimens based on the assessment of three free-drug plasma meropenem %T > MIC targets and 11,599 Enterobacteriaceae, 1,331 KPC-producing Enterobacteriaceae, and 2,806 *P. aeruginosa* isolates among simulated patients by renal function group

Pathogen	MV[a] MIC (µg/mL)	Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC, free-drug plasma meropenem %T>MIC target, and renal function group as defined by eGFR range (mL/min/1.73 m^2)[b]											
		Free-drug plasma meropenem %T>MIC ≥30				Free-drug plasma meropenem %T> MIC ≥35				Free-drug plasma meropenem %T>MIC ≥45			
		<15	≥15-29	≥30-49	≥50	<15	≥15-29	≥30-49	≥50	<15	≥15-29	≥30-49	≥50
All Enterobacteriaceae	2	100	100	100	100	100	100	100	100	100	99.9	99.8	99.9
	4	100	100	100	100	100	99.9	100	100	99.7	99.6	98.5	99.0
	8	99.4	99.9	99.6	100	99.1	99.7	98.9	99.9	96.1	97.4	90.9	94.8
	16	77.5	95.0	83.4	98.4	73.1	91.6	75.4	95.7	60.5	78.6	55.9	78.7
	Overall[c]	99.5	99.7	99.6	99.7	99.5	99.6	99.5	99.7	99.5	99.6	99.5	99.6
KPC-producing Enterobacteriaceae	2	100	100	100	100	100	100	100	100	100	99.9	99.8	99.9
	4	100	100	100	100	100	99.9	100	100	99.7	99.6	98.5	99.0
	8	99.4	99.9	99.6	100	99.1	99.7	98.9	99.9	96.1	97.4	90.9	94.8
	16	74.9	94.1	81.9	98.0	69.8	90.2	73.0	95.3	55.9	76.7	53.1	77.6
	Overall[c]	99.7	99.7	99.7	99.8	99.7	99.7	99.7	99.7	99.6	99.7	99.6	99.6
P. aeruginosa	2	100	100	100	100	100	100	100	100	100	100	99.8	99.9
	4	100	100	100	100	100	99.9	100	100	99.7	99.7	98.7	99.1
	8	99.4	99.9	99.6	100	99.1	99.8	98.9	99.9	96.2	97.4	91.2	95.0
	16	79.2	94.8	84.5	98.2	75.0	91.0	76.5	95.9	62.5	79.2	58.1	79.7
	Overall[c]	92.1	94.0	92.7	94.9	91.7	93.6	92.0	94.4	90.6	92.3	90.1	92.4

a. MV=meropenem-vaborbactam
b. Represents the weighted percent probability of PK-PD target attainment over the meropenem-vaborbactam MIC distribution.

Figure 2. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for meropenem-vaborbactam dosing regimens based on free-drug plasma meropenem %T>MIC ≥45% among simulated patients by renal function group, overlaid upon the meropenem-vaborbactam MIC distribution for 11,559 Enterobacteriaceae isolates (A), 1,331 KPC-producing Enterobacteriaceae isolates (B), and 2,806 *P. aeruginosa* isolates (C)



CONCLUSIONS

- Results of these analyses demonstrated high percent probabilities of PK-PD target attainment for the meropenem-vaborbactam dosing regimens evaluated at the upper margins of the meropenem-vaborbactam MIC distribution.
- These data support the dosing recommendation of meropenem 2 g - vaborbactam 2 g q8h administered as a 3-hour infusion, as well as dosage adjustments for renal function, provided in the meropenem-vaborbactam package insert [1].

REFERENCES

1. Meropenem-vaborbactam (VABOMERE) package insert. Parsippany, NJ; 2017.
2. Loutit JS *et al.*, Meropenem-vaborbactam (M-V) compared with piperacillin-tazobactam (P-T) in the treatment of adults with complicated urinary tract infections (cUTI), including acute pyelonephritis (AP) in a Phase 3 randomized, double-blind, double-dummy trial (TANGO 1). IDWeek 2016, platform presentation LB-7.
3. Kaye KS *et al.*, Clinical outcomes of serious infections due to carbapenem-resistant Enterobacteriaceae (CRE) in TANGO II, a Phase 3, randomized, multi-national, open-label trial of meropenem-vaborbactam (M-V) versus best available therapy (BAT), IDWeek 2017, poster 1862.
4. Trang M *et al.*, Population pharmacokinetics of meropenem and vaborbactam in healthy volunteers and infected patients. American Society for Microbiology 2017, poster SUNDAY-192.
5. Griffith D *et al.*, Pharmacodynamics of vaborbactam when administered in combination with meropenem. ASM Microbe 2017, poster SUNDAY-194.