# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209776Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Office of Clinical Pharmacology Review Addendum

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|---|---|
| **NDA or BLA Number** | 209776 |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA209776\209776.enx |
| **Submission Date** | 12/29/2016 |
| **Submission Type** | 505 (b)(2); priority |
| **Brand Name** | Meropenem-Vaborbactam |
| **Generic Name** | VABOMERE |
| **Dosage Form and Strength** | Injection vial; Each vial delivers 1000 mg each of meropenem and vaborbactam in 50 mL Type I clear glass vial |
| **Route of Administration** | IV Infusion |
| **Proposed Indication** | Complicated Urinary Tract Infections (cUTI), including Pyelonephritis in patients 18 years and older |
| **Applicant** | Rempex Pharmaceuticals, Inc |
| **Associated IND** | IND 120040 |
| **OCP Review Team** | Xiaohui (Tracey) Wei, PhD: Primary Reviewer<br>Seong H. Jang, PhD: Team Leader<br>Jeffry Florian, PhD: Team Leader<br>Luning (Ada) Zhuang, PhD: Reviewer |
| **OCP Final Signatory** | Kellie S. Reynolds, PharmD: Division of Clinical Pharmacology IV Deputy Director |

## 1. Executive Summary

This review serves as an addendum to the clinical pharmacology review for NDA 209776 (meropenem and vaborbactam; VABOMERE) entered into DARRTS on June 7th, 2017.

The review team had several discussions with the Applicant regarding dose adjustments in patients with renal impairment following the late-cycle meeting held on June 23th, 2017. This addendum describes two updates regarding dose adjustments in patients with renal impairment:

1) The recommended VABOMERE dosing regimen in patients with eGFR of 30 to 49 mL/min/1.73 $m^2$ is changed to VABOMERE 2 g (meropenem 1 g- vaborbactam 1g) Q8H.

In the clinical pharmacology review for NDA 209776 dated June 7th, 2017, we recommended a dosing regimen of VABOMERE 4 g (meropenem 2 g- vaborbactam 2g) Q12H for patients with eGFR of 30 to 49 mL/min/1.73 $m^2$. This dosing regimen was recommended because it provides daily AUC in patients with eGFR of 30 to 49 mL/min/1.73 $m^2$ comparable to daily AUC in patients who have eGFR >80 mL/min/1.73 $m^2$ and receive VABOMERE 4 g (meropenem 2 g- vaborbactam 2g) Q8H.

This recommendation was based on simulations conducted by the review team using the Applicant's population PK model.

However, the Applicant found that only 83% patients with eGFR of 30 to 49 mL/min/1.73 $m^2$ would achieve the meropenem PK/PD target, defined as 45% *f*T>MIC, at MIC of 8 µg/mL, using the FDA recommended dosing regimen. The Applicant proposed a dosing regimen of VABOMERE 2 g (meropenem 1 g- vaborbactam 1g) Q8H for patients with eGFR of 30 to 49 mL/min/1.73 $m^2$ because their analysis indicated 91% of patients would achieve the meropenem PK/PD target at this dosing regimen. The review team conducted an independent analysis to compare the target attainment between the FDA's recommended dose and the Applicant's proposed dose, and confirmed the Applicant's results. Therefore, we accepted the Applicant proposed dosing regimen of VABOMERE 2 g (meropenem 1 g- vaborbactam 1g) Q8H for patients with eGFR of 30 to 49 mL/min/1.73 $m^2$.

2) For ESRD patients who are maintained on hemodialysis, the recommendation is changed to administer doses of VABOMERE after a hemodialysis session.

In the clinical pharmacology review for NDA 209776 dated June 7th, 2017, we recommended VABOMERE be administered before hemodialysis for patients maintained on hemodialysis, based on the assumptions of high vaborbactam exposure when dosing after dialysis and the unknown safety risk associated with such high drug exposure. Following the completion of the clinical pharmacology review, we developed population PK models that describe the impact of hemodialysis on the drug exposures of meropenem and vaborbactam. Simulations were conducted to compare the drug exposures of meropenem and vaborbactam when dosing VABOMERE before or after a hemodialysis session assuming a 3 times/week dialysis cycle and a dosing regimen of VABOMERE 1 g (meropenem 0.5 g- vaborbactam 0.5 g) Q12H for 7 days in patients with eGFR < 15 mL/min/1.73 $m^2$. The results showed that hemodialysis given after dosing would result in lower meropenem percent target attainment (PTA) (i.e., <90%) at MIC of 8 µg/mL on the day of hemodialysis. In contrast, when VABOMERE is administered after a hemodialysis session, high PTA (i.e., >98%) can be achieved following each dose. In addition, simulated vaborbactam daily AUC levels are similar either administering VABOMERE after or before a hemodialysis session and are maintained below the reference AUC value (i.e.,2050 µg·h/mL, the 90th higher percentiles of $AUC_{0\text{-}24,ss}$ from Study 506) in both cases during the 7-day treatment period. Similar results were submitted by the Applicant based on their simulations showing that patients receiving pre-dialysis dosing will achieve <90% target attainment at MIC's of 8 µg/mL. Based on these results, the recommendation is updated to administer doses of VABOMERE after a hemodialysis session for patients maintained on the hemodialysis.

## 2. Supporting Analyses

In this review, the review team provides updated analyses addressing: i) the adequacy of the proposed dosing regimen in patients with eGFR of 30 to 49 mL/min/1.73 $m^2$; and ii) impact of

timing of hemodialysis on exposure and PTA in ESRD patients (eGFR < 15 mL/min/1.73 $m^2$ undergoing hemodialysis).

**Dosing Regimen in Patients with eGFR 30 to 49 mL/min/1.73 $m^2$**

Based on the re-analysis of PTA using the code submitted by the Applicant on July 19th, 2017, described below, the review team agrees with the proposed dosing regimen of 1 g – 1 g (meropenem - vaborbactam) Q8H in this population.

In the Applicant's analysis, a full concentration profile of meropenem was simulated for each subject (i.e., data point every 0.1 h for 240 PK data points over 24 hours) using population PK model. In contrast, the review team's original analysis utilized only 15-18 PK data points over 24 hours for each subject. The review team obtained the percent of time that free meropenem concentrations above a specific MIC value over 24 hours using the following methodology: 1) for any two consecutive time points, identify whether one time point has concentration below the MIC value and the other time point has concentration above the MIC value (i.e., does the time course intersect or fall below a specified MIC over a time interval); 2) assume a linear relationship between the two concentrations and calculate the "starting" time point where the profile exceeds the MIC; 3) repeat this process for when the time profile falls below the MIC after the end of the infusion 4) percentage of the dosing interval was then calculated as the total time above the MIC divided by the dosing interval. This approach was necessary because of the number of data points included in the Reviewer's simulation and resulted in an overestimation of PTA relative to the value obtained from the Applicant's analysis.

The review team conducted an independent PTA analysis using Applicant's sampling strategy and similar results were derived as those from Applicant (Table 1).

**Table 1. PTA analysis comparison at MIC of 8 µg/mL in patients with eGFR of 30 to 49 mL/min/1.73 $m^2$ (Applicant's sampling strategy)**

| Dosing regimen | MIC (µg/mL) | FDA's PTA results | | Applicant's PTA results |
|---|---|---|---|---|
| | | eGFR 30-39 | eGFR 40-49 | eGFR 30-49 |
| 2 g -2 g Q12H | 8 | 83.9% | 78.1% | 83.1% |
| 1 g- 1 g Q8H | 8 | 90.5% | 89.2% | 90.9% |

*Source: Reviewer's analysis*

**Dosing regimen in ESRD patients undergoing hemodialysis**

The clinical pharmacology review team agrees with the proposal that VABOMERE should be administered after a hemodialysis session.

In initial labeling comments to the Applicant, the clinical pharmacology review team recommended VABOMERE be administered before hemodialysis. This proposal was based on the desire to reduce vaborbactam exposures, which is predominantly renally eliminated and accumulates to a greater extent than meropenem in subjects with renal impairment. In ESRD patients, plasma exposure of vaborbactam could be higher than exposure supported by clinical experience, so the recommendation was an attempt to mitigate high exposures and potential safety risks.

The Applicant submitted PTA analyses for meropenem on July 19th, 2017, showing that a post-infusion hemodialysis session would result in only 77.8% patients with eGFR < 15mL/min/1.73 $m^2$ achieving the PK/PD target of meropenem, defined as 45% *f*T>MIC on Day 1 under a dose of 0.5 g-0.5 g meropenem-vaborbactam. The review team also conducted an independent analysis to assess the impact of timing of hemodialysis on PTA based on information from the dedicated renal impairment study and the Applicant's previously developed population PK model.

Briefly, the previous population PK model for meropenem and vaborbactam included patients from the Phase 3 trials and healthy volunteers from the dedicated renal impairment study. However, it did not include the subjects on hemodialysis from the dedicated renal impairment study. The Reviewer updated the model by including those patients in the dataset and only used PK data from dedicated renal impairment study. To accommodate the impact of hemodialysis on clearance, a parameter ($CL_{HD}$) was added to population PK model for both meropenem and vaborbactam. Several parameters were fixed due to limited PK data in dedicated renal impairment study (Tables 2 and 3). The estimates of $CL_{HD}$ were 7.9 and 5.68 L/h for meropenem and vaborbactam, respectively.

**Table 2. Final parameter estimates for meropenem based on dedicated renal impairment study**

| | Population mean (%SEM) | |
|---|---|---|
| **CL** | Applicant's model | Reviewer's model |
| $CL_{NR}$ | 3.78 (5.60) | 2.62 (10) |
| $CL_{r,max}$ | 6.6 (8.60) | 6.6 FIX |
| $eGFR_{50}$ | 40.8 (13.7) | 40.8 FIX |
| Hill coef | 1.94 (9.90) | 1.75 (8) |
| **Vc** | 17.4 (4.00) | 12.1 (5) |
| **Q** | 1.52 (12.6) | 2.83 (19) |
| **Vp** | 2.5 (7.30) | 3.59 (11) |
| **WT on Vc (power)** | 0.487 (31.8) | 0.487 FIX |
| **WT on Vp (power)** | 0.324 (37.0) | 0.324 FIX |
| **AGE on CL (power)** | -0.43 (14.4) | -0.43 FIX |
| **ESRD on $CL_{NR}$ (proportional)** | 0.349 (11.2) | 0.568 (13) |
| **$CL_{HD}$** | - | 7.9 (10) |

*Source: Applicant's population PK report and Reviewer's analysis*

**Table 3. Final parameter estimates for vaborbactam based on dedicated renal impairment study**

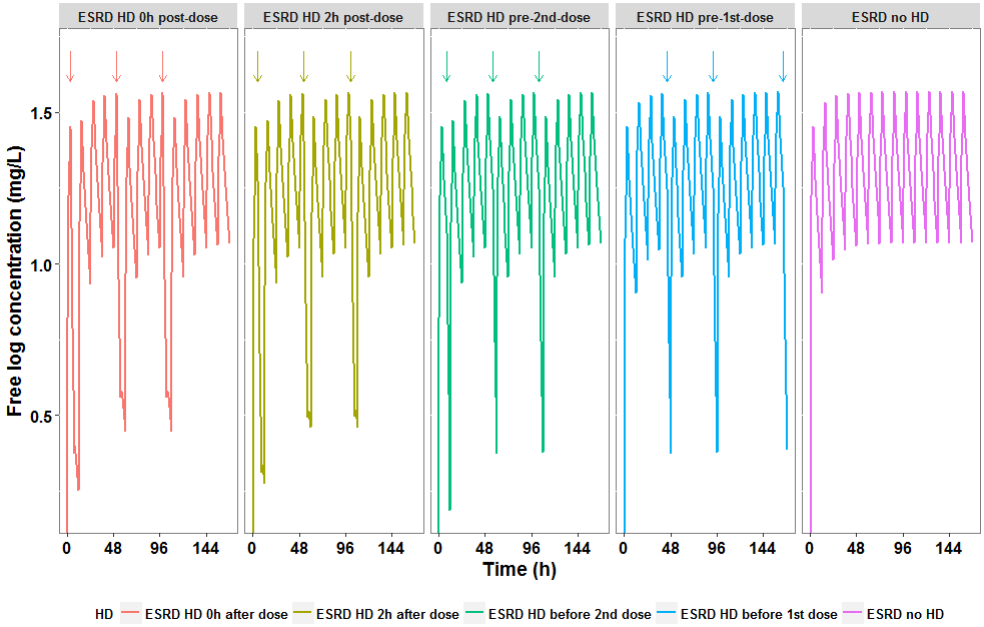
| | Population mean (%SEM) | |
|---|---|---|
| **CL** | Applicant's model | Reviewer's model |
| $CL_{NR}$ | 0.169 (12.5) | 0.085 (61) |
| $CL_{r,max}$ | 9.34 (3.3) | 9.34 FIX |
| $eGFR_{50}$ | 47.1 (3.0) | 47.1 FIX |
| Hill coef | 2.23 (3.4) | 2.1 (9) |
| **Vc** | 16.9 (3.9) | 17.9 (4) |
| **Q** | 3.12 (8.6) | 2.03 (16) |
| **Vp** | 1.41 (27.2) | 1.28 (7) |
| **HT on CL (power)** | 2.17 (20.6) | 2.17 FIX |
| **Phase on CL (proportional)** | 0.264 (43.6) | 0.264 FIX |
| **BSA on Vc (power)** | 1.14 (18.1) | 1.14 FIX |
| **Phase on Vc (proportional)** | -0.203 (37.3) | -0.203 FIX |
| **Phase on Vp (proportional)** | 1.78 (42.2) | 1.78 FIX |
| **$CL_{HD}$** | - | 5.68 (16) |

*Source: Applicant's population PK report and Reviewer's analysis*

The final model with $CL_{HD}$ was used to simulate the PK profile over 7 days at different scenarios assuming hemodialysis was given on Day 1, Day 3 and Day 5. The five scenarios included hemodialysis was given at the end of the infusion, hemodialysis was given 2 h after the end of the infusion, hemodialysis was given prior to the first dosing on Day 1, hemodialysis was given prior to the second dosing on Day 1, and no hemodialysis (Figures 1 and 2). Patients were administered 0.5 g – 0.5 g (meropenem - vaborbactam) Q12H assuming a three-hour infusion. Predicted AUC on each day under these scenarios for meropenem and vaborbactam are listed in Tables 4 and 5, respectively. The PTA analysis per dose over 4 days was conducted for meropenem-vaborbactam combination using two PK/PD targets: 45% *f*T>MIC for meropenem and fAUC/MIC ≥ 6 for vaborbactam (The original target for vaborbactam was *f*AUC/MIC≥12, since per dose PTA was calculated for BID dosing, this target was divided by 2)(Table 6).

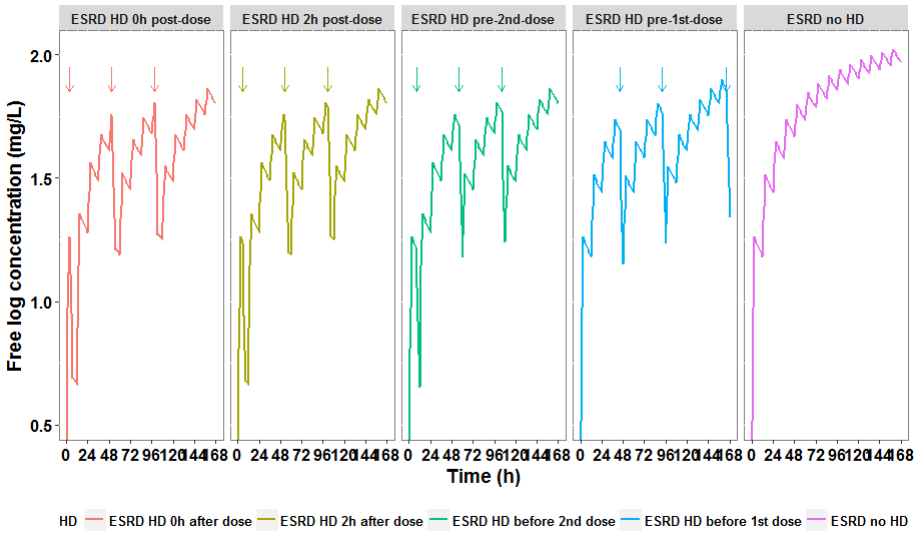
The results showed that hemodialysis given 0 h or 2 h after the end of the infusion would result in lower PTA results on the day of hemodialysis but would achieve the PTA target for an MIC of 8 µg/mL on non-hemodialysis days. In contrast, hemodialysis given before dosing, whether before the first or second dose on the day of hemodialysis, would result in the patients still achieving the desired PTA target for an MIC of 8 µg/mL.

**Figure 1. Simulated free concentrations of meropenem in ESRD patients under different hemodialysis (HD) scenarios (log10 scale). Arrows denote timing of HD. Patients were administered 0.5 g – 0.5 g (meropenem - vaborbactam) Q12H over a three-hour infusion**




*Source: Reviewer's analysis*

**Figure 2. Simulated free concentrations of vaborbactam in ESRD patients under different HD scenarios (log10 scale). Arrows denote timing of HD. Patients were administered 0.5 g – 0.5 g (meropenem - vaborbactam) Q12H over a three-hour infusion**




*Source: Reviewer's analysis*

**Table 4. Summary of free AUC in ESRD patients by day for meropenem based on the updated population PK model. Patients were administered 0.5 g – 0.5 g (meropenem - vaborbactam) Q12H over a three-hour infusion**

| Day of treatment | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| HD 0h after 1st dose on Day 1, 3, 5 | 290 | 496 | 347 | 500 | 347 | 500 | 523 |
| HD 2h after 1st dose on Day 1, 3, 5 | 323 | 496 | 390 | 500 | 390 | 501 | 524 |
| HD before 2nd dose on Day 1, 3, 5 | 355 | 496 | 433 | 500 | 434 | 501 | 524 |
| HD before 1st dose on Day 2, 4, 7 | 418 | 482 | 447 | 487 | 447 | 517 | 496 |
| No HD | 418 | 512 | 525 | 527 | 528 | 528 | 528 |

*Source: Reviewer's analysis*

**Table 5. Summary of free AUC in ESRD patients by day for vaborbactam based on the updated population PK model. Patients were administered 0.5 g – 0.5 g (meropenem - vaborbactam) Q12H over a three-hour infusion**

| Day of treatment | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| HD 0h after 1st dose on Day 1, 3, 5 | 319 | 898 | 702 | 1093 | 780 | 1140 | 1531 |
| HD 2h after 1st dose on day 1, 3, 5 | 344 | 898 | 778 | 1093 | 864 | 1140 | 1531 |
| HD before 2nd dose on Day 1, 3, 5 | 378 | 898 | 885 | 1093 | 983 | 1139 | 1530 |
| HD before 1st dose on Day 2, 4, 7 | 519 | 987 | 817 | 1199 | 882 | 1346 | 1564 |
| No HD | 519 | 1069 | 1462 | 1759 | 1992 | 2178 | 2332 |

*Source: Reviewer's analysis*

**Table 6. PTA results per dose for meropenem-vaborbactam combination therapy in ESRD patients under different HD scenarios. Patients were administered 0.5 g – 0.5 g (meropenem - vaborbactam) Q12H over a three-hour infusion. The PTA analysis per dose over 4 days was conducted for the meropenem-vaborbactam combination using two PK/PD targets: 45% *f*T>MIC for meropenem and fAUC/MIC ⩾ 6 for vaborbactam.**

| HD situation | MIC | Time on treatment (Dose number) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 h (1) | 12 h (2) | 24 h (3) | 36 h (4) | 48 h (5) | 60 h (6) | 72 h (7) | 84 h (8) |
| **HD 0h after 1st dose on day 1, 3, 5** | **8** | 5.7 | 98.5 | 98.8 | 98.8 | 40.3 | 98.4 | 98.8 | 98.8 |
| **HD 2h after 1st dose on day 1, 3, 5** | **8** | 83.8 | 98.5 | 98.8 | 98.8 | 95.7 | 98.4 | 98.8 | 98.8 |
| **HD before 2nd dose on Day 1, 3, 5** | **8** | 98.4 | 98.5 | 98.8 | 98.8 | 98.8 | 98.4 | 98.8 | 98.8 |
| **HD before 1st dose on Day 2, 4, 7** | **8** | 98.4 | 98.9 | 98.9 | 98.9 | 98.4 | 98.8 | 98.8 | 98.8 |
| **No HD** | **8** | 98.4 | 98.9 | 98.9 | 98.9 | 98.8 | 98.8 | 98.8 | 98.8 |

*Source: Reviewer's analysis*

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# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | 209776 |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA209776\209776.enx |
| **Submission Date** | 12/29/2016 |
| **Submission Type** | 505 (b)(2); priority |
| **Brand Name** | Meropenem-Vaborbactam |
| **Generic Name** | VABOMERE |
| **Dosage Form and Strength** | Injection vial; Each vial delivers 1000 mg each of meropenem and vaborbactam in 50 mL Type I clear glass vial |
| **Route of Administration** | IV Infusion |
| **Proposed Indication** | Complicated Urinary Tract Infections (cUTI), including Pyelonephritis in patients 18 years and older |
| **Applicant** | Rempex Pharmaceuticals, Inc |
| **Associated IND** | IND 120040 |
| **OCP Review Team** | Xiaohui (Tracey) Wei, PhD: Primary Reviewer<br>Seong H. Jang, PhD: Team Leader<br>Jeffry Florian, PhD: Team Leader<br>Luning (Ada) Zhuang, PhD: Reviewer |
| **OCP Final Signatory** | Kellie S. Reynolds, PharmD: Division of Clinical Pharmacology IV Deputy Director |

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# 1. EXECUTIVE SUMMARY

VABOMERE® (meropenem and vaborbactam) is a combination product consisting of meropenem, a carbapenem class antibacterial drug, and vaborbactam, a beta lactamase inhibitor. MERREM® (meropenem) was approved by the FDA for the treatment of complicated skin and skin structure infections (adults and pediatric patients), complicated intraabdominal infections (adult and pediatric patients), and bacterial meningitis (pediatric patients); whereas vaborbactam is a new molecular entity. The proposed indication for VABOMERE is complicated urinary tract infections (cUTI) including pyelonephritis in patients 18 years or older caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, (b) (4) (b) (4) *Enterobacter cloacae* species complex (b) (4).

The Applicant's proposed dosage regimen of VABOMERE is 4 g (meropenem 2 g and vaborbactam 2 g) administered every 8 hours (q8h) by intravenous (IV) infusion over 3 hours in patients 18 years of age and older (b) (4), with dose adjustments for reduced renal function. Results from the pivotal Study 505 show a 98.4% success rate in the meropenem-vaborbactam group compared to 94.0% in the comparator piperacillin-tazobactam group, with a treatment difference of 4.5% and 95% confidence interval (CI) of (0.7%, 9.1%). Meropenem-vaborbactam is noninferior to piperacillin-tazobactam based on the pre-specified noninferiority margin of -15%. Based on the available data, meropenem 2 g-vaborbactam 2 g administered IV over 3 hours q8h is safe and well tolerated in patients with cUTI including pyelonephritis and in patients with severe bacterial infections, including those with suspected or documented *Klebsiella pneumoniae* carbapenemase (KPC)-producing carbapenem-resistant Enterobacteriaceae (CRE) infections.

The key clinical pharmacology review questions focus on appropriateness of dose recommendations for meropenem-vaborbactam in patients with renal impairment.

## 1.1 Recommendations

The Office of Clinical Pharmacology, Divisions of Clinical Pharmacology IV and Pharmacometrics, have reviewed the information contained in NDA 209776. The application is approvable from a clinical pharmacology perspective, provided that an agreement is reached between the Applicant and the Agency on the dosing regimen for patients with renal impairment and labeling (Table 1.1-1).

**Table 1.1-1 Summary of OCP's Recommendations & Comments on Key Review Issues**

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td>Pivotal or supportive evidence of effectiveness</td><td>The pivotal effectiveness of meropenem-vaborbactam in patients with complicated urinary tract infections (cUTI) including pyelonephritis was supported by one Phase 3 trial (Study 505). Review of the Clinical Pharmacology data package (exposure-response relationship for efficacy and the target attainment analyses to support breakpoint determination) provided supportive evidence of effectiveness.</td></tr>
<tr><td>General dosing instructions</td><td>The recommended dosing regimen is VABOMERE 4 g (meropenem 2 g and vaborbactam 2 g) administered every 8 hours by intravenous (IV) infusion over 3 hours in patients 18 years of age and older with eGFR ≥ 50 mL/min/1.73m$^2$.</td></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>The Applicant proposed dose adjustment (b) (4) (b) (4). The Clinical Pharmacology review team conducted additional analyses and recommended dose adjustment based on eGFR calculated using the MDRD equation as follows.
<table>
<tr><th>Applicant Proposed Dosing Regimen</th><th colspan="2">FDA Recommended Dosing Regimen</th></tr>
<tr><td rowspan="5">(b) (4)</td><td>eGFR (mL/min/1.73m$^2$)[c]</td><td>Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam)[b]</td></tr>
<tr><td>≥50</td><td>VABOMERE 4 g (2 g-2 g) q8h</td></tr>
<tr><td>≥30-49</td><td>VABOMERE 4 g (2 g-2 g) q12h</td></tr>
<tr><td>≥15-29</td><td>VABOMERE 2 g (1 g-1 g) q12h</td></tr>
<tr><td><15</td><td>VABOMERE 1 g (0.5 g-0.5 g) q12h[d]</td></tr>
<tr><td colspan="3">(b) (4)</td></tr>
</table>
[b] All doses of VABOMERE are administered intravenously over 3 hours<br>
[c] Calculated using MDRD formula<br>
[d] Both meropenem and vaborbactam can be removed by hemodialysis. For patients maintained on hemodialysis, administer VABOMERE before hemodialysis.</td></tr>
</table>

| | |
|---|---|
| **Labeling** | The Applicant's proposed labeling is generally acceptable except for the aforementioned dosing regimen in patients with renal impairment. In addition, the review team has specific content and formatting change recommendations. |
| **Bridge between the to-be-marketed and clinical trial formulations** | Not applicable. |

## 1.2 Post-Marketing Requirements and Commitments

There are no post-marketing requirements or commitments.

# 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

## 2.1 Pharmacology and Clinical Pharmacokinetics

VABOMERE (meropenem and vaborbactam) is a combination product consisting of meropenem, a carbapenem class antibacterial drug, and vaborbactam, a β-lactamase inhibitor.

*Mechanism of Action:* The meropenem component of VABOMERE is a carbapenem antibacterial drug with *in vitro* activity against certain aerobic and anaerobic gram negative and gram positive bacteria. The bactericidal action of meropenem results from the inhibition of cell wall synthesis. Meropenem is stable to hydrolysis by most β-lactamases, including penicillinases and cephalosporinases produced by gram negative and gram positive bacteria, with the exception of carbapenem hydrolyzing β-lactamases. The vaborbactam component of VABOMERE does not have antibacterial activity of its own. Vaborbactam is a non-β lactam non-suicidal inhibitor of Class A serine carbapenemases with a particular potent activity against *Klebsiella pneumoniae* carbapenemase, KPC. By inhibiting KPC and related β-lactamases, vaborbactam protects meropenem from degradation by these enzymes.

*Pharmacodyanmics:* The % time of the dosing interval that the unbound (free) plasma concentration of meropenem exceeds the meropenem-vaborbactam minimum inhibitory concentration (MIC) (% $T_{Cf>MIC}/\tau$) against the infecting organism has been shown to correlate with efficacy in animal and *in vitro* models of infection. The ratio of the 24-hour unbound (free) plasma vaborbactam AUC to meropenem-vaborbactam MIC (fAUC/MIC) is the index that predicts efficacy of vaborbactam in combination with meropenem in animal and *in vitro* models of infection. In this review, meropenem-vaborbactam MIC is defined as meropenem MIC determined in the presence of 8 μg/mL of vaborbactam.

The following is a summary of the clinical pharmacokinetics of VABOMERE.

*Absorption:*
Absorption is not relevant to VABOMERE as both meropenem and vaborbactam are given as intravenous infusion.

*Distribution:*
The plasma protein binding of meropenem is approximately 2%. The plasma protein binding of vaborbactam is approximately 33%. The steady state volumes of distribution of meropenem and vaborbactam in patients were 20.2 L and 18.6 L, respectively.

*Elimination:*
The clearance (geometric mean [%CV]) is 10.5 L/h (61.3%) for meropenem and is 7.95 L/h (54.5%) for vaborbactam, based on population pharmacokinetic analyses. The geometric mean $t_{1/2}$ is 2.30 hours and 2.25 hours for meropenem and vaborbactam, respectively.

Metabolism*:*
A minor pathway of meropenem elimination is hydrolysis of the beta lactam ring to an inactive meropenem open lactam metabolite, which accounts for 28% of the dose eliminated via the urine. Vaborbactam does not undergo metabolism.

Excretion*:*
Results from the Applicant's studies showed that approximately 40–60% of a meropenem dose is excreted unchanged within 24 to 48 hours, with a further 28% recovered as the microbiologically inactive hydrolysis product.

For vaborbactam, 75 to 95% of the dose was excreted unchanged in the urine over a 24 to 48 hour period.

## 2.2 Dosing and Therapeutic Individualization

### *2.2.1 General dosing*

The Applicant's proposed dosage regimen of VABOMERE is 4 g (meropenem 2 g and vaborbactam 2 g) administered every 8 hours by intravenous (IV) infusion over 3 hours in patients 18 years of age and older (b) (4) .

The Applicant's proposed dosing regimen is supported by the efficacy, safety and PK data from the clinical trials submitted in the NDA.

### *2.2.2 Therapeutic individualization*

**Renal Impairment**
The Applicant identified renal impairment status as the only intrinsic factor warranting dose adjustment. Table 2.2.2-1 presents the Applicant's proposed dosing regimens and the FDA's recommendations for dose adjustments according to renal function.

PK of meropenem/vaborbactam in subjects with renal impairment and in subjects receiving hemodialysis (HD) therapy has been evaluated in a dedicated PK study (Study 504).

We recommend assigning patients with reduced renal function to appropriate groups for dose adjustment based on eGFR (mL/min/1.73m$^2$) since eGFR was used in Study 504 to categorize

subjects with different degrees of renal impairment (mild, moderate, severe, and end stage renal disease (ESRD; on and off dialysis)).

**Table 2.2.2-1. VABOMERE Dose Adjustments for cUTI/AP Patients with Reduced Renal Function - The Applicant's Proposal vs. FDA's Recommendation**

| Applicant Proposed Dosing Regimen | FDA Recommended Dosing Regimen | |
|---|---|---|
| (b) (4) | eGFR(mL/min/1.73m$^2$)[c] | Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam)[b] |
| | ≥50 | VABOMERE 4 g (2 g-2 g) q8h |
| | ≥30-49 | VABOMERE 4 g (2 g-2 g) q12h |
| | ≥15-29 | VABOMERE 2 g (1 g-1 g) q12h |
| | <15 | VABOMERE 1 g (0.5 g-0.5 g) q12h [d] |

[b] All doses of TRADENAME are administered intravenously over 3 hours
[c] Calculated using MDRD formula
[d] Both meropenem and vaborbactam can be removed by hemodialysis. For patients maintained on hemodialysis, administer VABOMERE before hemodialysis.

Based on the Applicant's analysis of a PK study in subjects with renal impairment (Study 504), meropenem and vaborbactam exposure in plasma increased with decreasing renal function. For meropenem, the $AUC_{0\text{-}inf}$ ratios to subjects with normal renal function are 1.28, 2.07, and 4.63 for subjects with mild, moderate, and severe renal impairment, respectively. In ESRD patients maintained on hemodialysis, the ratio increased to 3.28 when completing VABOMERE infusion ~ 2 hours before the start of dialysis (on dialysis) and to 7.22 when dosing VABOMERE 2 hours after the end of dialysis (off dialysis) . For vaborbactam, the $AUC_{0\text{-}inf}$ ratios to subjects with normal renal function are 1.18, 2.31, and 7.8, for subjects with mild, moderate, and severe renal impairment, respectively. In ESRD patients maintained on hemodialysis, the ratio increased to 10.2 on dialysis and to 37.5 off dialysis. Both meropenem and vaborbactam can be removed by hemodialysis.

Using the Applicant's population PK model, we conducted simulations to generate AUCs for meropenem and vaborbactam in patients with various renal functions (i.e., eGFR) at both the Applicant's proposed dosing regimens and the FDA's recommended dosing regimens. Our simulation results showed that the FDA's recommended dosing regimens, preferred over the Applicant's proposed ones, would provide more comparable AUCs of meropenem and vaborbactam in patients with eGFR <50 ml/min/1.73 $m^2$ to those in patients with eGFR >50 ml/min/1.73 $m^2$. See Section 3.3.2 for the results of simulations.

Because the contribution of renal clearance to total body clearance is greater for vaborbactam compared to meropenem, vaborbactam demonstrated a significantly higher degree of accumulation in subjects with ESRD (eGFR <15 ml/min/1.73 $m^2$) compared to meropenem. In addition, the effect of hemodialysis on meropenem and vaborbactam is quantitatively different although both can be removed by hemodialysis (see Section 4.5.5). Because VABOMERE is a fixed combination of meropenem and vaborbactam (1:1), it is not possible to adjust dosing regimen of meropenem and vaborbactam separately for patients with ESRD. We conducted a risk assessment of potential safety concerns due to high vaborbactam exposure when dosing VABOMERE after dialysis versus the possibility of compromised efficacy due to reduced meropenem exposure when dosing VABOMERE before dialysis (see Section 3.3.3 for details). Based on the considerations of unknown safety risk due to high vaborbactam exposure when dosing after dialysis and an anticipated low risk of reduced efficacy (i.e., due to lower meropenem exposure) when dosing before dialysis, we recommend VABOMERE be administered before the hemodialysis for patients maintained on hemodialysis.

## 2.3 Outstanding Issues

There are no outstanding issues.

## 2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert (Table 2.4-1).

**Table 2.4-1: Summary of Labeling Issue Identification and Recommendations**

| Section/heading | Acceptable to OCP? | | | Comment |
|---|---|---|---|---|
| | A | AWE | NA | |
| Highlights/Dosage and Administration | ☐ | ☐ | ☒ | Revise the dosing regimen in patients with renal impairment |
| Section 2.2/ Dose in RI patient | ☐ | ☐ | ☒ | Revise the dosing regimen in patients with renal impairment |
| Section 8.6/ Renal Impairment | ☐ | ☐ | ☒ | A statement will be added regarding close monitoring of patients maintained on hemodialysis who receive VABOMERE. |
| Section 8.7/ Hepatic Impairment | ☐ | ☐ | ☒ | Add this section with statement of "No dose adjustment is recommended for VABOMERE in subjects with hepatic impairment." |
| Section 12.2/ PD | ☒ | ☐ | ☐ | Minor editorial changes |
| 12.3/PK Parameters | ☐ | ☒ | ☐ | • Table 4 and 5 to be updated regarding consistent units for PK parameters and AUC in same time interval in healthy subjects vs. patients<br>• Number of patients from each Phase 3 study need to be specified in Table 5 |
| 12.3/ Distribution | ☐ | ☒ | ☐ | Minor editorial changes |
| 12.3/ Elimination | ☐ | ☐ | ☒ | • Values of total CL reported under Elimination are not consistent with sum of renal and non-renal CL reported under Excretion<br>• Promotional wording without supportive data were deleted |
| 12.3/specific populations/renal impairment | ☐ | ☐ | ☒ | • Add PK results from renal impairment PK study<br>• Revise dose adjustment (b) (4) eGFR |
| 12.3/specific populations/hepatic impairment | ☐ | ☒ | ☐ | Add information regarding no effect of hepatic impairment on meropenem PK |
| 12.3/specific | ☐ | ☒ | ☐ | Delete unnecessary information to be |

| | | | | |
|---|---|---|---|---|
| populations/Geriatric patients/Gender/Race | | | | consistent with the current labeling guidance |
| 12.3/DDI | ☐ | ☒ | ☐ | Add the statement of “No drug-drug interaction was observed between meropenem and vaborbactam in clinical studies with healthy subjects.” |
| 12.4/Microbiology | ☐ | ☐ | ☒ | Table 6 revised regarding the breakpoints |

A = Acceptable; AWE=Acceptable with minor edits; NA=not acceptable/substantive disagreement (must provide comment)

# 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

## 3.1 Overview of the Product and Regulatory Background

VABOMERE (meropenem and vaborbactam) is a fixed combination product consisting of the previously-approved antibacterial, meropenem, and the β-lactamase inhibitor vaborbactam. In the current submission, the indication being sought for meropenem and vaborbactam is the treatment of cUTI including pyelonephritis in patients 18 years and older caused by, or suspected to be caused by, susceptible isolates of designated microorganisms. Infections caused by β-lactamase expressing pathogens such as KPC is not supported for approval in this application since very limited patients infected by meropenem-resistant pathogens including KPC were tested in the submitted Phase 3 studies. Hence, the effectiveness of vaborbactam as a β-lactamase inhibitor cannot be fully demonstrated in this application. However, since the approved indications for MERREM® (meropenem) do not include cUTI, it is acceptable to consider the application of VABOMERE for the treatment of cUTI, including pyelonephritis.

The Applicant's proposed dosage regimen of VABOMERE is 4 grams (meropenem 2 g and vaborbactam 2g) administered every 8 hours as a 3-hour infusion in patients (b) (4) (b) (4)

The NDA was submitted under Section 505(b)(2) of the FD&C Act. The clinical development program for meropenem-vaborbactam relies on the previous findings of the safety and effectiveness of meropenem (without vaborbactam) in the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and bacterial meningitis (pediatric patients). To support this NDA, one Phase 1 study (Study 402) was conducted with vaborbactam alone and five clinical studies were conducted with meropenem-vaborbactam. The clinical studies with meropenem-vaborbactam include three Phase 1 studies (Study 501, Study 503, and Study 504) and two Phase 3 studies (Study 505 and Study 506). Study 505 (TANGO 1) is the pivotal trial that was conducted to support the indication for treatment of complicated urinary tract infections, including pyelonephritis. Interim data from the ongoing Study 506 (TANGO 2) provides supportive safety data for meropenem-vaborbactam in the treatment of cUTI, including pyelonephritis, and infections known or suspected to be caused by KPC-producing carbapenem-resistant Enterobacteriaceae (CRE).

The IND 120040 was accepted by the Division of Anti-infective Products (DAIP) on February 2, 2014. VABOMERE was designated as a Qualified Infectious Disease Product (QIDP) on December 19, 2013 and was granted Fast Track Status on March 21, 2016. The Applicant requested a deferral for pediatric studies in children from birth to less than 18 years since meropenem-vaborbactam is expected to be approved for use in adults before pediatric studies are complete.

## 3.2 General Pharmacology and Pharmacokinetic Characteristics

| **Pharmacology** | |
|---|---|
| **Mechanism of Action** | The meropenem component of VABOMERE is a carbapenem antibacterial drug with in vitro activity against certain aerobic and anaerobic gram negative and gram positive bacteria. The bactericidal action of meropenem results from the inhibition of cell wall synthesis. Meropenem is stable to hydrolysis by most beta lactamases, including penicillinases and cephalosporinases produced by gram negative and gram positive bacteria, with the exception of carbapenem hydrolyzing beta lactamases. The vaborbactam component of VABOMERE is a non-beta lactam non-suicidal inhibitor of Class A serine carbapenemases with a particular potent activity against *Klebsiella pneumoniae* carbapenemase, KPC. By inhibiting KPC and related beta lactamases, vaborbactam protects meropenem from degradation by these enzymes. |
| **Active Moieties** | Meropenem and vaborbactam |
| **QT Prolongation** | Vaborbactam: The results from Studies 402 and 501 failed to exclude 10 ms based on the by-time analysis and the concentration-QTc analysis, but ΔΔQTcF was not concentration-dependent for vaborbactam.<br><br>Meropenem: Meropenem has been approved by the FDA for more than two decades. The dose in the current submission is 2-fold higher than the highest approved dose. The current meropenem label does not include any labeling for QT results or warning and precautions regarding QT prolongation. No QT assessment was conducted based on data in the current submission. |
| | |
| **General Information** | |
| **Bioanalysis** | Validated HPLC/MS/MS methods were used to determine meropenem, meropenem open lactam metabolite, and vaborbactam concentrations in human plasma, urine, epithelial lining fluid (ELF) and alveolar macrophage (AM) (Refer to Section 4.1) |
| **Healthy vs. Patients** | Following administration of the same dosing regimen, vaborbactam exposure (i.e., AUC) is generally lower in healthy subjects than in patients, due to a ~40% higher population mean total clearance in healthy subjects than in cUTI patients, according to the population PK model. |

<table>
<tr><td rowspan="4">Drug exposure at steady state following the therapeutic dosing regimen</td><td></td><td>Meropenem</td><td>Vaborbactam</td></tr>
<tr><td></td><td>Mean (CV%) N=294[a]</td><td>Mean (CV%) N=294[a]</td></tr>
<tr><td>$AUC_{0-24}$ (µg•h/mL)</td><td>650 (56)</td><td>835 (60.9)</td></tr>
<tr><td>$C_{max}$ (µg/mL)</td><td>57.3 (40.2)</td><td>71.3 (40.1)</td></tr>
<tr><td colspan="4">[a] Include 271 patients with cUTI/ including pyelonephritis and 23 patients with serious infections caused by CRE; among them 35 patients had creatinine clearance ≤50 mL/min</td></tr>
<tr><td>Range of effective dose or exposure</td><td colspan="3">Meropenem 2 g and vaborbactam 2 g administered every 8 hours by intravenous (IV) infusion over 3 hours</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td colspan="3">Meropenem 2 g and vaborbactam 2 g administered every 8 hours by intravenous (IV) infusion over 3 hours is the highest dose regimen evaluated. No significant safety findings were observed when giving this dose regimen to infected patients for at least 5 days. Therefore, no maximally tolerated dose was identified.<br><br>The following are the 90th percentile of $AUC_{0-24,ss}$ observed from infected patients from Study 506. There were no significant safety findings:<br><br>Meropenem: 1333 µg•h/mL<br><br>Vaborbactam: 2050 µg•h/mL</td></tr>
<tr><td>Dose Proportionality</td><td colspan="3">Exposures ($C_{max}$ and AUC) of meropenem and vaborbactam are dose proportional across the dose range studied (1 g to 2 g for meropenem and 0.25 g to 2 g for vaborbactam) when administered as a single 3 hour intravenous infusion.</td></tr>
<tr><td>Accumulation</td><td colspan="3">There is no accumulation of meropenem or vaborbactam following multiple intravenous infusions administered every 8 hours for 7 days in subjects with normal renal function, as expected from relatively short half-lives of meropenem and vaborbactam. However, a significant accumulation of vaborbactam was observed in patients with severe renal impairment (see section 3.3.3).</td></tr>
<tr><td>Variability</td><td colspan="3">Healthy subjects following meropenem 2 g and vaborbactam 2 g q8h by 3-hour IV infusion for 7 days (Study 501):<br><br>Day 1 CV% (N=8): 35.7% and 45.8% for $C_{max}$ and $AUC_{0-inf}$, respectively, for meropenem; 42.6% and 45.2% for $C_{max}$ and $AUC_{0-inf}$, respectively, for vaborbactam</td></tr>
</table>

| | |
|---|---|
| | Day 7 CV% (N=8): 48.5% and 46.8% for $C_{max}$ and $AUC_{0\text{-}inf}$, respectively, for meropenem; 47.1% and 45% for $C_{max}$ and $AUC_{0\text{-}inf}$, respectively, for vaborbactam |
| **$T_{max}$** | 3 hours (end of infusion) |
| **Distribution** | |
| **Volume of Distribution** | Infected patients:<br>Meropenem $V_{ss}$ = 20.2 L<br>Vaborbactam $V_{ss}$ = 18.6 L |
| **Plasma Protein Binding** | Meropenem: 2%<br>Vaborbactam: 33% |
| **Substrate transporter systems [*in vitro*]** | Vaborbactam is not a substrate of OAT1, OAT3, OCT2, P gp, and BCRP.<br>Meropenem is a substrate of OAT1 and OAT3 and as such, probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. |
| **Elimination** | |
| **Terminal Elimination half-life** | Mean value in cUTI patients with normal renal function (estimated by population PK model)<br>Meropenem: 2.3 hour<br>Vaborbactam: 2.25 hour |
| ***Metabolism*** | |
| **Fraction metabolized (% dose)** | Meropemen: ~ 28%<br>Vaborbactam: no metabolism |
| **Primary metabolic pathway(s) [*in vitro*]** | A minor pathway of meropenem elimination is hydrolysis of the β lactam ring (meropenem open lactam) |
| ***Excretion*** | |
| **Primary excretion pathways (% dose) ±SD** | Meropenem: approximately 40–60% of dose was excreted unchanged within 24 to 48 hours with a further 28% recovered as the microbiologically inactive hydrolysis product; fecal elimination accounts for ~2% of dose.<br>Vaborbactam: 75 to 95% of the dose was excreted unchanged in the |

| | |
|---|---|
| | urine over a 24 to 48 hour period. |
| ***In vitro interaction liability (Drug as perpetrator)*** | |
| **Inhibition/Induction of metabolism** | Studies evaluating the potential for meropenem to interact with CYP450 enzymes or active transport systems have not been conducted. However, carbapenems as a class have not shown the potential for inhibition or induction of CYP450 enzymes and clinical experience suggests that such effects are unlikely.<br><br>Vaborbactam, at clinically relevant concentrations, does not inhibit the cytochrome P450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in vitro in human liver microsomes. Vaborbactam showed no potential for in vitro induction of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes. |
| **Inhibition/Induction of transporter systems** | Studies evaluating the potential for meropenem to interact with active transport systems have not been conducted.<br><br>Vaborbactam does not inhibit the following hepatic and renal transporters in vitro at clinically relevant concentrations: P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP. |

## 3.3 Clinical Pharmacology Review Questions

### *3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?*

The primary evidence of efficacy of meropenem-vaborbactam in the treatment of cUTI, including pyelonephritis, was provided by one adequate and well-controlled pivotal Phase 3 study (Study 505). Supportive evidence of efficacy was provided by a second ongoing Phase 3 study (Study 506) that includes a cohort of patients with cUTI including pyelonephritis. No apparent exposure-response relationship for efficacy was observed from Study 505 because the overall clinical response rate was close to 100%. The results from the animal and in *vitro* models of infection and PK/PD target attainment analyses provide additional supportive evidence of effectiveness of meropenem-vaborbactam for the treatment of cUTI including pyelonephritis.

**Table 3.3.1-1 Summary of Study Designs for Key Studies in Support of cUTI including pyelonephritis Indication**

| Study No. | Design | Meropenem-Vaborbactam Dosage Regimen [a] | Comparator Dosage Regimen [a] | Treatment Duration | Population Size |
|---|---|---|---|---|---|
| 505 | Multicenter, randomized, double-blind, noninferiority study<br><br>(cUTI including pyelonephritis) | Meropenem 2 g-vaborbactam 2 g IV infusion over 3 hours (plus normal saline IV infused over 30 minutes ) Q8h | Piperacillin/tazobactam 4.5 g (piperacillin 4 g/tazobactam 0.5 g) IV infusion over 30 minutes (plus normal saline IV infused over 3 hours ) Q8h | Minimum of 15 doses of IV therapy; 10 days of total treatment (IV + oral), but up to 14 days in subjects with baseline bacteremia | Meropenem/ Vaborbactam: N=272<br><br>Piperacillin/ Tazobactam: N=273 |
| 506 | Multicenter, randomized, open-label study<br><br>(severe gram-negative infections suspected or known to be caused by CRE) | Meropenem 2 g-vaborbactam 2 g IV infusion over 3 hours | Best available therapy (BAT) with the following IV antibiotics either in combination or alone[b] | 7 days to 14 days of total treatment | Meropenem/ Vaborbactam: N=23 (15 with cUTI including pyelonephritis)<br><br>BAT: N=16 (8 with cUTI including pyelonephritis) |

[a]: For patients with CrCL ≥50 mL/min

[b]: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycosides (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam (alone only)

For meropenem-vaborbactam and comparator (piperacillin/tazobactam) arms in Study 505, after a minimum of 15 doses of IV therapy, subjects could be switched to oral levofloxacin (500 mg

once every 24 hours [q24h]) to complete a total treatment course (IV plus oral) of 10 days. Treatment was up to 14 days if clinically indicated in subjects with concurrent bacteremia.

In Study 505, the primary efficacy endpoint was the proportion of subjects in the microbiological Modified Intent-to-Treat (m-MITT) population who achieved overall success, a composite outcome including both clinical outcome and microbiologic outcome.

During the interim analysis of Study 506, efficacy from meropenem-vaborbactam arm was compared to the best available therapy (BAT) at end of treatment (EOT, i.e. last day of total therapy) and test of cure (TOC, EOT + 7 days) using efficacy endpoints relevant to cUTI (including pyelonephritis) including proportion of subjects with a clinical outcome of cure, proportion of subjects with a microbiologic outcome of eradication, and proportion of subjects with overall success.

Table 3.3.1-2 summarizes the efficacy results in patients with cUTI including pyelonephritis from Study 505 and Study 506 (interim analysis). From Study 505, the overall success rate in the meropenem-vaborbactam group was 98.4% compared to the success rate of 94% in the piperacillin-tazobactam group, with a treatment difference of 4.5% (95% CI: 0.7%, 9.1%). Meropenem-vaborbactam is noninferior to piperacillin/tazobactam, since the lower limit of the 95% CI for treatment difference is greater than the prespecified noninferiority margin of -15%. In addition, cure, eradication, and overall success rates at the end of IV treatment (EOIVT) visit from patients with cUTI(including pyelonephritis) were higher in the meropenem-vaborbactam arm than best available therapy (BAT) in Study 506 based on limited data from interim analysis.

**Table 3.3.1-2: Clinical Outcomes of Cure, Eradication, and Overall Success Rates at EOIVT in Study 505 and cUTI Subjects in Study 506 (m-MITT Population)**

| | Study 505 | | Study 506 (cUTI/AP subjects) | |
|---|---|---|---|---|
| | Meropenem-Vaborbactam n/N' (%) | Piperacillin/ Tazobactam n/N' (%) | Meropenem-Vaborbactam n/N' | BAT n/N' |
| Cures [1] | 189/192 ( 98.5) | 174/182 (95.6) | 8/10 | 4/6 |
| Eradication (FDA's CFU/mL criterion) | 188/192 (97.9) | 168/182 (92.3) | 7/10 | 4/6 |
| Eradication (EMA's CFU/mL criterion) | 188/192 (97.9) | 168/182 (92.3) | 7/10 | 4/6 |
| Overall Success (FDA) [2] | 189/192 (98.4) | 171/182 (94.0) | 8/10 | 4/6 |

[1] Clinical outcomes of Cure and Improvement.
[2] Overall Success is defined as a clinical outcome of Cure or Improvement and microbiologic outcome of Eradication.
Microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^4$ CFU/mL of urine per FDA criteria, or to $<10^3$ CFU/mL of urine per EMA criteria.
AP = acute pyelonephritis; BAT = best available therapy; CFU = colony forming units/mL; cUTI = complicated urinary tract infection; EMA = European Medicine's Agency; EOIVT = End of Intravenous Treatment; FDA = Food and Drug Administration; m-MITT = Microbiological Modified Intent-to-Treat.

Analyses of probability of target achievement in patients with cUTI were conducted based on a population PK model developed with PK data from Phase 1 and Phase 3 studies (see section 4.3 for detail). These analyses demonstrated that 97% of patients with cUTI achieved the plasma PK/PD target of meropenem (i.e., 45% $T_{Cf>MIC}/\tau$), which has been associated with 2-log reduction in bacteria loads in nonclinical models of infection. Vaborbactam fAUC:MIC ratios in patients with baseline KPC-producing Enterobacteriaceae were 2,252 or higher, which is over 50-fold higher than vaborbactam fAUC:MIC ratio target of 38 identified in mice thigh infection model to restore 1-$\log_{10}$ bacterial reduction effect of meropenem against KPC-producing Enterobacteriaceae. Given the high target attainment rates for both meropenem and vaborbactam, along with high clinical or microbiological responses in these patients, meropemen and vaborbactam exposure in Phase 3 studies may have reached a plateau of the exposure-response curve for efficacy. Accordingly, no apparent relationship between clinical or microbiological response rates and PK/PD targets could be identified.

### *3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

Yes, the proposed following dosing regimens of meropenem-vaborbactam are acceptable for the general patient population with cUTI including pyelonephritis:

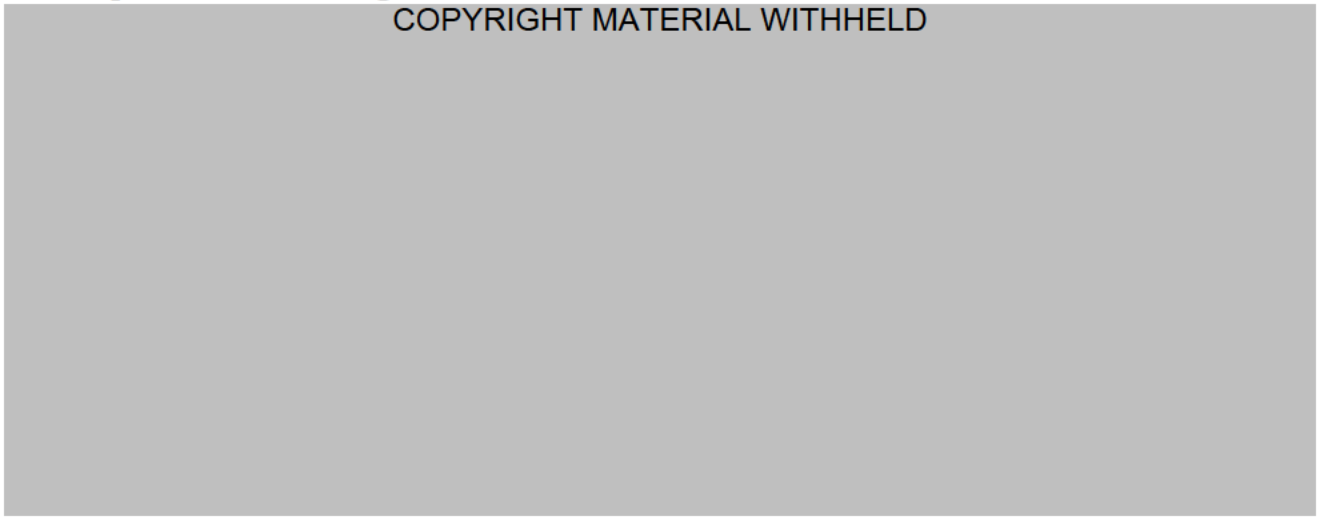
- VABOMERE 4 grams (meropenem 2 g and vaborbactam 2 g) administered every 8 hours by intravenous (IV) infusion over 3 hours

Meropenem dose:

The highest recommended dose of meropenem in the labeling of MERREM is 1 gram every 8 hours by intravenous infusion over 15 to 30 minutes for intra-abdominal infections for adult patients. However, the Applicant studied a higher meropenem dose with a longer infusion time in Phase 3 studies, to address the increased resistance in gram-negative bacteria, particularly that due to KPC-producing CRE. As reported in literature, a dose of meropenem of 2 g q8h with a 3-hour infusion is recommended for the treatment of meropenem non-susceptible isolates, in febrile neutropenic patients with bacteremia, and in infections due to CRE. In addition, the efficacy and safety of the higher dose regimen (2 g IV over 3 hours q8h) in treatment of serious infections, including those from Enterobacteriaceae spp. and *P. aeruginosa*, were demonstrated in a study in patients with severe pneumonia. Several Phase 1 studies and PK/PD simulations were conducted for meropenem at higher doses and with prolonged infusions. Figure 3.3.2-1 shows the results of Monte Carlo simulation for the probability of PK/PD target attainment in 10,000 simulated patients with normal renal function following administrations of different meropenem dosage regimens, including 2 g q8h as a 3-hour infusion. The PK/PD target in this analysis is 40% $T_{Cf>MIC}/\tau$. The higher dose and prolonged infusion of meropenem (i.e., 2 g q8h by 3-hour infusion) achieves the PK/PD target in 100% of simulated subjects for MICs up to 8

μg/mL. The currently approved dosing regimen of 1 g q8h over a 30 minute infusion achieves the PK/PD target in ~90% of simulated patients for MICs up to 1 μg/mL.

**Figure 3.3.2-1: Monte Carlo PK/PD Analysis (10,000 Simulated Patients) of Higher Dose Meropenem on Gram-negative Bacteria**




Source: Kuti et al, 2003, Lee et al, 2010, Bhavnani S, 2010.

Meropenem-vaborbactam dose:

Based on the results from the studies using the animal infection model, the % $T_{Cf>MIC}/\tau$ and the ratio of 24 hour free-drug plasma vaborbactam AUC to meropenem-vaborbactam MIC (fAUC:MIC) were identified as the PK/PD indices associated with the antibacterial activity of meropenem and the β-lactamase inhibiting activity of vaborbactam, respectively. The magnitude of % $T_{Cf>MIC}/\tau$ associated with net bacterial stasis, and a 1- and 2- $\log_{10}$ CFU reduction from baseline was determined to be 30%, 35% and 45%, respectively, for Gram negative bacilli in neutropenic murine infection models. A fAUC:MIC of at least 38 is required for vaborbactam to restore 1- $\log_{10}$ bacterial reduction effect of meropenem against KPC-Producing Enterobacteriaceae in mice thigh infection model. The Applicant's proposed dose regimens for the general patient population produced sufficient drug exposures for meropenem and vaborbactam to achieve their nonclinical PK/PD targets as discussed in Section 3.3.1. Table 3.3.2-1 shows the meropenem and vaborbactam plasma $AUC_{0-24}$ on Day 1 and at steady-state which were derived from a population PK model for cUTI patients from Studies 505 and 506.

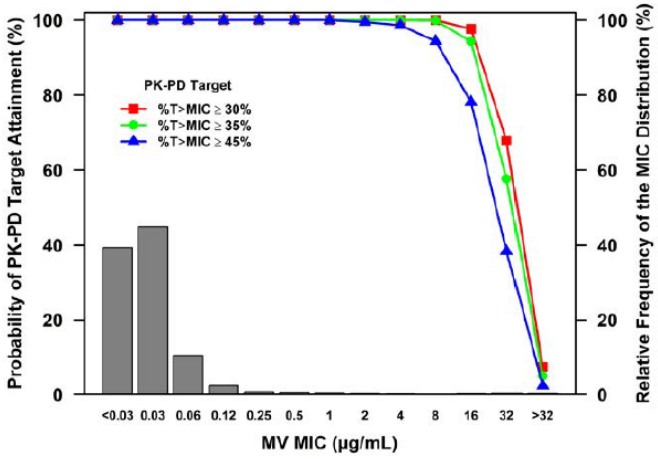
**Table 3.3.2-1: Mean (CV%) Meropenem and Vaborbactam Plasma $AUC_{0-24}$ on Day 1 and at Steady-State in Infected Patients**

| Study | $AUC_{0-24}$ (µg•h/mL) | |
|---|---|---|
| | Day 1 | Steady-State |
| **Meropenem** | | |
| Study 505 | 621 (46.3%) | 628 (57.2%) |
| Study 506 | 821 (39.9%) | 907 (36.6%) |
| **Vaborbactam** | | |
| Study 505 | 803 (45.3%) | 798 (60.6%) |
| Study 506 | 1041 (36.0%) | 1272 (47.1%) |

CV% = percent coefficient of variation; $AUC_{0-24}$ = area under the concentration-time curve from 0 to 24 hours

A Monte Carlo simulation of meropenem plasma concentrations following administration of the proposed dosage regimen was conducted in 3000 cUTI patients based on data resampled from Phase 3 patients with cUTI and baseline Enterobacteriaceae. The probabilities of PK/PD target (i.e., 30%, 35%, and 45% $T_{Cf>MIC}/\tau$ for net bacterial stasis, and a 1- and 2- $\log_{10}$ CFU reduction, respectively) attainment by meropenem-varborbactam MIC are shown in Figure 3.3.2-2 overlaid on meropenem-varborbactam MIC distributions of Enterobacteriaceae. Under the proposed dose regimen, probabilities of PK/PD target attainment ranged from 94.4 to 100% at a MIC value of 8 µg/mL based on the three meropenem PK/PD targets (i.e., 30%, 35%, and 45% $T_{Cf>MIC}/\tau$).

**Figure 3.3.2-2: Probability of PK/PD Target Attainment at Various Meropenem-Vaborbactam MICs using 30%, 35%, and 45% $T_{Cf>MIC}/\tau$ as PK/PD Targets among Simulated Patients with cUTI, Overlaid Upon the Meropenem-Vaborbactam MIC Distribution for 11,559 Enterobacteriaceae Isolates**




PK/PD = pharmacokinetic-pharmacodynamic; MV = meropenem-vaborbactam, MIC = minimum inhibitory concentration; % $T_{Cf>MIC}/\tau$ = percentage time of dosing interval in which free-drug concentrations remain above the MIC

Taken together with the results of clinical response and target attainment rates to achieve PK/PD targets for both meropenem-vaborbactam, the proposed meropenem 2 g and vaborbactam 2 g dose given every 8 hours by IV infusion over 3 hours for the general patient population is acceptable from a Clinical Pharmacology perspective.

### *3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?*

Based on the population pharmacokinetic analysis, the pharmacokinetics of meropenem and vaborbactam are not significantly impacted by age, sex, race, and body size (including weight, height and body surface area) to the extent that dose adjustment is needed (see Section 4.2). Hepatic impairment has no effect on the PK of meropenem and vaborbactam.

However, meropenem and vaborbactam exposure in plasma increased with decreasing renal function. Renal impairment was identified to be an intrinsic factor warranting dose adjustment. We recommend dose adjustment in patients with renal impairment be revised to the one presented in Table 2.2.2-1. We also recommend meropenem-vabobactam be administered before dialysis for patients maintained on hemodialysis.

***Hepatic Impairment***

Hepatic metabolism is involved in elimination of meropenem by hydrolysis of the beta lactam ring to an inactive meropenem open lactam metabolite, which accounts for 28% of a dose eliminated via the urine. According to MERREM label, a pharmacokinetic study with MERREM IV in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem. Vaborbactam does not undergo hepatic metabolism. Therefore, dose adjustment in patients with hepatic impairment is not necessary.

***Renal Impairment***

Both meropenem and vaborbactam are primarily excreted as unchanged drug in the urine. For meropenem, approximately 40 – 60% of the dose was excreted unchanged within 24 to 48 hours, with a further 25% recovered in the urine as the microbiologically inactive open lactam metabolite. For vaborbactam, 75 to 95% of the dose was excreted unchanged in the urine over a 24 to 48 hour period. A clinical study was conducted to assess the PK of meropenem/vaborbactam in subjects with renal insufficiency and in subjects receiving hemodialysis (HD) therapy. Results of the study showed that the plasma exposure of meropenem, meropenem metabolite, and vaborbactam increased with decreasing renal function, which warrants dose adjustment of meropenem-vaborbactam in subjects with reduced renal function.

Table 2.2.2-1 shows the Applicant's proposed dose regimens and the FDA's recommendations for dose adjustments according to the renal function of infected patients. We do not agree with the Applicant's proposal (b) (4) (b) (4) to classify the renal function groups for dose adjustment. We recommend assigning patients with renal impairment to appropriate groups for dose adjustment based on eGFR (mL/min/1.73m$^2$, calculated by MDRD equation) since eGFR was used in Study 504 to categorize subjects with different degrees of renal impairment. In addition, we do not agree with the Applicant's proposed dosing regimen of meropenem-vaborbactam for patients with renal impairment (Table 2.2.2-1). It should be noted that the Applicant's proposed and the FDA's recommended dose adjustment for patients with renal impairment are different from that in the labeling of MERREM.

Results from Renal Impairment Study

The results of a PK study in subjects with renal impairment (Study 504, see Section 4.5.5) showed that meropenem and vaborbactam plasma exposure increased with decreasing renal function. Table 3.3.3-1 summarizes the fold changes in $AUC_{0\text{-inf}}$ for both meropenem and vaborbactam across different levels of renal impairment compared to normal renal function group. It should be noted that the $AUC_{0\text{-inf}}$ of vaborbactam increased to a greater degree than meropenem in subjects with severe renal impairment and in ESRD hemodialysis patients. Accordingly, unlike the Applicant's conclusion, the proportional dose adjustment of meropenem and vaborbactam in subjects with severe renal impairment and in ESRD hemodialysis patients would not result in a consistent ratio of meropenem and vaborbactam exposure in these patient populations. Both meropenem and vaborbactam are removed by hemodialysis. Based upon the recovery of drug in dialysate, 38% of the meropenem dose and 53% of the vaborbactam dose can be removed by dialysis. Hence, administration of the combination just prior to dialysis in patients with ESRD resulted in an increase in the clearance of all analytes relative to administration between dialysis sessions.

**Table 3.3.3-1 Fold Change in AUC for both Meropenem and Vaborbactam across Different Levels of Renal Function Compared to Normal Renal Function Group**

| Renal Function | Normal | Mild | Moderate | Severe | ESRD | |
|---|---|---|---|---|---|---|
| | | | | | on dialysis [d] | off dialysis [e] |
| eGFR (mL/min/1.73m$^2$) criterial [a] | | 60-89.9 | 30-59 | <30 [c] | <15 | |
| (b) (4) | | | | | | |
| Meropenem $AUC_{0\text{-}inf}$ (µg•h/mL) ratio to normal | | 1.28 | 2.07 | 4.63 | 3.28 | 7.22 |
| Vaborbactam $AUC_{0\text{-}inf}$ (µg•h/mL) ratio to normal | | 1.18 | 2.31 | 7.81 | 10.2 | 37.5 |

[a] Calculated using MDRD formula

(b) (4)

[c] Observed eGFR ranged from 10 to 30 mL/min/1.73m$^2$

[d] On dialysis: IV infusion of VABOMERE was completed about 2 hours before the start of dialysis

[e] Off dialysis: Dosing of VABOMERE was started 2 hours after the end of dialysis

Results and Simulations from Population PK Analyses

Using the results from the PK study in subjects with reduced renal function, doses were adjusted for patients with renal impairment in Phase 3 studies (i.e., 1 g meropenem-1 g vaborbactam q8h for patients with CrCL ≥30-50 mL/min; 1 g meropenem-1 g vaborbactam q12h for patients with CrCL ≥20-30 mL/min; 0.5 g meropenem-0.5 g vaborbactam q12h for patients with CrCL ≥10-20 mL/min; 0.5 g meropenem-0.5 g vaborbactam q24h for patients with CrCL< 10 mL/min) . However, limited data are available from patients with CrCL <30 mL/min since only three patients with CrCL <30 mL/min were enrolled in the Phase 3 studies at the time this NDA was submitted. Based on population PK analyses, the Applicant proposed a different dose scheme from what was evaluated in the Phase 3 studies, as shown in Table 2.2.2-1. The population PK models were used to predict meropenem and vaborbactam exposures at the Applicant's proposed dose regimens for patients with renal impairment. Figure 3.3.3-1 shows the Applicant predicted distributions of free-drug plasma meropenem and vaborbactam $AUC_{0\text{-}24}$ values at steady-state among simulated patients by renal function group.

**Figure 3.3.3-1. Boxplots Showing the Distribution of Free-drug Plasma Meropenem (Left) and Vaborbactam (Right) $AUC_{0-24}$ Values at Steady-state among Simulated Patients by Renal Function Group (Conducted by the Applicant)**


As shown in Figure 3.3.3-1, vaborbactam exposure significantly accumulated in subjects with (b) (4). Free-drug plasma vaborbactam $AUC_{0-24}$ values in subjects (b) (4) (b) (4) are approaching or exceeding the free vaborbactam $AUC_{0-inf}$ (b) (4) obtained from the NOAEL dose of 1000 mg/kg/day in dogs. In addition, the Applicant predicted the free-drug plasma meropenem and vaborbactam $AUC_{0-24}$ under the assumption that the fractions of plasma protein binding of meropenem and vaborbactam in patients with reduced renal function are the same to the patients with normal renal function. However, the validity of this assumption is unknown since the Applicant did not measure the plasma protein binding of meropenem and vaborbactam in patients with renal impairment.

Since no adverse event of concern was identified for either meropenem or vaborbactam in the Phase 3 trials, the following reference AUC values for meropenem and vaborbactam were used to evaluate whether the simulated exposures are considered to be safe or not:

The 90$^{th}$ percentiles of $AUC_{0-24,ss}$ observed from infected patients from Study 506 (based on n=23):

(There were no significant safety findings in Study 506)

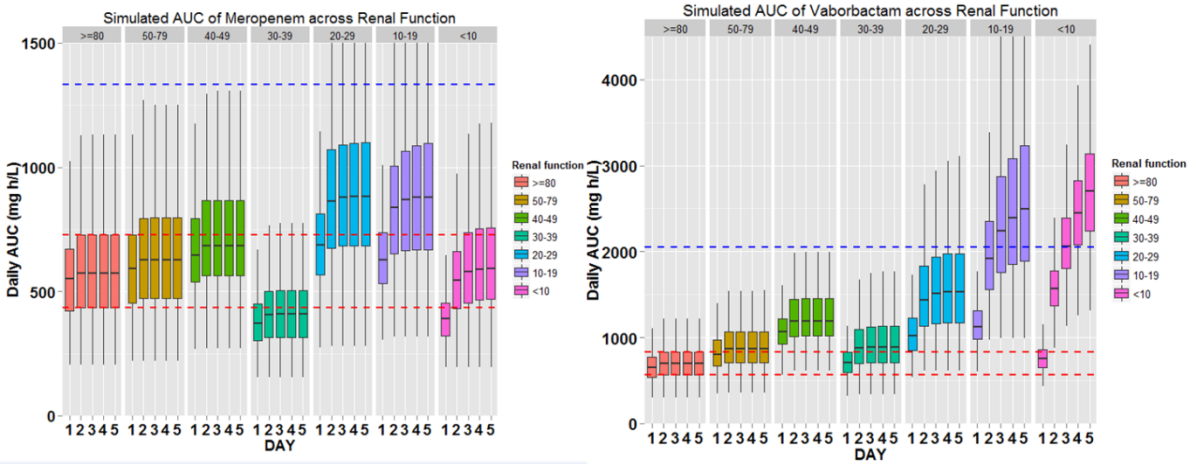
Meropenem: 1333 µg•hr/mL

Vaborbactam: 2050 µg•hr/mL

Using the Applicant's population PK model, meropenem and vaborbactam AUCs were simulated for patients with various levels of renal function (i.e., eGFR) at both the Applicant's proposed dosing regimens and the FDA's recommended dosing regimens. The simulations were conducted assuming that patients with ESRD receive VABOMERE after hemodialysis is completed. Figure 3.3.3-2 shows the simulated daily AUCs from Day 1 to Day 5 for meropenem and vaborbactam

[redacted](b) (4) Compared to the AUCs in subjects with eGFR ≥80 mL/min/1.73 $m^2$, the simulation results show that (a) meropenem AUC in >50% of patients with eGFR 30-39 mL/min/1.73 $m^2$ are lower than the 25$^{th}$ percentile of AUCs among subjects with eGFR ≥80 mL/min/1.73 $m^2$ and (b) meropenem AUCs in >50% of patients with eGFR 10-29 mL/min/1.73 $m^2$ are higher than the 75$^{th}$ percentile of AUCs among subjects with eGFR ≥80 mL/min/1.73 $m^2$ with some exposures approaching or exceeding the reference AUC value of 1333 µg·h/mL. For vaborbactam, AUCs from most subjects with eGFR <30 mL/min/1.73 $m^2$ are higher than the 75$^{th}$ percentile of AUCs among subjects with eGFR ≥80 mL/min/1.73 $m^2$ and are approaching or exceeding the reference AUC value of 2050 µg·h/mL.

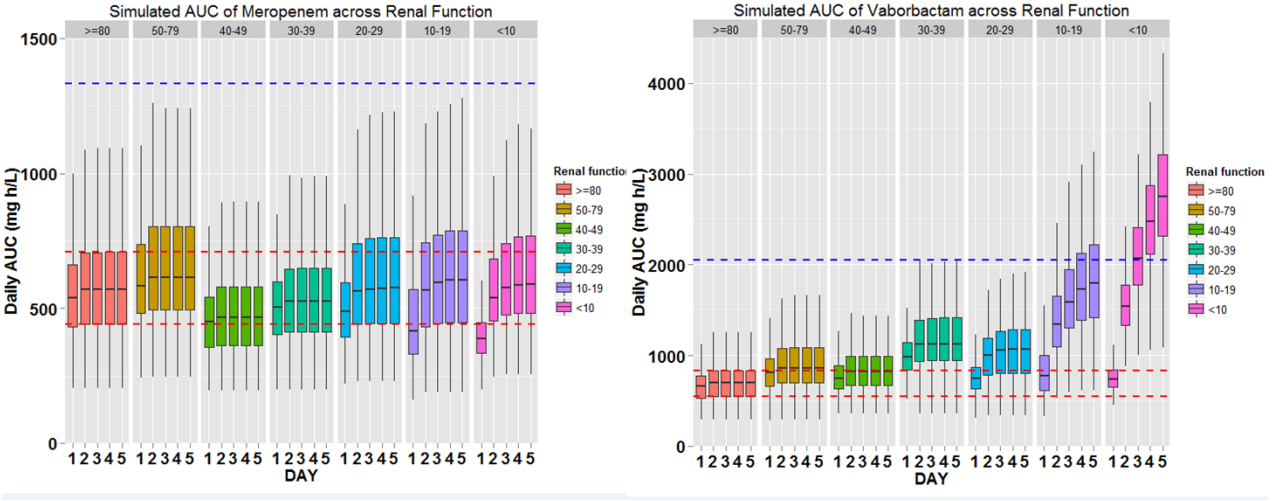
**Figure 3.3.3-2. Simulated Daily AUCs from Day 1 to Day 5 for Meropenem (Left) and Vaborbactam (Right) [redacted](b) (4) (Conducted by Reviewer)**




Red dashed lines represent the 25$^{th}$ and 75th percentile of daily AUCs on Day 5 among subjects with eGFR≥ 80 mL/min/1.73 $m^2$ based on the population PK model. The blue dashed lines represent the reference $AUC_{0\text{-}24,ss}$ for meropenem (1333 µg·h/mL) and vaborbactam (2050 µg·h/mL).

Accordingly, additional simulations were conducted by the clinical pharmacology review team to optimize meropenem-vaborbactam dose adjustments for patients with renal impairment. Based on those simulations, the dose adjustment described in Table 2.2.2-1 is recommended by the clinical pharmacology review team. Figure 3.3.3-3 shows the simulated daily AUCs from Day 1 to Day 5 for meropenem and vaborbactam following the administration of the recommended dose regimens in subjects with renal impairment.

**Figure 3.3.3-3. Simulated Daily AUC from Day 1 to 5 for Meropenem (Left) and Vaborbactam (Right) at the FDA's Recommended Dose Regimens (Conducted by the Reviewer)**




Red dashed lines represent the 25th and 75th percentile of daily AUC on Day 5 in subjects with eGFR≥ 80 mL/min/1.73 $m^2$ based on population PK model. The blue dashed lines represent the reference $AUC_{0\text{-}24,ss}$ for meropenem (1333 µg·h/mL) and vaborbactam (2050 µg·h/mL).

As shown in Figure 3.3.3-3, the recommended dosing regimens are expected to provide more comparable daily AUCs of meropenem in the renal function groups with eGFR <50 mL/min/1.73 $m^2$ to the group with eGFR >80 mL/min/1.73 $m^2$ (b) (4) . For vaborbactam, the simulated AUCs from the groups with eGFR 20-50 mL/min/1.73 $m^2$ are generally higher than those AUCs in the group with eGFR >50 mL/min/1.73 $m^2$ but still below the reference AUC value of 2050 µg·h/mL. However, the simulation results show that the clinical pharmacology review team's recommended dose adjustment may provide vaborbactam steady state AUCs exceeding the reference AUC value of 2050 µg·h/mL to approximately 89% subjects with eGFR <15 mL/min/1.73 $m^2$.

Since VABOMERE is a fixed combination of meropenem and vaborbactam (1:1), it is not possible to adjust dosing regimen of meropenem and vaborbactam separately for patients with ESRD. In addition, the effect of hemodialysis on meropenem and vaborbactam is quantitatively different although both can be removed by hemodialysis (see Section 4.5.5). When VABOMERE is dosed 2 hours after dialysis in patients maintained on hemodialysis, the clinical pharmacology review team's recommended dose adjustment for this patient population is expected to provide comparable meropenem exposure to patients with eGFR >15 mL/min/1.73$m^2$, but substantially higher exposure of vaborbactam (Figure 3.3.3-3). On the other hand, when the infusion of VABOMERE is completed 2 hours prior to dialysis in patients maintained on hemodialysis, the increase in vaborbactam exposure is expected to be lower compared to when VABOMERE is dosed 2 hours after dialysis. However, meropenem exposure

would become lower than expected from patients with eGFR >15 mL/min/1.73m$^2$. Currently, there are insufficient data to determine whether the high vaborbactam exposure when dosed after dialysis would lead to safety concern or whether the lower meropenem exposure when dosed before dialysis would result in compromised efficacy. However, based on (a) the proportion of meropenem dose that can be removed by dialysis (i.e., 38% after a single dose administration) is not significantly high and (b) the frequency of dialysis (3 times per week according to common practice) is much less than the VABOMERE dosing frequency in patients maintained on hemodialysis (BID dosing), we anticipate that the reduction of meropenem exposure would not be substantial when VABOMERE is administered before dialysis. Hence, the risk of reduced efficacy of meropenem is anticipated to be low when VABOMERE is administered before dialysis in patients with cUTI including pyelonephritis. Based on the considerations of unknown safety risk due to high vaborbactam exposure when dosing after dialysis and an anticipated low risk of reduced efficacy (i.e., due to lower meropenem exposure) when dosing before dialysis, we recommend VABOMERE be administered before hemodialysis for patients maintained on hemodialysis.

Results from Probability Target Attainment Analysis

The Reviewer conducted an independent analysis for assessing the probability of target attainment at the FDA's recommended dose regimens. Details of target attainment methodology are described in Section 4.3. Briefly, using the Applicant's developed population PK model, a Monte Carlo simulation of meropenem plasma concentrations was conducted in 4,000 patients distributed among the following renal function groups with eGFR 1) ≥50 mL/min/1.73m$^2$; 2) ≥40 to 50 mL/min/1.73m$^2$; 3) ≥30 to 40 mL/min/1.73m$^2$; 4) ≥20 to 30 mL/min/1.73m$^2$; 5) ≥10 to 20 mL/min/1.73m$^2$; 6) <10 mL/min/1.73m$^2$. Each group contained 1,000 patients, generated by simulating eGFR values using a uniform probability distribution. Probabilities of PK/PD target attainment by meropenem-vaborbactam MIC range of 0.125 to 128 μg/mL in each renal function group were determined for three meropenem PK/PD targets (i.e., 30, 35, and 45% $T_{Cf>MIC}/\tau$ which are associated with net-stasis, 1-$\log_{10}$ and 2- $\log_{10}$ bacterial reduction effect in animal infection model). Results of probabilities of PK/PD target attainment are presented in Table 3.3.3-2. At the FDA's recommended dose adjustment, percent probabilities of PK/PD target attainment based on the above-described three PK/PD targets are all >97% across simulated patients in each renal function group at an meropenem-vaborbactam MIC value of 8 μg/mL, the susceptibility breakpoint proposed by the Applicant.

**Table 3.3.3-2. Probability of PK/PD target attainment by meropenem-vaborbactam MIC at the review team recommended dosing regimens based on a 45% $T_{Cf>MIC}/\tau$ PK/PD target among simulated patients by renal function group (by eGRF, mL/min/1.73m$^2$)**

| MIC (µg/mL) | eGFR ≥ 50 | eGFR 40-50 | eGFR 30-40 | eGFR 20-30 | eGFR 10-20 | eGFR <10 |
|---|---|---|---|---|---|---|
| 0.12 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0.25 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0.5 | 1 | 1 | 1 | 1 | 1 | 1 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 1 | 1 | 1 | 1 | 1 | 1 |
| 8 | 1 | 0.99 | 0.99 | 0.99 | 0.97 | 0.97 |
| 16 | 0.94 | 0.75 | 0.81 | 0.81 | 0.75 | 0.79 |
| 32 | 0.39 | 0.18 | 0.24 | 0.27 | 0.27 | 0.28 |
| 64 | 0.03 | 0.01 | 0.02 | 0.03 | 0.03 | 0.02 |

### *3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?*

Meropenem-vaborbactam will be administered via IV infusion; hence there is no concern of food effect.

Drug-drug interaction between meropenem and vaborbactam was evaluated in Study 501. Study 501 was a double-blind, randomized, placebo-controlled, single and multiple ascending dose study of meropenem and vaborbactam alone and in combination conducted in healthy adult subjects. The results showed that the plasma exposure to either meropenem or vaborbactam is not different when the drugs are given alone or in combination.

Lack of PK interactions between meropenem and vaborbactam also indicates that the Clinical Pharmacology information in the labeling of MERREM may be used for the labeling of VABOMERE as needed.

Based upon the in vitro and in vivo data available to date, there is a low potential for clinically significant drug interactions with vaborbactam. Vaborbactam at clinically relevant concentrations does not inhibit the cytochrome P450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in vitro in human liver microsomes. Vaborbactam showed no potential for in vitro induction of CYP1A2, CYP2B6, and CYP3A4 in human

hepatocytes. Vaborbactam does not inhibit the following hepatic and renal transporters in vitro at clinically relevant concentrations: P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP. Vaborbactam does not undergo hepatic metabolism and was not a substrate of OAT1, OAT3, OCT2, P-gp, and BCRP.

Studies evaluating the potential for meropenem to interact with CYP450 enzymes or active transport systems have not been conducted. However, carbapenems as a class have not shown the potential for inhibition or induction of CYP450 enzymes and clinical experience suggests that such effects are unlikely. Meropenem is a substrate of OAT1 and OAT3 and as such, probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. According to the information in the Merrem® labeling, following administration of probenecid with meropenem, the mean systemic exposure increased 56% and the mean elimination half-life increased 38%. Co-administration of probenecid with VABOMERE is not recommended. Concomitant administration of meropenem and valproic acid has been associated with reductions in valproic acid concentrations with subsequent loss in seizure control. Thus, supplemental anti-convulsant therapy should be administered when concomitant administration of valproic acid and VABOMERE cannot be avoided.

### *3.3.5 Are the proposed susceptibility breakpoints acceptable?*

The results of the probability of target attainment analyses (PTA) support the Applicant's proposed susceptibility interpretive criteria (breakpoints hereafter) against Enterobacteriaceae and *Pseudomonas aeruginosa* for meropenem-vaborbactam (Table 3.3.5-1).

**Table 3.3.5-1. Applicant's Proposed Susceptibility Interpretive Criteria for Meropenem-Vaborbactam**

(b) (4)

S=Susceptible; I=intermediate; R=Resistant

1. MIC Distributions for Clinical Isolates of Target Species

Analysis of meropenem-vaborbactam (vaborbactam tested at 8 µg/mL which was determined as a critical concentration of vaborbactam to restore bacteria killing effect of meropenem to 1-$\log_{10}$ CFU reduction in KPC-producing Enterobacteriaceae: See Section 4.5.1) MIC distributions for

target species were used to identify microbiological cutoff values that were likely to distinguish between susceptible and resistant organisms, with a particular focus on KPC-producing carbapenem-resistant Enterobacteriaceae.

The summary of meropenem-vaborbactam surveillance studies of large collections for the recent (2014-2015) clinical isolates of Enterobacteriaceae, KPC-producing Enterobacteriaceae and *P. aeruginosa* collected worldwide (SENTRY surveillance program) is presented in Table 3.3.5-2. For all Enterobacteriaceae, and the subset of KPC-producing Enterobacteriaceae, ~95% and ~50% of isolates are inhibited at the meropenem ≤ 0.06 µg/mL (tested with vaborbactam at 8 µg/mL), respectively. The "non-wild-type" KPC-producing strains have a wide distribution of meropenem-vaborbactam MICs ranging from 0.125 to >32 µg/Ml with ~99% of isolates inhibited by meropenem at 8 µg/mL when tested with vaborbactam at 8 µg/mL. In *P. aeruginosa*, 86.4% of isolates were inhibited by meropenem at 8 µg/mL when tested with vaborbactam at 8 µg/mL.

**Table 3.3.5-2: Meropenem-Vaborbactam MIC distributions for Enterobacteriaceae, KPC-producing Enterobacteriaceae, and *P. aeruginosa* based on In Vitro Surveillance Data Collected from Regions Worldwide[a]**

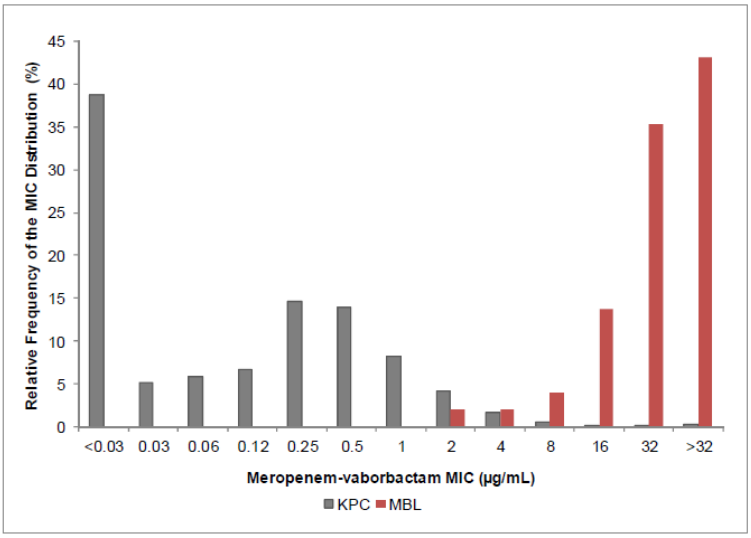
| Drug | Number of isolates at MIC (µg/mL; cumulative %) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <0.03 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | >32 | $MIC_{50}$ | $MIC_{90}$ |
| **All Enterobacteriaceae[a] (n=11,559)** | | | | | | | | | | | | | | | |
| Meropenem | 5595 (48.4) | 3799 (81.3) | 1321 (92.7) | 338 (95.6) | 73 (96.3) | 44 (96.6) | 36 (96.9) | 44 (97.3) | 48 (97.7) | 44 (98.1) | 62 (98.7) | 48 (99.1) | 107 (100) | 0.03 | 0.06 |
| Meropenem-vaborbactam | 4551 (39.4) | 5193 (84.3) | 1208 (94.7) | 271 (97.1) | 89 (97.9) | 69 (98.5) | 50 (98.9) | 28 (99.1) | 14 (99.3) | 9 (99.3) | 22 (99.5) | 32 (99.8) | 23 (100) | 0.03 | 0.06 |
| **All KPC-producing Enterobacteriaceae[b] (n=1,331)** | | | | | | | | | | | | | | | |
| Meropenem | – | – | – | – | – | – | 5 (0.40) | 58 (4.70) | 116 (13.4) | 159 (25.4) | 200 (40.4) | 179 (53.9) | 614 (100) | 32 | >32 |
| Meropenem-vaborbactam | 515 (38.7) | 68 (43.8) | 78 (49.7) | 89 (56.3) | 195 (71.0) | 186 (85.0) | 110 (93.2) | 55 (97.4) | 22 (99.0) | 7 (99.5) | 2 (99.7) | 1 (99.8) | 3 (100) | 0.12 | 1 |
| **All *P. aeruginosa*[a] (n=2,806)** | | | | | | | | | | | | | | | |
| Meropenem | 15.0 (0.50) | 47.0 (2.20) | 194 (9.10) | 321 (20.6) | 540 (39.8) | 477 (56.8) | 293 (67.2) | 193 (74.1) | 170 (80.2) | 189 (86.9) | 173 (93.1) | 64 (95.4) | 130 (100) | 0.50 | 16 |
| Meropenem-vaborbactam | 30 (1.10) | 65 (3.40) | 193 (10.3) | 310 (21.3) | 525 (40.0) | 462 (56.5) | 298 (67.1) | 186 (73.7) | 187 (80.4) | 167 (86.4) | 187 (93.0) | 71 (95.5) | 125 (100) | 0.50 | 16 |

[a]: Enterobacteriaceae, KPC-producing Enterobacteriaceae, and *P. aeruginosa* isolates were collected as part of the 2014-2015 SENTRY Antimicrobial Surveillance Program.
[b]: Shaded cells represent the MIC values up to and/or including the $MIC_{90}$ value.

Meropenem-vaborbactam MIC distributions were constructed using 51 metallo-beta-lactamase (MBL)-producing isolates collected worldwide in 2015 as a part of SENTRY surveillance program and the MIC distribution for 1331 KPC-producing strains in Figure 3.3.5-1. Vaborbactam does not inhibit MBL and consequently, does not potentiate the activity of meropenem against isolates that produce MBL. Analysis of MIC distributions for KPC and MBL-producing isolates showed that KPC-producing strains with meropenem-vaborbactam MIC values that are >8 µg/mL are rare, while a majority of MBL-producing strains have meropenem-vaborbactam MIC values that are >8 µg/mL. Thus, an epidemiological cutoff of meropenem-

vaborbactam MIC of 8 µg/mL would largely discriminate between KPC- and MBL-producing isolates. Hence, the surveillance data for meropenem-vaborbactam MIC distributions support the proposed meropenem-vaborbactam susceptibility breakpoint of 8 µg/mL.

**Figure 3.3.5-1: Relative Frequency Distribution of Meropenem-Vaborbactam MIC Values in 2015 KPC-Producing (n=1331) and MBL-producing (n=51) Strains of Enterobacteriaceae**




2. PK/PD Cutoff for Susceptibility of Meropenem-Vaborbactam

*Animal Models to Determine the PK/PD Targets*

Improved antibacterial effects of meropenem in combination with vaborbactam were demonstrated when compared with those of meropenem alone in a neutropenic mouse thigh infection model, a neutropenic mouse lung infection model, and a mouse ascending UTI model using carbapenem-resistant, Class A serine carbapenemase producing strains of *K. pneumonia*, *E. coli*, and *E. cloacae*. These strains had meropenem MICs ranging from 8 µg/mL to 512 µg/mL and meropenem-vaborbactam MICs (with vaborbactam at 8 µg/mL) ranging from ≤0.06 µg/mL to 16 µg/mL.

Animal and in *vitro* models of infection were used to determine meropenem and vaborbactam PK/PD targets associated with antibacterial effects (see Section 4.5.1). These studies considered 30-45% $T_{Cf>MIC}/\tau$ based on the meropenem-vaborbactam MIC (i.e., MIC of meropenem with a fixed vaborbactam concentration of 8 µg/mL) as the PK/PD targets for meropenem. The magnitudes of meropenem % $T_{Cf>MIC}/\tau$ associated with net bacterial stasis, and a 1- and 2- $\log_{10}$ CFU reduction from baseline were determined to be 30, 35 and 45%, respectively, for Gram-negative bacilli studied in neutropenic murine infection models. To identify the PK/PD index for vaborbactam associated with restoring the antibacterial effect of meropenem against KPC-

producing carbapenem-resistant Enterobacteriaceae, dose fractionation studies for vaborbactam were conducted in animal infection models and in a hollow-fiber model with concentrations of meropenem corresponding to human exposures at meropenem 2 g infused over 3 hour q8h. Eight *K. pneumoniae*, four *E. cloacae*, and one *E. coli* with the meropenem-vaborbactam MICs that ranged from ≤0.06 to 16 μg/mL were studied in a neutropenic mouse thigh infection model. Seventeen KPC-producing strains (13 *K. pneumoniae*, 3 *E. cloacae*, and 1 *E. coli*) with meropenem-vaborbactam MICs that ranged from ≤0.06 μg/mL to 64 μg/mL were tested in an *in vitro* hollow-fiber model. Both neutropenic mouse thigh infection model and hollow-fiber model identified ratio of free vaborbactam 24h AUC:meropenem-vaborbactam MIC (fAUC/MIC) as the best correlate with the reduction in the log number of CFU for the tested species (i.e., by restoring bacteria killing effect of meropenem). The Applicant concluded an fAUC/MIC of (b) (4) to be the PK/PD target of vaborbactam, which corresponded to a bacteriostasis effect by meropenem on the growth of the tested KPC-producing strains from in vitro hollow-fiber model. We do not agree with the Applicant's conclusion since the in vitro hollow-fiber infection model is not a good model to determine the PK/PD target and only provides an estimate of the type of PK/PD index that is associated with the bacteria killing effect. We recommend using 24h fAUC/MIC of 38 as the vaborbactam PK/PD target since this value was determined from studies with neutropenic mouse thigh infection model and was associated with restoring bacteria killing effect of meropenem to 1-$\log_{10}$ CFU reduction from baseline in the tested KPC- producing strains.

*Probability of Target Attainment (PTA)*

Target attainment methodology is described in detail in Section 4.3. Using meropenem $T_{Cf>MIC}/\tau$ of 30, 35 and 45%, the probabilities of PK/PD target attainment were evaluated for the proposed meropenem-vaborbactam dosing regimens administered to simulated cUTI patients with baseline Enterobacteriaceae across a meropenem-vaborbactam MIC range of 0.125 to 64 μg/mL. As shown in Table 3.3.5-3, percent probabilities of PK/PD target attainment based on the above-described three meropenem PK/PD targets for the population of simulated patients with cUTI ranged from 94.4 to 100% at an MIC value of 8 μg/mL. At an MIC value of 16 μg/mL, percent probabilities of PK/PD target attainment ranged from 76.3 to 97.0%. Using a criterion of ≥ 90% of simulated patients to achieve the specified PK/PD target for 2-$\log_{10}$ CFU reduction, the results of the PTA analysis indicate a PK/PD cutoff of 8 μg/mL. In addition, based on vaborbactam exposure data from Study 506, >90% of patients achieved fAUC/MIC ≥ 38 at meropenem-vaborbactam MIC of 8 μg/mL, indicating that vaborbactam exposure is sufficient to maintain at least 1-$\log_{10}$ bactericidal effect of meropenem against pathogens with meropenem-vaborbactam MIC of 8 μg/mL. Hence, PTA analysis supports the proposed meropenem-vaborbactam susceptibility breakpoint of 8 μg/mL.

**Table 3.3.5-3: Percent probabilities of PK/PD target attainment by meropenem-vaborbactam MIC and overall for meropenem-vaborbactam dosing regimens based on the assessment of three free-drug plasma meropenem % $T_{Cf>MIC}/\tau$ targets and 1,331 KPC producing Enterobacteriaceae isolates among simulated patients with cUTI**

| MV[a] MIC (µg/mL) | Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for free-drug plasma meropenem %T>MIC targets | | |
|---|---|---|---|
| | %T>MIC ≥ 30 | %T>MIC ≥ 35 | %T>MIC ≥ 45 |
| 0.12 | 100 | 100 | 100 |
| 0.25 | 100 | 100 | 100 |
| 0.5 | 100 | 100 | 100 |
| 1 | 100 | 100 | 99.9 |
| 2 | 100 | 100 | 99.5 |
| 4 | 100 | 100 | 98.6 |
| 8 | 100 | 99.9 | 94.4 |
| 16 | 97.0 | 93.7 | 76.3 |
| 32 | 59.0 | 48.9 | 29.1 |
| 64 | 4.74 | 2.92 | 1.20 |
| Overall[b] | 99.7 | 99.7 | 99.6 |

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

3. Clinical and Microbiological Outcomes by Meropenem-Vaborbactam MIC

The rate of favorable responses in subjects that received meropenem-vaborbactam in the Phase 3 study in patients with cUTIs (Study 505) was evaluated according to meropenem-vaborbactam MICs. Table 3.3.5-4 and Table 3.3.5-5 show the results for clinical, microbiological, and combined endpoints for pooled baseline Enterobacteriaceae and for individual Enterobacteriaceae, respectively, for the modified Microbiologically Intent-To-Treat (m-MITT) population. Most isolates in the clinical studies had an MIC of ≤0.06 µg/mL. The rate of overall success in each group was >90%. Therefore, the analysis of outcomes for Enterobacteriaceae demonstrated no obvious cutoff in MIC that discriminated between successes and failures.

**Table 3.3.5-4: Clinical, Microbiological and Overall Responses by Meropenem-Vaborbactam MIC against All Enterobacteriaceae from Study 505 at the End of IV Treatment for the Microbiological Modified Intent-to-Treat Population**

| Meropenem-vaborbactam MIC (µg/mL) | Microbiological Eradication rate, n/N (%) | Clinical Cure** rate, n/N (%) | Overall Success Rate, n/N (%) |
|---|---|---|---|
| ≤0.06 | 146/149 (98.0) | 146/149 (98.0) | 146/149 (98.0) |
| 0.125 | 11/12* (91.7) | 12/12 (100.0) | 12/12 (100.0) |
| 0.25 | 2/2 (100.0) | 2/2 (100.0) | 2/2 (100.0) |
| 0.5 | 1/1 (100.0) | 1/1 (100.0) | 1/1 (100.0) |
| 1 | 0/0 (0.0) | 0/0 (0.0) | 0/0 (0.0) |
| 2 | 0/0 (0.0) | 0/0 (0.0) | 0/0 (0.0) |
| 4 | 0/0 (0.0) | 0/0 (0.0) | 0/0 (0.0) |
| 8 | 0/0 (0.0) | 0/0 (0.0) | 0/0 (0.0) |
| 16 | 0/0 (0.0) | 0/0 (0.0) | 0/0 (0.0) |
| 32 | 1/1 (100.0) | 1/1 (100.0) | 1/1 (100.0) |

Percentage was calculated using N as the denominator, where N is the number of subjects who had a baseline pathogen with the specified MIC. Only pathogens with a frequency of at least 1 in the meropenem-vaborbactam group are included. If more than one Enterobacteriaceae was isolated at baseline, the pathogen with the highest meropenem-vaborbactam MIC was used.

*One case of microbiological outcome of "Indeterminate" for *K. oxytoca*.

** Outcomes of improvement are included in the clinical cure definition.

**Table 3.3.5-5: Clinical, Microbiological and Overall Responses by Meropenem-Vaborbactam by MIC against Individual Enteric Gram-negative Bacilli from Study 505**

| Meropenem-vaborbactam MIC (µg/mL) | Microbiological Eradication rate, n/N (%) | Clinical Cure* rate, n/N (%) | Overall Success Rate, n/N (%) |
|---|---|---|---|
| *Escherichia coli* | | | |
| ≤0.06 | 115/117 (98.3) | 115/117 (98.3) | 115/117 (98.3) |
| 0.125 | 3/3 (100.0) | 3/3 (100.0) | 3/3 (100.0) |
| 0.25 | 1/1 (100.0) | 1/1 (100.0) | 1/1 (100.0) |
| *Klebsiella pneumoniae* | | | |
| ≤0.06 | 23/24 (95.8) | 23/24 (95.8) | 23/24 (95.8) |
| 0.12 | 5/5 (100.0) | 5/5 (100.0) | 5/5 (100.0) |
| 32 | 1/1 (100.0) | 1/1 (100.0) | 1/1 (100.0) |
| *Enterobacter cloacae species complex* | | | |
| ≤0.06 | 8/8 (100.0) | 8/8 (100.0) | 8/8 (100.0) |
| 0.12 | 1/1 (100.0) | 1/1 (100.0) | 1/1 (100.0) |
| *Proteus mirabilis* | | | |
| ≤0.06 | 3/3 (100.0) | 3/3 (100.0) | 3/3 (100.0) |
| 0.125 | 1/1 (100.0) | 1/1 (100.0) | 1/1 (100.0) |
| 0.25 | 1/1 (100.0) | 1/1 (100.0) | 1/1 (100.0) |
| 0.5 | 1/1 (100.0) | 1/1 (100.0) | 1/1 (100.0) |

Percentage was calculated using N as the denominator, where N is the number of subjects who had a baseline pathogen with the specified MIC. Only pathogens with a frequency of at least 1 in the meropenem-vaborbactam group are included. If the same pathogen was isolated from the same type of specimen, only the pathogen with the highest MIC was used.

* Outcomes of improvement are included in the clinical cure definition.

4. Recommended Susceptibility Interpretive Criteria

Taking together the results from the surveillance studies of MIC distributions for target species and probability of target attainment analyses, we agree with the Applicant's proposed susceptibility interpretive criteria for meropenem-vaborbactam against Enterobacteriaceae as presented in Table 3.3.5-1.

Vaborbactam does not increase the potency of meropenem against clinical isolates of *P. aeruginosa* and meropenem-vaborbactam *in vitro* activity against *P. aeruginosa* is similar to that of meropenem alone. The target attainment analyses conducted based on three meropenem PK/PD targets (30%, 35%, and 45% $T_{Cf>MIC}/\tau$) against Enterobacteriaceae can be used to support the determination of PK/PD cutoff for *P. aeruginosa*, since the three meropenem PK/PD targets also apply to *P. aeruginosa*. In addition, meropenem and meropenem-vaborbactam MIC distributions for *P. aeruginosa* are similar based on *in vitro* surveillance data. Finally, it should be noted that the MERREM label includes a susceptibility breakpoint for *P. aeruginosa*, albeit at a lower dose and for different indications. However, limited clinical outcome data for patients infected with *P. aeruginosa* are available from the current application since only four patients with baseline isolates of *P. aeruginosa* were evaluated in the Phase 3 studies. The insufficient clinical evidence provided by the Applicant may prevent the determination of susceptibility breakpoints for *P. aeruginosa*. Given the available information, the clinical pharmacology review team concludes that the PTA analysis support a susceptible breakpoint of 8 μg/mL for *P. aeruginosa.*

It should be noted that the determination of breakpoints involves multiple disciplines, including clinical and microbiological perspectives in addition to the nonclinical and clinical PK/PD considerations. The ultimate determination of the meropenem-vaborbactam breakpoint will depend on the totality of information provided by each discipline and continues to be assessed at the time of the completion of this review.

# 4. APPENDICES

## 4.1 Summary of Bioanalytical Method Validation and Performance

High Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC/MS/MS) was used for the detection and quantification of meropenem, its major metabolite, meropenem open-lactam, and vaborbactam. The study matrices involved are plasma, urine, bronchoalveolar lavage fluid (BAL) containing epithelial lining fluid (ELF) and alveolar macrophages (AM), and dialysate fluid. The urea concentrations in plasma and BAL were performed with a microplate-based method with an O-phthalaldehyde chromogenic solution.

The analytical methods to determine the concentrations of meropenem, meropenem open-lactam, vaborbactam and urea in the above-mentioned matrices were validated and found acceptable to support the individual study reports (Table 4.1-1) reviewed in the current review cycle. The relevant validation reports and validation parameters are summarized in Tables 4.1-2 to 4.1-15.

**Table 4.1-1: List of Individual Study Reports Reviewed with the Bioanalytical and Method Validation Reports**

| Study (Phase) | Study Design | Molecular Entities | Matrix | Bioanalytical Report | Validation Report |
|---|---|---|---|---|---|
| Study 402 Phase I | Safety & PK | Vaborbactam | Plasma | MC12B-0025 | MC12B-0022 |
| | | | Urine | MC12B-0025 | MC12B-0023 |
| Study 501 Phase I | Safety & PK | Vaborbactam | Plasma | MC13B-0162 | MC13R-0016 |
| | | | Urine | MC13B-0163 | MC13R-0017 |
| | | Meropenem | Plasma | MC13B-0162 | MC13B-0105 |
| | | | Urine | MC13B-0163 | MC13B-0106 |
| | | Meropenem Open-Lactam | Plasma | MC13B-0162 | MC13B-0105 |
| | | | Urine | MC13B-0163 | MC13B-0106 |
| Study 503 Phase I | Safety & PK | Vaborbactam | Plasma | MC14B-0013 | MC13R-0016 |
| | | | ELF | MC14B-0014 | MC14R-0007 |
| | | | AM | MC14B-0015 | MC14R-0008 |
| | | Meropenem | Plasma | MC14B-0013 | MC13B-0105 |
| | | | ELF | MC14B-0014 | MC14B-0020 |
| | | | AM | MC14B-0015 | MC14B-0021 |
| | | Meropenem Open-Lactam | Plasma | MC14B-0013 | MC13B-0105 |
| | | | ELF | MC14B-0014 | MC14B-0020 |
| | | | AM | MC14B-0015 | MC14B-0021 |
| Study 504 Phase I | Safety & PK | Vaborbactam | Plasma | MC14B-0003 | MC13R-0016 |
| | | | Dialysate | MC14B-0004 | MC14R-0034 |
| | | | Urine | MC14B-0004 | MC13R-0017 |
| | | Meropenem | Plasma | MC14B-0003 | MC13B-0105 |
| | | | Dialysate | MC14B-0004 | MC14B-0172 |
| | | | Urine | MC14B-0004 | MC13B-0106 |
| | | Meropenem Open-Lactam | Plasma | MC14B-0003 | MC13B-0105 |
| | | | Dialysate | MC14B-0004 | MC14B-0172 |
| | | | Urine | MC14B-0004 | MC13B-0106 |
| Study 505 Phase III | Safety, Efficacy & PK | Vaborbactam | Plasma | MC14B-0175 | MC13R-0016 |
| | | Meropenem | Plasma | MC14B-0175 | MC13B-0105 |
| | | Meropenem Open-Lactam | Plasma | MC14B-0175 | MC13B-0105 |
| Study 506 Phase III | Safety, Efficacy & PK | Vaborbactam | Plasma | MC14B-0176 | MC13R-0016 |
| | | Meropenem | Plasma | MC14B-0176 | MC13B-0105 |
| | | Meropenem Open-Lactam | Plasma | MC14B-0176 | MC13B-0105 |

PK = Pharmacokinetic

**Table 4.1-2: Summary of Method and Method Validation Data for Meropenem and Meropenem Open-Lactam in Human Plasma (MC13B-0105)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of Meropenem and Meropenem Metabolite in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC13B-0105 is an LC/MS/MS method for the determination of meropenem and meropenem metabolite (meropenem open-lactam (b) (4) in human plasma. Stabilized human plasma samples (with $K_2$EDTA as the anticoagulant) containing meropenem, meropenem metabolite and RPX7009, with (b) (4) (b) (4) as the internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. Meropenem and meropenem metabolite were analyzed on a Supelco Discovery® HS F5 column. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 0.2 - 100 µg/mL |
| QC Concentrations | 0.2, 0.6, 7.5, and 80 µg/mL |
| Lower Limit of Quantitation (LLOQ) | 0.2 µg/mL |
| **Analyte** | **Meropenem** |
| QC Intra-day Precision (%CV) | 1.77% to 5.63% |
| QC Intra-day Accuracy (%Nominal) | -8.38% to 7.67% |
| QC Inter-day Precision (%CV) | 3.40% to 6.44% |
| QC Inter-day Accuracy (%Nominal) | -2.00% to 1.60% |
| Stability | Re-injection Integrity (5°C) - 107 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 25 hours |
| | Frozen (-20°C) - 31 days |
| | Frozen (-70°C) - 31 days |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 500-fold 6 times |
| Specificity | 100% of 6 lots tested |
| **Analyte** | **Meropenem Metabolite (Meropenem Open-Lactam: (b) (4)** |
| QC Intra-day Precision (%CV) | 2.67% to 6.98% |
| QC Intra-day Accuracy (%Nominal) | -7.63 to 3.67% |
| QC Inter-day Precision (%CV) | 5.11% to 5.40% |
| QC Inter-day Accuracy (%Nominal) | -4.00% to 0.00% |
| Stability | Re-injection Integrity (5°C) - 107 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 25 hours |
| | Frozen (-20°C) - 31 days |
| | Frozen (-70°C) - 31 days |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 500-fold 6 times |
| Specificity | 100% of 6 lots tested |

**Table 4.1-3: Summary of Method and Method Validation Data for Meropenem and Meropenem Open-Lactam in Human Urine (MC13B-0106)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of Meropenem and Meropenem Metabolite in Human Urine using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC13B-0106 is an LC/MS/MS method for the determination of meropenem and meropenem metabolite (meropenem open-lactam; (b) (4) in human urine. Stabilized human urine samples containing meropenem, meropenem metabolite and RPX7009, with (b) (4) as the internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. Meropenem and meropenem metabolite were analyzed on a Supelco Discovery® HS F5 column. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 0.2 - 100 µg/mL |
| QC Concentrations | 0.2, 0.6, 7.5, and 80 µg/mL |
| Lower Limit of Quantitation (LLOQ) | 0.2 µg/mL |
| **Analyte** | **Meropenem** |
| QC Intra-day Precision (%CV) | 0.913% to 4.95% |
| QC Intra-day Accuracy (%Nominal) | -4.38% to 3.00% |
| QC Inter-day Precision (%CV) | 3.28% to 3.44% |
| QC Inter-day Accuracy (%Nominal) | -1.63% to 0.00% |
| Stability | Re-injection Integrity (5°C) - 81 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 24 hours |
| | Frozen (-20°C) - 30 days |
| | Frozen (-70°C) - 30 days |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 500-fold 6 times |
| Specificity | 100% of 6 lots tested |
| **Analyte** | **Meropenem Metabolite (Meropenem Open-Lactam; (b) (4)** |
| QC Intra-day Precision (%CV) | 1.25% to 5.00% |
| QC Intra-day Accuracy (%Nominal) | -3.50% to 3.88% |
| QC Inter-day Precision (%CV) | 3.33% to 4.92% |
| QC Inter-day Accuracy (%Nominal) | -0.667% to 0.800% |
| Stability | Re-injection Integrity (5°C) - 81 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 24 hours |
| | Frozen (-20°C) - 30 days |
| | Frozen (-70°C) - 30 days |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 500-fold 6 times |
| Specificity | 100% of 6 lots tested |

**Table 4.1-4: Summary of Method and Method Validation Data for Meropenem and Meropenem Open-Lactam in Human ELF (BAL) (MC14B-0020)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of Meropenem and Meropenem Metabolite in Stabilized Human ELF using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC14B-0020 is an LC/MS/MS method for the determination of meropenem and meropenem metabolite (meropenem open-lactam; (b) (4) in human BAL (ELF). Stabilized human ELF samples containing meropenem, meropenem metabolite and RPX7009, with (b) (4) as the internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. Meropenem and meropenem metabolite were analyzed on a Supelco Discovery® HS F5 column. The assay employed electrospray positive ionization and MS/MS mode. As lidocaine was used during sample collection, lack of interference was confirmed. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 10 - 5000 ng/mL |
| QC Concentrations | 10, 30, 375, and 4000 ng/mL |
| Lower Limit of Quantitation (LLOQ) | 10 ng/mL |
| **Analyte** | **Meropenem** |
| QC Intra-day Precision (%CV) | 1.00% to 12.2% |
| QC Intra-day Accuracy (%Nominal) | -9.25% to 7.20% |
| QC Inter-day Precision (%CV) | 4.65% to 5.61% |
| QC Inter-day Accuracy (%Nominal) | -4.00 to 0.267% |
| Stability | Re-injection Integrity (5°C) - 74 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 3 hours |
| | Frozen (-70°C) - 68 days |
| Dilution Integrity | 25,000 ng/mL diluted 10-fold 6 times and 100-fold 6 times |
| Specificity | 66.7 % of 6 lots tested; Lots were only used for specificity, not QC or standard prep |
| **Analyte** | **Meropenem Metabolite (Meropenem Open-Lactam** (b) (4) |
| QC Intra-day Precision (%CV) | 0.316% to 3.405 |
| QC Intra-day Accuracy (%Nominal) | -7.20% to 9.00% |
| QC Inter-day Precision (%CV) | 2.65% to 6.56% |
| QC Inter-day Accuracy (%Nominal) | -3.73% to 1.75% |
| Stability | Re-injection Integrity (5°C) - 74 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 3 hours |
| | Frozen (-20°C) - 34 days |
| | Frozen (-70°C) - 68 days |
| Dilution Integrity | 25,000 ng/mL diluted 10-fold 6 times and 100-fold 6 times |
| Specificity | 66.7 % of 6 lots tested; Lots were only used for specificity, not QC or standard prep |

**Table 4.1-5: Summary of Method and Method Validation Data for Meropenem and Meropenem Open-Lactam in Human AM (MC14B-0021)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of Meropenem and Meropenem Metabolite in Stabilized Human Alveolar Macrophage Resuspension Solution using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC14B-0021 is an LC/MS/MS method for the determination of meropenem and meropenem metabolite (meropenem open-lactam [redacted] (b) (4) in human alveolar macrophages (AM). Resuspended AM samples containing meropenem, meropenem metabolite and RPX7009, with [redacted] (b) (4) as the internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. Meropenem and meropenem metabolite were analyzed on a Supelco Discovery® HS F5 column. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 10 - 5000 ng/mL |
| QC Concentrations | 10, 30, 375, and 4000 ng/mL |
| Lower Limit of Quantitation (LLOQ) | 10 ng/mL |
| **Analyte** | **Meropenem** |
| QC Intra-day Precision (%CV) | 1.24% to 3.95% |
| QC Intra-day Accuracy (%Nominal) | -4.67% to 0.750% |
| QC Inter-day Precision (%CV) | 2.43% to 2.86% |
| QC Inter-day Accuracy (%Nominal) | -3.33% to -0.750% |
| Stability | Re-injection Integrity (5°C) - 43 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 23 hours |
| | Frozen (-20°C) - 35 days |
| | Frozen (-70°C) - 76 days |
| Dilution Integrity | 25,000 ng/mL diluted 10-fold 6 times and 100-fold 6 times |
| **Analyte** | **Meropenem Metabolite (Meropenem Open-Lactam: [redacted] (b) (4) )** |
| QC Intra-day Precision (%CV) | 0.606% to 5.17% |
| QC Intra-day Accuracy (%Nominal) | -14.0% to 8.00% |
| QC Inter-day Precision (%CV) | 3.45% to 8.18% |
| QC Inter-day Accuracy (%Nominal) | -5.33% to 3.20% |
| Stability | Re-injection Integrity (5°C) - 6 days |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 23 hours |
| | Frozen (-20°C) - 35 days |
| | Frozen (-70°C) - 76 days |
| Dilution Integrity | 25,000 ng/mL diluted 10-fold 6 times and 100-fold 6 times |

**Table 4.1-6: Summary of Method and Method Validation Data for Meropenem and Meropenem Open-Lactam in Human Dialysate (MC14B-0172)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of Meropenem and Meropenem Metabolite in Human Dialysate using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC14B-0172 is an LC/MS/MS method for the determination of meropenem and meropenem metabolite in human Dialysate. Human stabilized dialysate fluid samples containing meropenem and meropenem metabolite, with (b) (4) (b) (4) as their Appears this way on original respective internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. Meropenem and meropenem metabolite were analyzed on a Supelco Discovery® HS F5 column. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 0.2 - 100 µg/mL |
| QC Concentrations | 0.2, 0.6, 7.5, and 80 µg/mL |
| Lower Limit of Quantitation (LLOQ) | 0.2 µg/mL |
| **Analyte** | **Meropenem** |
| QC Intra-day Precision (%CV) | 2.10% to 10.7% |
| QC Intra-day Accuracy (%Nominal) | -3.00% to 1.47% |
| QC Inter-day Precision (%CV) | 2.72% to 6.94% |
| QC Inter-day Accuracy (%Nominal) | -1.38% to 0.800% |
| Stability | Re-injection Integrity (5°C) - 71 hours |
| | Freeze/Thaw (-70°C/On Ice) - 5 cycles |
| | Thawed (On Ice) - 4 hours |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 500-fold 6 times |
| Specificity | 100% of 6 lots tested |
| **Analyte** | **Meropenem Metabolite (Meropenem Open-Lactam; (b) (4)** |
| QC Intra-day Precision (%CV) | 0.823% to 6.81% |
| QC Intra-day Accuracy (%Nominal) | -3.00 to 0.875% |
| QC Inter-day Precision (%CV) | 1.93% to 4.20% |
| QC Inter-day Accuracy (%Nominal) | -2.17% to 0.00% |
| Stability | Re-injection Integrity (5°C) - 71 hours |
| | Freeze/Thaw (-70°C/On Ice) - 5 cycles |
| | Thawed (On Ice) - 4 hours |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 100-fold 6 times |
| Specificity | 100% of 6 lots tested |

**Table 4.1-7: Summary of Method and Method Validation Data for Vaborbactam in Human Plasma (MC12B-0022)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of RPX7009 in Stabilized Human Plasma using High-Performance Liquid Chromatography with Spectrometric Detection |
| Method Description | Method MC12B-0022 is an LC/MS/MS method for the determination of vaborbactam in human plasma. Stabilized plasma samples (with K2EDTA as the anticoagulant) containing biapenem, biapenem metabolite and RPX7009, with meropenem, hydrolyzed meropenem and (b) (4) as their respective internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. The extracts were analyzed for RPX7009 using a Waters Xbridge Shield RP column. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 0.2 - 100 µg/mL |
| QC Concentrations | 0.2, 0.6, 7.5, and 80 µg/mL |
| Analyte | Vaborbactam |
| Lower Limit of Quantitation (LLOQ) | 0.2 µg/mL |
| QC Intra-day Precision (%CV) | 1.20% to 5.04% |
| QC Intra-day Accuracy (%Nominal) | -6.00% to 4.50% |
| QC Inter-day Precision (%CV) | 2.36% to 4.98% |
| QC Inter-day Accuracy (%Nominal) | -3.47% to 3.13% |
| Stability | Re-injection Integrity (5°C) - 72 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 24 hours |
| | Frozen (-20°C) - 36 days |
| | Frozen (-70°C) - 36 days |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 50-fold 6 times |
| Specificity | 100% of 6 lots tested |

**Table 4.1-8: Summary of Method and Method Validation Data for Vaborbactam in Human Urine (MC12B-0023)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of RPX7009 in Stabilized Human Urine using High-Performance Liquid Chromatography with Spectrometric Detection |
| Method Description | Method MC12B-0023 is an LC/MS/MS method for the determination of vaborbactam in human urine. Stabilized urine samples containing biapenem, biapenem metabolite and RPX7009, with meropenem, hydrolyzed meropenem and (b) (4) as their respective internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. The extracts were analyzed for RPX7009 using a Waters Xbridge Shield RP column. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 0.2 - 100 µg/mL |
| QC Concentrations | 0.2, 0.6, 7.5, and 80 µg/mL |
| Analyte | Vaborbactam |
| Lower Limit of Quantitation (LLOQ) | 0.2 µg/mL |
| QC Intra-day Precision (%CV) | 1.19% to 9.86% |
| QC Intra-day Accuracy (%Nominal) | -2.88% to 9.83% |
| QC Inter-day Precision (%CV) | 2.18% to 6.90% |
| QC Inter-day Accuracy (%Nominal) | -0.50% to 1.33% |
| Stability | Re-injection Integrity (5°C) - 72 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 24 hours |
| | Frozen (-20°C) - 40 days |
| | Frozen (-70°C) - 35 days |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 50-fold 6 times |
| Specificity | 100% of 6 lots tested |

**Table 4.1-9: Summary of Method and Method Validation Data for Vaborbactam in Human Plasma (MC13R-0016)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of RPX7009 in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC13R-0016 is an LC/MS/MS method for the determination of vaborbactam in human plasma. Stabilized human plasma samples (with K2EDTA as the anticoagulant) containing meropenem, meropenem metabolite and RPX7009, with [redacted] (b) (4) as the internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 0.2 - 100 µg/mL |
| QC Concentrations | 0.2, 0.6, 7.5, and 80 µg/mL |
| Analyte | Vaborbactam |
| Lower Limit of Quantitation (LLOQ) | 0.2 µg/mL |
| QC Intra-day Precision (%CV) | 0.60% to 6.35% |
| QC Intra-day Accuracy (%Nominal) | -8.67% to 5.17% |
| QC Inter-day Precision (%CV) | 2.92% to 7.51% |
| QC Inter-day Accuracy (%Nominal) | -1.50% to -1.33% |
| Stability | Re-injection Integrity (5°C) - 5 days |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 25 hours |
| | Frozen (-20°C) - 31 days |
| | Frozen (-70°C) - 31 days |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 50-fold 6 times |
| Specificity | 83.3% of 6 lots tested |

**Table 4.1-10: Summary of Method and Method Validation Data for Vaborbactam in Human Urine (MC13R-0017)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of RPX7009 in Human Urine using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC13R-0017 is an LC/MS/MS method for the determination of vaborbactam in human urine. Human urine samples containing meropenem, meropenem metabolite and RPX7009, with [redacted] (b) (4) as their respective internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. RPX7009 was analyzed using a Water's Xbridge Shield RP column. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 0.2 - 100 µg/mL |
| QC Concentrations | 0.2, 0.6, 7.5, and 80 µg/mL |
| Analyte | Vaborbactam |
| Lower Limit of Quantitation (LLOQ) | 0.2 µg/mL |
| QC Intra-day Precision (%CV) | 1.03% to 6.73% |
| QC Intra-day Accuracy (%Nominal) | -4.17% to 4.50% |
| QC Inter-day Precision (%CV) | 2.48% to 5.34% |
| QC Inter-day Accuracy (%Nominal) | -1.75% to -0.167% |
| Stability | Re-injection Integrity (5°C) - 5 days |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 24 hours |
| | Frozen (-20°C) - 30 days |
| | Frozen (-70°C) - 30 days |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 50-fold 6 times |
| Specificity | 83.3% of 6 lots tested |

**Table 4.1-11: Summary of Method and Method Validation Data for Vaborbactam in Human ELF (BAL) (MC14R-0007)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of RPX7009 in Stabilized Human Epithelial Lining Fluid using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC14R-0007 is an LC/MS/MS method for the determination of vaborbactam in human BAL (ELF). Stabilized human ELF samples containing meropenem, meropenem metabolite and RPX7009, with (b) (4) as their respective internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. Meropenem and meropenem metabolite were analyzed on a Supelco Discovery®HS F5 column and RPX7009 was analyzed using a Waters XBridge Shield RP column. Both assays employed electrospray positive ionization and MS/MS mode. As lidocaine was used during sample collection, lack of interference was confirmed. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 2.0 to 1000 ng/mL |
| QC Concentrations | 2.0, 6.0, 75.0, and 800 ng/mL |
| Analyte | Vaborbactam |
| Lower Limit of Quantitation (LLOQ) | 2.0 ng/mL |
| QC Intra-day Precision (%CV) | 0.385% to 3.74% |
| QC Intra-day Accuracy (%Nominal) | -8.33% to 9.33% |
| QC Inter-day Precision (%CV) | 2.54% to 5.61% |
| QC Inter-day Accuracy (%Nominal) | -1.73% to 1.17% |
| Stability | Re-injection Integrity (5°C) - 72 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 24 hours |
| | Frozen (-20°C) - 34 days |
| | Frozen (-70°C) - 68 days |
| Dilution Integrity | 5000 ng/mL diluted 10-fold 12 times and 100-fold 6 times |
| Specificity | 66.7 % of 6 lots tested; Lots were only used for specificity, not QC or standard prep |

**Table 4.1-12: Summary of Method and Method Validation Data for Vaborbactam in Human AM (MC14R-0008)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of RPX7009 in Human Alveolar Macrophage Resuspension Solution using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC14R-0008 is an LC/MS/MS method for the determination of vaborbactam in human Alveolar Macrophages (AM). Resuspended AM samples containing meropenem, meropenem metabolite and RPX7009, with (b) (4) as their respective internal standards, were precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. Meropenem and meropenem metabolite were analyzed on a Supelco Discovery®HS F5 column and RPX7009 was analyzed using a Waters XBridge Shield RP column. Both assays employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 2.0 to 1000 ng/mL |
| QC Concentrations | 2.0, 6.0, 75.0, and 800 ng/mL |
| Analyte | Vaborbactam |
| Lower Limit of Quantitation (LLOQ) | 2.0 ng/mL |
| QC Intra-day Precision (%CV) | 0.73% to 2.46% |
| QC Intra-day Accuracy (%Nominal) | -2.50% to 3.67% |
| QC Inter-day Precision (%CV) | 2.52% to 2.81% |
| QC Inter-day Accuracy (%Nominal) | 0.250% to 0.400% |
| Stability | Re-injection Integrity (5°C) - 104 hours |
| | Freeze/Thaw (-70°C/On Ice) - 4 cycles |
| | Thawed (On Ice) - 23 hours |
| | Frozen (-20°C) - 35 days |
| | Frozen (-70°C) - 76 days |
| Dilution Integrity | 5000 ng/mL diluted 10-fold 6 times and 100-fold 6 times |

**Table 4.1-13: Summary of Method and Method Validation Data for Vaborbactam in Human Dialysate (MC14R-0034)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of RPX7009 in Human Dialysate using High-Performance Liquid Chromatography with Mass Spectrometric Detection |
| Method Description | Method MC14R-0034 is an LC/MS/MS method for the determination of vaborbactam in human Dialysate. Human stabilized dialysate samples containing RPX7009, with [redacted] (b) (4) as its internal standard, was precipitated with a methanol:acetonitrile solution. The supernatant was further diluted and the sample extract was divided for analysis on two separate LC/MS/MS systems. RPX7009 was analyzed using a Water's Xbridge Shield RP column. The assay employed electrospray positive ionization and MS/MS mode. |
| Sample Volume | 20 µL |
| Regression | log-transformed linear regression |
| Dynamic Range | 0.2 - 100 µg/mL |
| QC Concentrations | 0.2, 0.6, 7.5, and 80 µg/mL |
| Analyte | Vaborbactam |
| Lower Limit of Quantitation (LLOQ) | 0.2 µg/mL |
| QC Intra-day Precision (%CV) | 0.671% to 3.06% |
| QC Intra-day Accuracy (%Nominal) | -4.00% to 0.133% |
| QC Inter-day Precision (%CV) | 1.61% to 2.72% |
| QC Inter-day Accuracy (%Nominal) | -3.00% to 0.00% |
| Stability | Re-injection Integrity (5°C) - 6 days |
| | Freeze/Thaw (-70°C/On Ice) - 5 cycles |
| | Thawed (On Ice) - 4 hours |
| Dilution Integrity | 400 µg/mL diluted 10-fold 6 times and 100-fold 6 times |
| Specificity | 100 % of 6 lots tested |

**Table 4.1-14: Summary of Method and Method Validation Data for Determination of Urea in Human Plasma (MC14I-0022)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of Urea in Human Plasma using a Microplate-Based Method with an O-phthalaldehyde Chromogenic Solution |
| Method Description | Method MC14I-0022 is a method for the determination of urea concentrations in human plasma containing K2EDTA as the anticoagulant using colorimetric detection. Human plasma standards, QC's and samples were incubated with a chromogenic solution of O-phthalaldehyde on a microplate. The O-phthalaldehyde and urea formed a colored complex. Color development was proportional to the quantity of urea and was measured using a microplate reader. |
| Sample Volume | 10 µL |
| Regression | Linear |
| Dynamic Range | 2.50 - 50.0 mg/dL |
| QC Concentrations | 36.1, 41.1, 48.6, and 73.6 mg/dL |
| Analyte | Urea |
| Lower Limit of Quantitation (LLOQ) | 2.50 mg/dL |
| QC Intra-day Precision (%CV) | 1.00% to 10.8% |
| QC Intra-day Accuracy (%Nominal) | -19.0% to 9.25% |
| QC Inter-day Precision (%CV) | 3.905 to 9.95% |
| QC Inter-day Accuracy (%Nominal) | -9.105 to -6.08% |
| Hemolysis Effect Precision (%CV) | 1.89% to 12.3% |
| Hemolysis Effect Accuracy (%CV) | 13.1% to 16.0% |
| Stability | Process Sample (RT) - 30 minutes |
| | Freeze/Thaw (-70°C/On Ice) - 5 cycles |
| | Thawed (On Ice) - 24 hours |
| | Frozen (-20°C) - 33 days |
| | Frozen (-70°C) - 33 days |
| Dilution Integrity Precision (%CV) | 2.28% |
| Dilution Integrity Accuracy (%CV) | -13.0% |

**Table 4.1-15: Summary of Method and Method Validation Data for Determination of Urea in Bronchoalveolar Lavage Fluid (ELF) (MC14I-0023)**

| | |
|---|---|
| Report Title | Validation of a Method for the Determination of Urea in Human ELF using a Microplate-Based Method with an O-phthalaldehyde Chromogenic Solution |
| Method Description | Method MC14I-0023 is a method for the determination of urea concentrations in human epithelial lining fluid (ELF) as collected through 0.9% saline bronchoalveolar lavage (BAL) based on BioChain Urea Assay Kit procedures. Standards, QCs and samples Appears this way on original were incubated with a chromogenic solution of o-phthalaldehyde on a microplate. The o-phthalaldehyde and urea formed a colored complex. Color development was proportional to the quantity of urea and is measured using a microplate reader. |
| Sample Volume | 150 µL |
| Regression | Linear |
| Dynamic Range (s) | Normal (0.15 - 2.5 mg/dL); High Sensitivity (0.05 - 1.00 mg/dL) |
| QC Concentrations | Normal (0.15, 0.30, 0.75, and 2.0 mg/dL); High Sensitivity (0.05, 0.15, 0.30, 0.80 mg/dL) |
| Analyte | Urea |
| Lower Limit of Quantitation (LLOQ) | Normal (0.15 mg/dL); High Sensitivity (0.05 mg/dL) |
| QC Intra-day Precision (%CV) | Normal (0.43% to 7.07%); High Sensitivity (0.69% to 4.44%) |
| QC Intra-day Accuracy (%Nominal) | Normal (-12.0% to 17.3%); High Sensitivity (0.67% to 1.63%) |
| QC Inter-day Precision (%CV) | 3.30% to 8.03% |
| QC Inter-day Accuracy (%Nominal) | 1.00% to 2.00% |
| Lidocaine Impact Precision (%CV) | 0.50% to 1.23% |
| Lidocaine Impact Accuracy (%CV) | 0.50% to 3.00% |
| Stability | Process Sample (RT) - 30 minutes |
| | Freeze/Thaw (-70°C/On Ice) - 5 cycles |
| | Thawed (On Ice) - 25 hours |
| | Frozen (-20°C) - 33 days |
| | Frozen (-70°C) - 33 days |
| Dilution Integrity Precision (%CV) | 1.85% |
| Dilution Integrity Accuracy (%CV) | 0.00% |

## 4.2 Population PK Analysis

Population PK models were developed separately for meropenem and vaborbactam using data pooled from the Phase 1 and 3 studies. Since concomitant administration of meropenem and vaborbactam does not impact the PK of either drug (Study 504), separate population PK models were constructed for each compound. PK data for these analyses were obtained from two Phase 1 studies, Study 501 and Study 504 from healthy subjects, pooled with two Phase 3 studies, Study 505 and Study 506 from patients with ongoing infections.

Study 501: This study was conducted to assess the PK and safety of meropenem and vaborbactam in healthy subjects who received various combinations of meropenem (1 or 2 g) and/or vaborbactam (0.25, 1, 1.5, or 2 g) as a single intravenous (IV) infusion or multiple IV infusions. A total of 98 healthy subjects were randomized to receive meropenem-vaborbactam at various combinations of doses. Intensive blood and urine samples were collected. PK data from Cohort 6 was excluded from the population PK analysis as the drug was administered over 1 hour infusion.

Study 504: This study was conducted to assess the PK of meropenem and vaborbactam in healthy subjects with normal and varying degrees of renal insufficiencies. All subjects received a single dose of 1 g meropenem and 1 g vaborbactam in combination. A total of 40 subjects were enrolled in one of five groups (eight per renal insufficiency group and eight normal healthy adults). Impact of hemodialysis on the PK of meropenem and vaborbactam was assessed in subjects with end-stage renal disease (ESRD) (eGFR < 10 mL/min/1.73 $m^2$ calculated using the MDRD equation) by giving the dose before and after hemodialysis separated with a 7 days washout period. Intensive blood and 24 to 48 hours post-dose urine samples were collected for PK evaluation.

Study 505: This study was a Phase 3 clinical trial conducted to determine the efficacy, safety and tolerability in patients with acute pyelonephritis (AP) or complicated urinary tract infections (cUTI). A total of 271 patients randomized to receive meropenem-vaborbactam were administered 2 g meropenem and 2 g vaborbactam IV every 8 hours (q8h), including 31 renal impairment patients with a dose adjustment of 1 g meropenem and 1 g vaborbactam IV q8h for a minimum 15 doses. All subjects contributed blood samples for the determination of meropenem and vaborbactam concentrations. Samples were collected on Day 1 within 0.5 hour and 2 to 3 hours after the end of infusion and on Day 3 and the day of the end of IV therapy within 0.5 hour after the end of one of that day's infusions.

Study 506: This study was Phase 3 clinical trial conducted in patients with selected serious infections known or suspected to be caused by carbapenem-resistant Enterobacteriaceae (CRE). At the time of the interim analysis, a total of 23 patients randomized to receive meropenem-vaborbactam were administered 2 g meropenem and 2 g vaborbactam IV every 8 hours (q8h),

including 7 renal impairment patients with a dose adjustment of 1 g meropenem and 1 g vaborbactam IV q8h for up to 14 days. All subjects contributed blood samples for the determination of meropenem and vaborbactam concentrations. Samples were collected for PK analysis on Day 1 within 0.5 hour and 2 to 3 hours after the end of the first infusion and on Days 3 and 5 at 0.5 h after the end of one of that day's infusions.

**Table 4.2-1. Summary statistics or counts of the subject demographic characteristics of analysis population**

| Variable | Phase 1 studies | | Phase 3 studies | | Total |
|---|---|---|---|---|---|
| | Study 501 N = 70 | Study 504 N = 40 | Study 505 N = 271 | Study 506 N = 23 | N = 404 |
| | Median (Min. - Max.) | Median (Min. - Max.) | Median (Min. - Max.) | Median (Min. - Max.) | Median (Min. - Max.) |
| Age (yr) | 24.0 (18.0 – 50.0) | 56.5 (44.0 – 73.0) | 58.0 (18.0 – 92.0) | 66.0 (33.0 – 88.0) | 52.0 (18.0 – 92.0) |
| BMI ($kg/m^2$) | 24.0 (19.7 – 29.4) | 31.3 (21.2 – 43.7) | 26.1 (16.5 – 53.2) | 26.3 (17.1 – 52.9) | 26.1 (16.5 – 53.2) |
| BSA ($m^2$) | 1.91 (1.58 – 2.20) | 2.07 (1.63 – 2.66) | 1.80 (1.35 – 2.48) | 1.84 (1.32 – 2.83) | 1.83 (1.32 – 2.83) |
| Height (cm) | 175 (159 – 193) | 174 (156 – 190) | 165 (148 – 192) | 170 (153 – 185) | 168 (148 – 193) |
| eGFR ($mL/min/1.73\ m^2$) | 117 (81.1 – 203) | 46.4 (4.80 – 142) | 86.9 (12.6 – 241) | 75.5 (7.8 – 209) | 90.9 (4.80 – 241) |
| Weight (kg) | 74.6 (56.0 – 94.7) | 92.8 (58.2 – 143) | 73.8 (43.8 – 150) | 74.4 (40.1 – 177) | 75.0 (40.1 – 177) |
| Gender | | | | | |
| Male | 52 (74%) | 25 (63%) | 90 (33%) | 13 (57%) | 180 (45%) |
| Female | 18 (26%) | 15 (37%) | 181 (67%) | 10 (43%) | 224 (55%) |

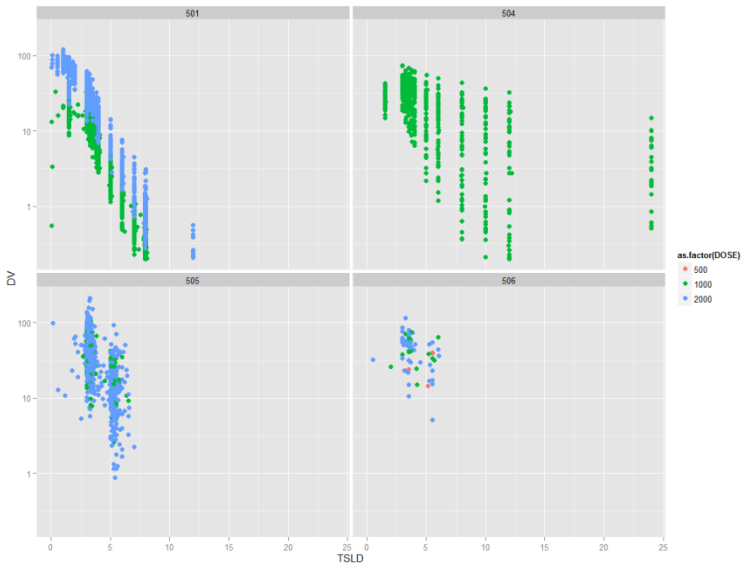
*Source: Applicant's population PK report (Study 00373-1 Report), Page 39, Table 7*

The final population PK analysis dataset for meropemen contained 386 subjects and 4172 meropenem plasma concentrations and 834 urine meropenem concentrations from 84 subjects. The final population PK analysis dataset for vaborbactam contained 387 subjects and 3988 vaborbactam plasma concentrations and 746 urine vaborbactam concentrations from 75 subjects.

Semilog scatterplots of meropenem plasma concentrations versus time, stratified by study and dose are provided in Figure 4.2-1. After IV administration, meropenem plasma concentrations appeared to decline in a poly-phasic manner.

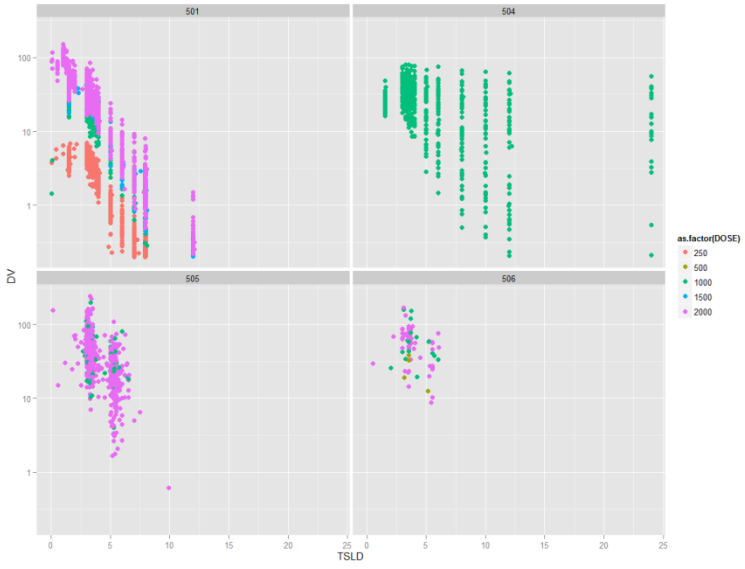
Semilog scatterplots of vaborbactam plasma concentrations versus time, stratified by study and dose are provided in Figure 4.2-2. After IV administration, vaborbactam plasma concentrations appeared to decline in a poly-phasic manner.

**Figure 4.2-1. Semi-log scatterplots of meropenem plasma concentrations versus time, stratified by study**




The 1000 mg dose of meropenem in Study 505 was used in patients with renal impairment according to protocol mandated dose adjustments.

**Figure 4.2-2. Semi-log scatterplots of vaborbactam plasma concentrations versus time, stratified by study**

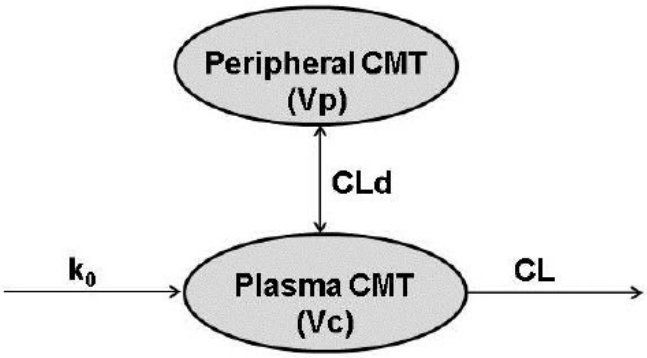



The 1000 mg dose of vaborbactam in Study 505 was used in patients with renal impairment according to protocol mandated dose adjustments.

**Meropenem Population Pharmacokinetic Modeling**

A two-compartment model with zero-order input and first-order elimination was used to describe the plasma and urine meropenem concentration-time data. Interindividual variability was described for the following parameters using a log-normal parameter distribution: CL, Vc, and Vp. Residual variability (RV) for plasma and urine was described using a combined additive plus proportional error model. eGFR (from MDRD) was evaluated as a covariate for meropenem CL (through its impact on $CL_R$) in the base structural model using either a linear, power, or a sigmoidal Hill-type function each of which were evaluated with an intercept term to account for $CL_{NR}$. The sigmoidal Hill-type function with estimation of an intercept term representing $CL_{NR}$ provided a more accurate characterization of CL, as indicated by having a larger drop in objective function, and by explaining more of the inter-individual variability in CL than did the other functions (reduced IIV CL to 59.3% from 82.3% compared to 78.8% and 69.8% for the linear and power-law models, respectively). Therefore, the sigmoidal Hill-type function was selected to describe the relationship between CL and eGFR. This model served as the comparator for subsequent covariate analysis. The diagram of the base structural population PK model is provided in Figure 4.2-3.

**Figure 4.2-3. Structural population PK model diagram for meropenem**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 47, Figure 7*

Body weight and age were evaluated as potential covariates of PK variability by testing the effect of weight and age on CL, Vc, Vp. Incorporating weight on Vc or Vp resulted in a significant decrease in the objective function values (>6.86 units) but showed no improvement in objective function when incorporating weight on CL. Thus, body weight was identified to be a significant covariate on Vc and Vp. However, CL was found to be over-predicted in subjects with severe renal impairment or ESRD based on data from Study 504 after incorporating the effects from body weight. In order to account for this misspecifiation, various models were

evaluated allowing for alterations in $CL_{NR}$ in patients with eGFR ≤ 30 mL/min/1.73 $m^2$. The best fit to the data was obtained when $CL_{NR}$ was allowed to be proportionally lower in subjects with eGFR ≤ 30 mL/min/1.73 $m^2$ (i.e., proportional shift permitting a reduction in the $CL_{NR}$ clearance by 35%). Finally, the plots of PK parameters versus covariates show that there appeared to be an additional relationship between age and meropenem CL. Age was added to the covariate model for CL and resulted in a significant decrease in the objective function values and thus the relationship between age and CL was retained in the model.
The final covariate model includes: the relationships between WTKG and Vc and Vp described using power functions; a power function relationship between age and CL; the relationship between CLr and eGFR modeled with a sigmoidal Hill-type function plus a proportional shift factor to allow for a lower $CL_{NR}$ in subjects with eGFR ≤ 30 mL/min/1.73 m2 (RGRP=1). The equations describing the covariate relationships are provided in Equations (1) through (3), below:

$$CLt = \left(3.78 \bullet (1\text{-RGRP}) + 3.78 \bullet (\text{RGRP}) \bullet 0.349 + \frac{6.60 \bullet eGFR^{1.94}}{40.8^{1.94} + eGFR^{1.94}}\right) \bullet \left[\frac{AGE}{58}\right]^{-0.430} \quad (1)$$

$$Vc = 17.4 \bullet \left[\frac{WTKG}{80}\right]^{0.487} \quad (2)$$

$$Vp = 2.50 \bullet \left[\frac{WTKG}{80}\right]^{0.324} \quad (3)$$

Where: RGRP is an indicator variable with values equal to 0 for patients with eGFR > 30 mL/min/1.73 $m^2$ and 1 for patients with eGFR ≤ 30 mL/min/1.73 $m^2$.

The population PK parameter estimates and associated standard errors from the final population PK model are provided in Table 4.2-2.

**Table 4.2-2. Final meropenem population PK model — Parameter estimates and standard errors**

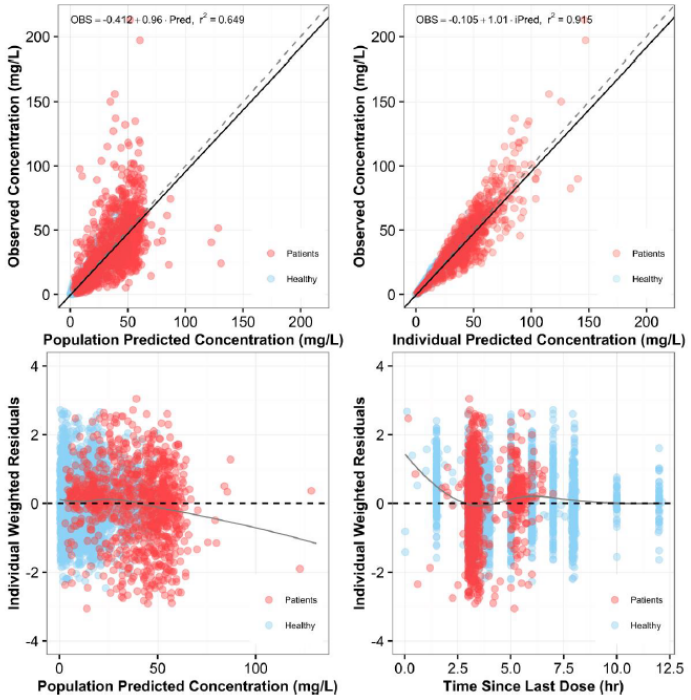
| Parameter | Population mean | | Magnitude of interindividual variability (%CV) | |
|---|---|---|---|---|
| | Final estimate | %SEM | Final estimate | %SEM |
| CL | | | 44.8 | 15.7 |
| $CL_{NR}$ | 3.78 | 5.60 | | |
| CLr,max | 6.60 | 8.60 | | |
| eGFR50 | 40.8 | 13.7 | | |
| Hill coefficient | 1.94 | 9.90 | | |
| Vc | 17.4 | 4.00 | 44.3 | 23.5 |
| CLd | 1.52 | 12.6 | | |
| Vp | 2.50 | 7.30 | 11.6 | 19.9 |
| Power coefficient of WTKG on Vc | 0.487 | 31.8 | | |
| Power coefficient of WTKG on Vp | 0.324 | 37.0 | | |
| Power coefficient of AGE on CL | -0.430 | 14.4 | | |
| Proportional shift with Renal Group on $CL_{NR}$ | 0.349 | 11.2 | | |
| Plasma residual variability | | | | |
| Plasma proportional error | 0.0388 | 5.60 | | |
| Plasma additive error | 0.0213 | 11.2 | | |
| Urine residual variability | | | | |
| Urine proportional error | 0.210 | 19.5 | | |
| Urine additive error | 0.0575 | 50.1 | | |
| Minimum value of the objective function = 17912.463 | | | | |

*Source: Applicant's population PK report (Study 00373-1 Report), Page 51, Table 10*

The primary goodness-of-fit plots for the final population PK model are provided in Figure 4.2-4. These plots demonstrate the adequacy of the model fit across healthy subjects and patients. Additionally, the VPC plots of meropenem plasma concentrations based on Phase 3 data and data from Study 504 are provided in Figure 4.2-5 and Figure 4.2-6, respectively. As shown in Figure 4.2-5, there was reasonable agreement between the observed data and the median and 5$^{th}$ and 95$^{th}$ percentiles of the simulated data over time following IV dosing of meropenem in patients. A small degree of bias was observed in predicting the concentration-time profiles in healthy subjects where concentrations from subjects with normal renal function and mild renal impairment are being over-predicted and those from subjects with severe renal impairment or ESRD are being under-predicted.

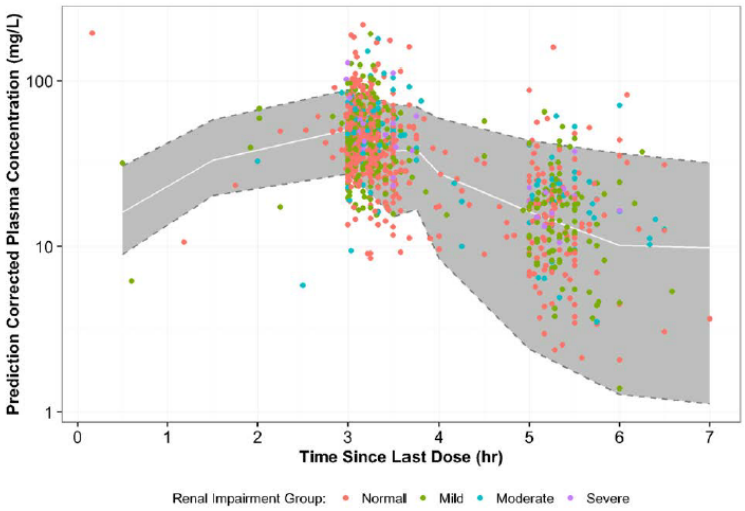
Figure 4.2-7 shows the relationship between the population mean predicted CL and eGFR overlaid upon the individual post-hoc estimates for CL. It appears that the clearance is faster in normal healthy volunteers relative to patients from Study 505 and Study 506 who had normal renal function. Given that the ultimate goal is to predict the PK in infected patients, coupled with the robust fit to that population, further attempts to perfect the fit in subjects from the two Phase 1 studies was not undertaken.

**Figure 4.2-4. Standard goodness-of-fit plots for the final population PK model for meropenem**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 53, Figure 9*

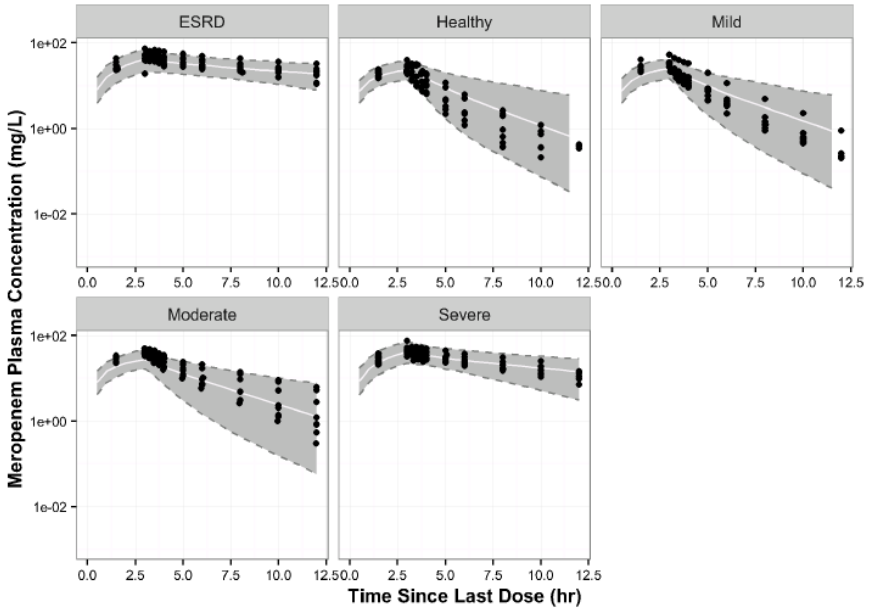
**Figure 4.2-5. Prediction-corrected visual predictive check for the final population PK model for meropenem: Phase 3 data and simulations only**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 55, Figure 10*

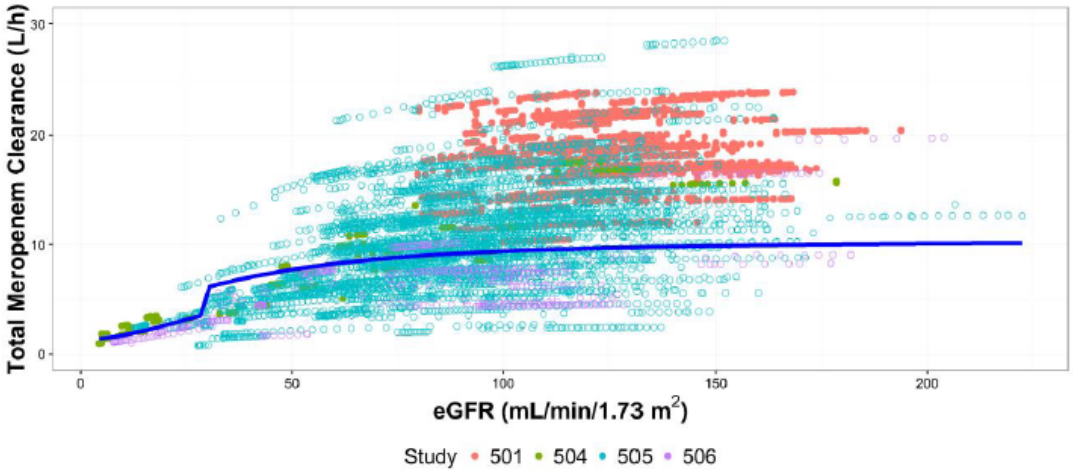
Solid line/grey shaded area: Median/90% confidence interval of model simulations for Phase 3 patients; Solid dots: Observed meropenem concentrations from Study 505 (red) and Study 506 (blue).

**Figure 4.2-6. Visual predictive check plots for the final population PK model for meropenem: Study 504 only**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 57, Figure 12*

**Figure 4.2-7. Relationship between clearance and eGFR for meropenem using the final population PK model**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 58, Figure 13*

*Reviewer's comments: In general, the Applicant's population PK model for meropenem adequately describes meropenem concentration data in patients and in healthy volunteers with impaired renal function. Model parameters are in general well-estimated; however, the provided pcVPC plots do show slight bias with respect to renal function. Specifically, the pcVPC suggests that the model over-predicts exposure in subjects with normal renal function and mild renal impairment. As such, exposure in such individuals may be lower than predicted by the model.*

*The Applicant was also forced to introduce a proportional shift in non-renal clearance to account for the lower the predicted total clearance observed in subjects with eGFR ≤ 30 mL/min/1.73 m$^2$. The main purpose of this model structure was to correct the over-prediction of PK data in the dedicated renal impairment study (Study 504) but the selection of the cut-off appeared arbitrary. This cut-off value had a significant impact on dose evaluation, such that the total CL (CLnr+CLr) may have a dramatic drop when eGFR is less than or equal to 30 mL/min/1.73m2. The following table was generated the total CL vs eGFR using estimated PK parameter from meropenem population PK model considering sigmoid hill-type covariate but not considering other covariates, like age.*

***Table 4.2-3 Estimated total CL vs eGFR based on meropenem population PK model***

| *eGFR (mL/min/1.73m²)* | *Maximum CLr (L/h)* | *CLnr (L/h)* | *Total CL (L/h)* |
|---|---|---|---|
| *0* | *6.6* | *1.323* | *1.323* |
| *5* | *6.6* | *1.323* | *1.430312* |
| *10* | *6.6* | *1.323* | *1.716605* |
| *15* | *6.6* | *1.323* | *2.129786* |
| *20* | *6.6* | *1.323* | *2.614732* |
| *25* | *6.6* | *1.323* | *3.123584* |
| *30* | *6.6* | *1.323* | *3.621542* |
| *35* | *6.6* | *3.78* | *6.5442* |
| *40* | *6.6* | *3.78* | *6.966894* |
| *45* | *6.6* | *3.78* | *7.343312* |
| *50* | *6.6* | *3.78* | *7.67457* |
| *55* | *6.6* | *3.78* | *7.964107* |
| *60* | *6.6* | *3.78* | *8.216337* |
| *65* | *6.6* | *3.78* | *8.435863* |
| *70* | *6.6* | *3.78* | *8.627061* |
| *75* | *6.6* | *3.78* | *8.793887* |
| *80* | *6.6* | *3.78* | *8.939816* |
| *85* | *6.6* | *3.78* | *9.067847* |
| *90* | *6.6* | *3.78* | *9.180541* |
| *95* | *6.6* | *3.78* | *9.280074* |
| *100* | *6.6* | *3.78* | *9.368287* |
| *105* | *6.6* | *3.78* | *9.446736* |

| | | | |
|---|---|---|---|
| *110* | *6.6* | *3.78* | *9.51674* |
| *115* | *6.6* | *3.78* | *9.579413* |
| *120* | *6.6* | *3.78* | *9.635703* |

*Source: Reviewer's independent analysis*

*Specifically, it would not be expected that the non-renal elimination component for meropenen (hydrolysis of beta-lactam bond to open beta-lactam form) would be decreased in patients with reduced renal function. Instead, a potential explanation for the data could be competition for active tubular secretion in the kidneys between meropenem and its inactive metabolite. In subjects with impaired renal impairment, the metabolite substantially accumulates, reaching concentrations similar to that of meropenem in subjects with severe renal impairment or ESRD. It is also known that the renal elimination of meropenem occurs by active tubular secretion, and it could be that the metabolite is eliminated in the same manner. Other hypotheses for why the factor was needed could include that eGFR is not necessarily the ideal equation for representing the impact of renal impairment on a drug that undergoes tubular secretion.*

*While the reviewer does not agree with the physiological implications of the included parameter, the reviewer does agree that an adjustment was needed to describe the observations from Study 504. The reviewer also agrees that with the proposed adjustment the model describes the observed data in these subpopulations reasonably well and that the developed model can be used to simulate meropenem exposures in patients with renal impairment.*

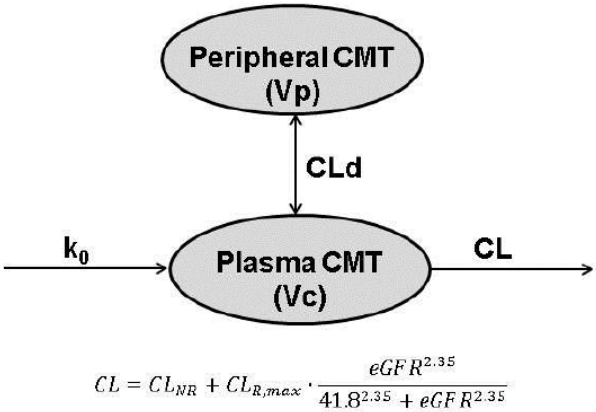
**Vaborbactam Population Pharmacokinetic Modeling**

A two-compartment model with zero-order input and first-order elimination was used to describe the plasma and urine vaborbactam concentration-time data. Interindividual variability was described for each parameter using a log-normal parameter distribution. Residual variability (RV) for plasma and urine was described using a combined additive plus proportional error model.

eGFR was evaluated as a covariate for vaborbactam CL (through its relationship with $CL_R$) in the base structural model using either a linear, power, or a sigmoidal Hill-type function each of which were evaluated with an intercept term to account for $CL_{NR}$. The sigmoidal Hill-type function with estimation of an intercept term representing $CL_{NR}$ provided a more accurate characterization of CL, as indicated by having a larger drop in objective function, and explained more of the interindividual variability in CL than did the other functions and was therefore selected to describe the relationship between CL and eGFR. This model served as the comparator

for subsequent covariate analysis. The diagram of the base structural population PK model is provided in Figure 4.2-8.

**Figure 4.2-8. Structural population PK model diagram for vaborbactam**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 59, Figure 14*

A forward selection was used to screen covariate candidates, the following covariates were selected based on the magnitude of objective function value drop: 1) Study phase on CL; 2) height (HTCM) on CL; 3) body surface area (BSA) on Vc; 4) BSA on Vp; 5) study phase on Vc; 6) study phase on Vp.

The equations describing the covariate relationships are provided below:

$$CL = \left(0.169 + 9.34\frac{eGFR^{2.23}}{47.1^{2.23} + eGFR^{2.23}}\right) \bullet (1 + 0.264 \bullet Phase) \bullet \left[\frac{HTCM}{168}\right]^{2.17}$$

$$Vc = 16.9 \bullet (1 - 0.203 \bullet Phase) \bullet \left[\frac{BSA}{1.88}\right]^{1.14}$$

$$Vp = 1.41 \bullet (1 + 1.78 \bullet Phase)$$

Where: Phase is an indicator variable with values equal to 0 for Phase III patients and 1 for Phase I subjects.

The population PK parameter estimates and associated standard errors for the model are provided in Table 4.2-4.

**Table 4.2-4. Final vaborbactam population PK model — Parameter estimates and standard errors**

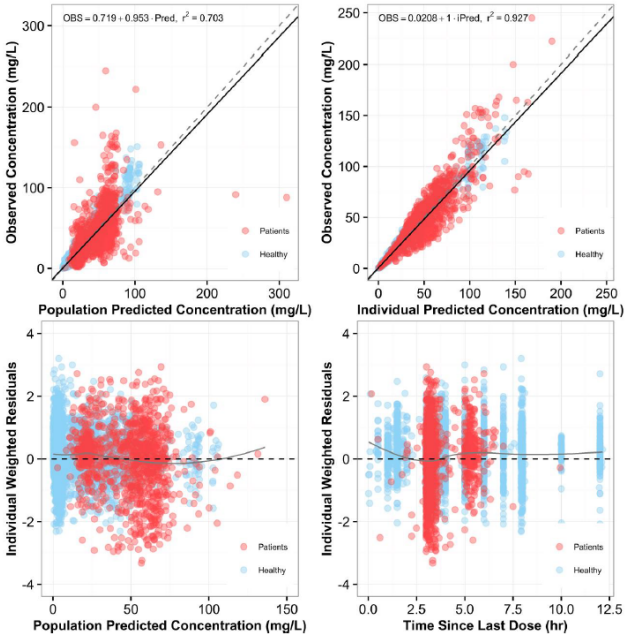
| Parameter | Population mean | | Magnitude of interindividual variability (%CV) | |
|---|---|---|---|---|
| | Final estimate | %SEM | Final estimate | %SEM |
| CL | | | 42.4 | 5.9 |
| $CL_{NR}$ | 0.169 | 12.5 | | |
| CLr,max | 9.34 | 3.3 | | |
| eGFR50 | 47.1 | 3.0 | | |
| Hill coefficient | 2.23 | 3.4 | | |
| Vc | 16.9 | 3.9 | 35.6 | 12.5 |
| CLd | 3.12 | 8.6 | 30.8 | 55 |
| Vp | 1.41 | 27.2 | 17.5 | 36.7 |
| Power coefficient of HTCM on CL | 2.17 | 20.6 | | |
| Proportional shit with Phase on CL | 0.264 | 43.6 | | |
| Power coefficient of BSA on Vc | 1.14 | 18.1 | | |
| Proportional shit with Phase on Vc | -0.203 | 37.3 | | |
| Proportional shit with Phase on Vp | 1.78 | 42.2 | | |
| Plasma residual variability | | | | |
| Plasma proportional error | 0.035 | 1.8 | | |
| Plasma additive error | 0.0236 | 7.1 | | |
| Urine residual variability | | | | |
| Urine proportional error | 0.127 | 4.3 | | |
| Urine additive error | 5.97 | 8.9 | | |
| Minimum value of the objective function = 18303.73 | | | | |

*Source: Applicant's population PK report (Study 00373-1 Report), Page 66, Table 13*

The primary goodness-of-fit plots for the final population PK model are provided in Figure 4.2-9. These plots demonstrate the adequacy of the model fit across healthy subjects and patients. The VPC plots of vaborbactam plasma concentrations based on Phase 3 data and data from Study 504 are provided in Figure 4.2-10 and Figure 4.2-11 respectively. There was reasonable agreement between the observed data and the median and 5$^{th}$ and 95$^{th}$ percentiles of the simulated data over time following IV dosing of vaborbactam. In contrast to what was observed

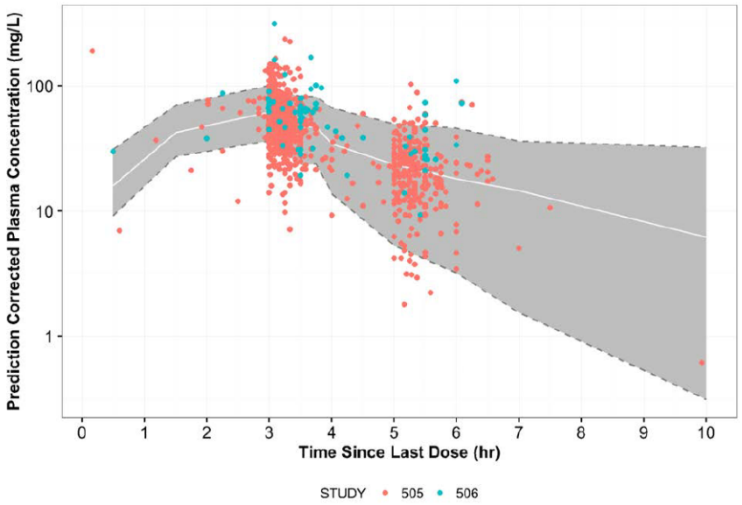
for the meropenem model (Section 4.2.5), the fit of the vaborbactam model was consistently unbiased in subjects with impaired renal function from Study 504.

**Figure 4.2-9. Standard goodness-of-fit plots for the final population PK model for vaborbactam**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 68, Figure 17*

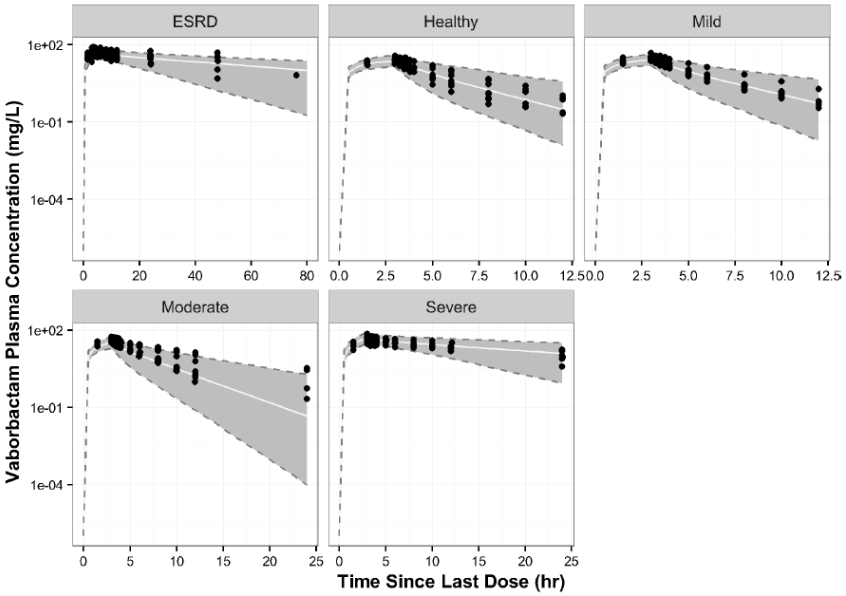
**Figure 4.2-10. Prediction-corrected visual predictive check for the final population PK model for vaborbactam: Phase 3 data and simulations only**




Solid line/grey shaded area: Median/90% confidence interval of model simulations for Phase 3 patients; Solid dots: Observed vaborbactam concentrations from Study 505 (red) and Study 506 (blue).

*Source: Applicant's population PK report (Study 00373-1 Report), Page 70, Figure 18*

**Figure 4.2-11. Visual predictive check plots for the final population PK model for vaborbactam: Study 504 only**



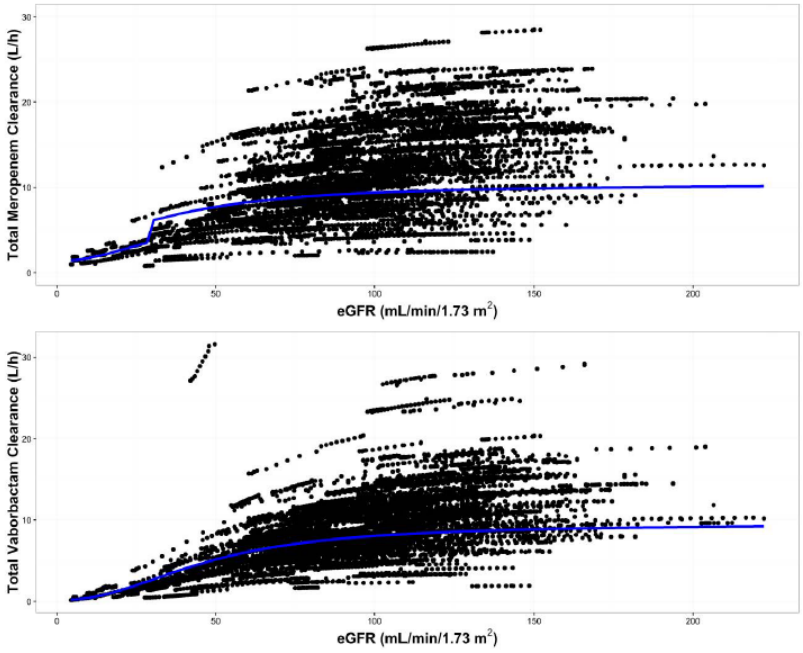

*Source: Applicant's population PK report (Study 00373-1 Report), Page 72, Figure 20*

The impact of subject covariates on the exposures of meropenem and vaborbactam was evaluated and is summarized below for renal impairment, body size, age, sex, and race.

1) Renal impairment

Statistically significant relationships were identified for both meropenem and vaborbactam between clearance and renal function (as approximated by eGFR from the MDRD equation). These relationships are such that drug clearance increases in a sigmoidal fashion with increasing eGFR. Of note, the shape of the two relationships are similar, suggesting that dose adjustments that are made based upon eGFR for meropenem will allow for appropriate dosing of vaborbactam (Figure 4.2-12).

**Figure 4.2-12. Relationships between clearance and eGFR for meropenem (top panel) and vaborbactam (bottom panel)**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 73, Figure 21*

*Reviewer's comments: While eGFR is a covariate for both meropenem and vaborbactam, it should be noted that vaborbactam is almost entirely renally eliminated while meropenem has a fairly meaningful percentage of elimination (30%) due to metabolism. This is illustrated by the observed $AUC_{0\text{-}inf}$ of vaborbactam which increases to a greater degree than meropenem in subjects with severe renal impairment and in ESRD patients with or without hemodialysis. As such, the reviewer does not agree with the Applicant's statement that "* (b) (4) *for subjects with*

*severe renal impairment or ESRD. A similar shape of relationship of eGFR and CL for meropenem and vaborbactam does not inform that the proportional dose adjustments would result in consistent ratio of meropenem and varborbactam exposure in patients with severe renal impairment or ESRD. Instead, the exposures should be simulated to ensure that for any proposed dose adjustments that vaborbactam exposures both attain the identified target threshold while simultaneously not being excessively high. This is further evaluated in the reviewer's simulation assessment of meropeneme and vaborbactam PK.*

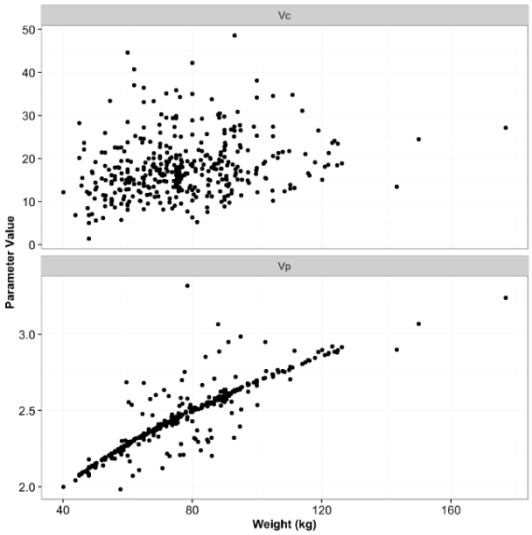
*The Review does not agree with including height as a significant covariate on CL. As both body weight and height were identified as significant covariates on CL based on forward selection, height was finally selected due to larger numerically drop in objective function values. However, the body weight and height were also correlated and height is not clinically relevant to drug elimination. Therefore, including height as significant covariate to CL in the population PK model would lead to improper interpretation of which patient factors are responsible for drug disposition.*

2) Body Size

Two different measures of body size were identified as significant covariates in the population PK models for meropenem (weight) and vaborbactam (height and BSA). For meropenem, body weight was found to be a significant predictor of the IIV in both Vc and Vp. As shown in the upper panel of Figure 4.2-13, the relationship between body weight and Vc is such that there is only a modest increase in Vc with increasing body weight. The relationship between Vp and body weight is tighter overall but the range of Vp values is still small, especially in relation to Vc (lower panel of Figure 4.2-13).

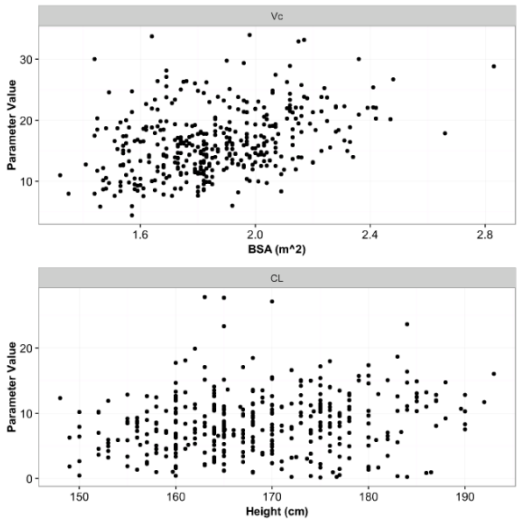
For vaborbactam, BSA was a significant predictor of the IIV in Vc and height was a significant predictor of the IIV in CL (Figure 4.2-14). These relationships are less pronounced than that observed for meropenem. In both cases, the modest nature of the relationships indicates that a dose adjustment on the basis of body size is not warranted.

**Figure 4.2-13. Relationships between body weight and meropenem Vc (upper panel) and Vp (lower panel)**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 75, Figure 22*

**Figure 4.2-14. Relationships between BSA and vaborbactam Vc (upper panel) and height and CL (lower panel)**



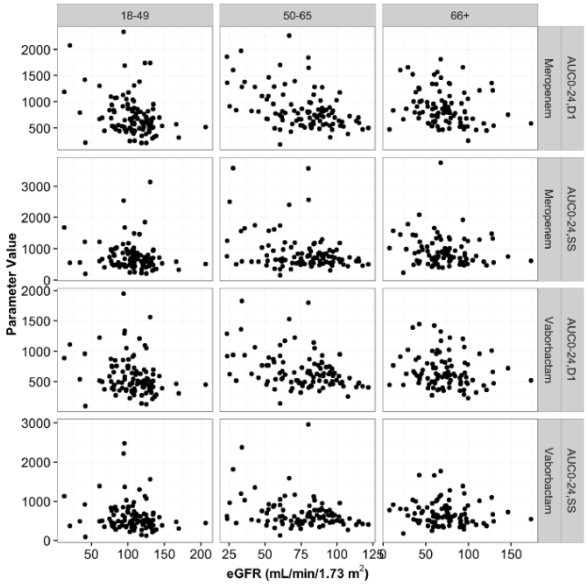

*Source: Applicant's population PK report (Study 00373-1 Report), Page 76, Figure 23*

3) Age

Age was identified as a statistically significant predictor of the IIV in meropenem CL but not vaborbactam CL. Given the correlation between age and renal function, it is important to

consider potential changes in exposure across age groups relative to eGFR. As shown in Figure 4.2-15, there also appears to be no discernible trend for increased exposure in the oldest patients, after taking renal function into account. This suggests that, despite the statistical significance of the relationship between age and meropenem CL, dose adjustment is not warranted on the basis of age for either meropenem or vaborbactam.

**Figure 4.2-15. Scatterplot of Bayesian post-hoc AUC0-24 versus eGFR, stratified by age category (18-49 yr, 50-65 yr, and ≥66 yr) for patients enrolled in the Phase 3 studies**

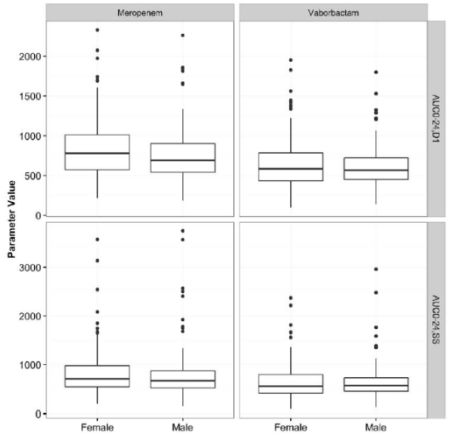



*Source: Applicant's population PK report (Study 00373-1 Report), Page 79, Figure 25*

4) Sex

Sex was not a statistically significant predictor of the IIV in meropenem or vaborbactam PK. As shown in Figure 4.2-16, $AUC_{0-24}$ estimates were similar in males and females for both meropenem and vaborbactam. These data suggest that dose adjustments are not warranted on the basis of sex.

**Figure 4.2-16. Box-and-whisker plots of the post-hoc AUC0-24 estimates for meropenem and vaborbactam in patients enrolled in the Phase 3 studies, stratified by sex**

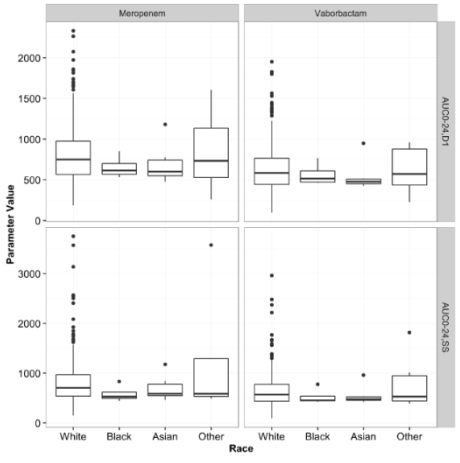



*Source: Applicant's population PK report (Study 00373-1 Report), Page 80, Figure 26*

5) Race

Race was not a statistically significant predictor of the IIV in meropenem or vaborbactam PK. As shown in Figure 4.2-17, $AUC_{0-24}$ estimates were similar in patients regardless of race. These data suggest that dose adjustments are not warranted on the basis of race.

**Figure 4.2-17. Box-and-whisker plots of the post-hoc AUC0-24 estimates for meropenem and vaborbactam in patients enrolled in the Phase 3 studies, stratified by race**




*Source: Applicant's population PK report (Study 00373-1 Report), Page 81, Figure 27*

**Derived Pharmacokinetic Parameters in Phase 3 Patients**

The maximum concentration ($C_{max}$), area under the concentration-time curve over 24 hours on Day 1 and at steady-state ($AUC_{0\text{-}24,\ Day\ 1}$ and, $AUC_{0\text{-}24,\ steady\text{-}state}$), and the alpha and beta half-life ($t_{1/2,\ \alpha}$ and $t_{1/2,\ \beta}$) estimates were generated for all Phase 3 patients included in the population PK analyses using a simulated PK profile for each patient and the individual post-hoc PK parameters from the final population PK models and the mrgsolve package in R.

Summary statistics for the key PK exposure parameters ($C_{max}$, $AUC_{0\text{-}24,\ Day\ 1}$ and, $AUC_{0\text{-}24,\ steady\text{-}state}$) and $t_{1/2,\ \alpha}$ and $t_{1/2,\ \beta}$ are provided in Table 4.2-5 and Table 4.2-6 for meropenem and vaborbactam, respectively.

**Table 4.2-5. Summary [mean (CV%)] of key meropenem PK parameters in Phase 3 patients receiving meropenem 2 g – vaborbactam 2 g q8h derived from the fit of the meropenem population PK model**

| Parameter | Rempex 505 (n = 272[a]) | Rempex 506 (n = 23[a]) | Pooled (n = 295) |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 55.9 (40.1) | 74.0 (32.4) | 57.3 (40.2) |
| $AUC_{0\text{-}24,\ Day\ 1}$ (µg•h/mL) | 621 (46.3) | 821 (39.9) | 637 (46.3) |
| $AUC_{0\text{-}24,\ steady\text{-}state}$ (µg•h/mL) | 628 (57.2)[b] | 907 (36.6) | 650 (56.0)[b] |
| CL (L/h) | 10.9 (59.3) | 6.16 (72.4) | 10.5 (61.3) |
| $t_{1/2,\ \alpha}$ (h) | 0.748 (24.1) | 0.848 (14.9) | 0.756 (23.7) |
| $t_{1/2,\ \beta}$ (h) | 2.19 (110) | 3.67 (79.7) | 2.30 (107) |

Note: Abbreviations are provided in the Abbreviation Listing.
a. Based protocol-mandated dose adjustment guidelines, 28 patients with renal impairment in Study 505 received a dose of meropenem 1 g – vaborbactam 1 g; similarly, 7 patients in Study 506 received reduced doses of meropenem-vaborbactam due to renal impairment
b. $AUC_{0\text{-}24,\ steady\text{-}state}$ estimates were not available for USUBJID 112004508 and 604004502 from Study 505 as these two patients received less than three doses of meropenem-vaborbactam

*Source: Applicant's population PK report (Study 00373-1 Report), Page 82, Table 14*

**Table 4.2-6. Summary [mean (CV%)] of key vaborbactam PK parameters in Phase 3 patients receiving meropenem 2g – vaborbactam 2 g q8h derived from the fit of the vaborbactam population PK model**

| Parameter | Rempex 505 (n = 272[a]) | Rempex 506 (n = 23[a]) | Pooled (n = 295) |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 69.3 (39.1) | 94.7 (37.6) | 71.3 (40.1) |
| $AUC_{0\text{-}24,\ Day\ 1}$ (µg•h/mL) | 803 (45.3) | 1041 (36.0) | 821 (45.0) |
| $AUC_{0\text{-}24,\ steady\text{-}state}$ (µg•h/mL) | 798 (60.6)[b] | 1272 (47.1) | 835 (60.9)[b] |
| CL (L/h) | 8.23 (51.7) | 4.70 (86.3) | 7.95 (54.5) |
| $t_{1/2,\ \alpha}$ (h) | 0.277 (6.34) | 0.28 (6.16) | 0.277 (6.32) |
| $t_{1/2,\ \beta}$ (h) | 2.10 (86.5)[c] | 4.15 (100)[c] | 2.25 (94.7)[c] |

Note: Abbreviations are provided in the Abbreviation Listing.
a. Based protocol-mandated dose adjustment guidelines, 28 patients with renal impairment in Study 505 received a dose of meropenem 1 g – vaborbactam 1 g; similarly, 7 patients in Study 506 received reduced doses of meropenem-vaborbactam due to renal impairment
b. $AUC_{0\text{-}24,\ steady\text{-}state}$ estimates were not available for USUBJID 112004508 and 604004502 from Study 505 as these two patients received less than three doses of meropenem-vaborbactam
c. $t_{1/2,\ \beta}$ estimates were excluded for USUBJID 300001613 and 300001610 from Study 506 and USUBJID 604005502 from Study 505 due to extremely high values (59.0, 26.0, and 33.8 h, respectively).

*Source: Applicant's population PK report (Study 00373-1 Report), Page 83, Table 15*

**Reviewer's independent analysis:**

*The proposed dosing regimen by Applicant was as follows:*

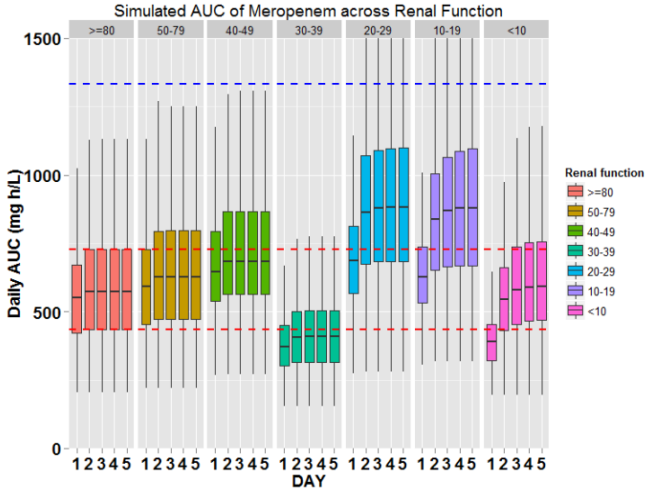
***Table 4.2-7 Applicant proposed dosing regimen for meropenem and vaborbactam***

(b) (4)

*Source: Proposed labeling from original submission by Applicant*

*Daily AUC values of meropenem and vaborbactam were simulated based on the respective population PK model* (b) (4) *. The simulation dataset was created based on the demographics of Phase 3 studies (Study 505 and 506, n=295) and a comparable number of eGFR values was simulated using a uniform distribution in each subpopulation. A total of 100 simulations were run to generate the PK profiles. The mean PK profiles of 100 simulations were used to calculate the daily AUC using the trapezoidal method. Daily AUC for meropenem and vaborbactam based on different eGFR groupings and the dosing in Table 4.2-7 are plotted in Figure 4.2-18As eGFR was used as a covariate in the population PK model, the plots were all based on eGFR cut-off* (b) (4)

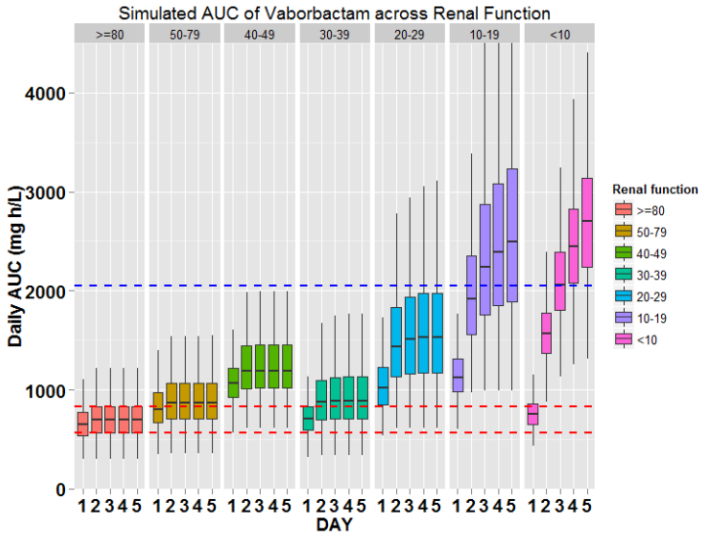
***Figure 4.2-18 Simulated AUC of meropenem across renal function*** [redacted] (b) (4) ***)***




*The red reference line represents the 25% and 75% quantile of daily AUC on Day 5 in patients with eGFR≥80 mL/min/1.73m$^2$; the blue reference line represents clinically observed max AUC at steady state (AUCss).*

*Source: Reviewer's independent analysis*

***Figure 4.2-19 Simulated AUC of vaborbactam across renal function*** [redacted] (b) (4)




*The red reference line represents the 25% and 75% quantile of daily AUC on Day 5 in patients with eGFR≥80 mL/min/1.73m$^2$; the blue reference line represents clinically observed max AUC at steady state (AUCss).*

*Source: Reviewer's independent analysis*

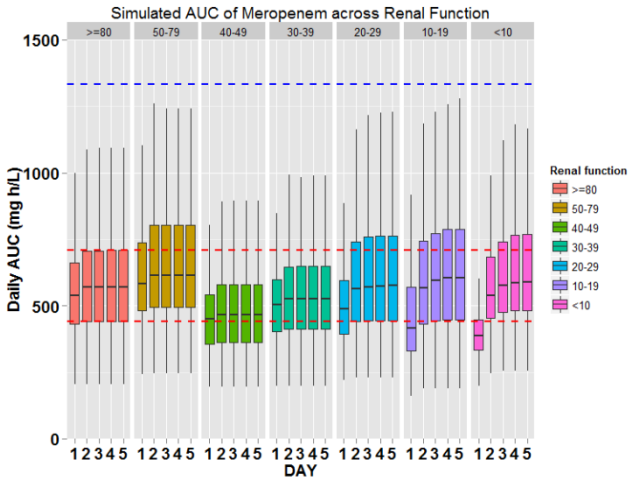
*From Figure 4.2-18, we can clearly observe that with the same dosing regimen, the daily meropenem AUC was much lower for patients with eGFR of 30-39 mL/min/1.73m$^2$ than for patients with eGFR of 20-29 mL/min/1.73m$^2$. This was expected because the developed population PK model for meropenem includes a factor (proportional shift in clearance) in patients with eGFR <30 mL/min/1.73m$^2$ in order to describe the higher than expected clearance in such patients. Given that the model predicts a change in clearance at this eGFR value and as eGFR <30 mL/min/1.73m$^2$ is a commonly used cut-off for classifying patients with severe renal impairment, the review team proposes that the dose adjustment should be based on this cut-off. In addition, the classification cut-off between patients with mild and moderate renal impairment is typically 50-60 mL/min/1.73m$^2$ and between severe and ESRD is 15 mL/min/1.73m$^2$. As such, the team proposes that these cut-offs also be used in the proposed dosing.* (b) (4) *o address this, the review team proposed the following dose regimens based on population PK model.*

***Table 4.2-8 Review team proposed dosing regimen for meropenem and vaborbactam***

| eGFR (mL/min/1.73m$^2$) | Proposed dosing regimen (meropenem-vaborbactam) | Dosing interval |
|---|---|---|
| ≥ 50 | 2 g-2 g | Q8H |
| ≥ 30-49 | 2 g-2 g | Q12H |
| ≥ 15-29 | 1 g -1 g | Q12H |
| <15 | 0.5 g-0.5 g | Q12H |

*Source: Reviewer's independent analysis*

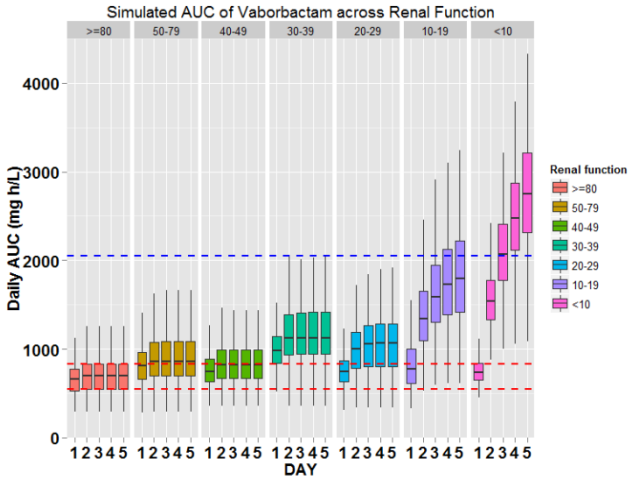
***Figure 4.2-20 Simulated AUC of meropenem across renal function (FDA proposal)***




*The red reference line represent the 25% and 75% quantile of daily AUC on Day 5 in patients with eGFR≥80 mL/min/1.73m$^2$; the blue reference line represent clinically observed max at steady state (AUCss).*

*Source: Reviewer's independent analysis*

***Figure 4.2-21 Simulated AUC of vaborbactam across renal function (FDA proposal)***




*The red reference line represent the 25% and 75% quantile of daily AUC on Day 5 in patients with eGFR≥80 mL/min/1.73m$^2$; the blue reference line represent clinically observed max at steady state (AUCss).*

*Source: Reviewer's independent analysis*

*The review team proposed dosing regimen would result in comparable meropenem exposure across renal function. However, the proposed dosing regimen may not be appropriate in ESRD patients as the impact of hemodialysis was not considered in this simulation. A lower exposure was expected on hemodialysis day. On the other hand, the exposure of vaborbactam based on review team proposed dosing regimen appeared to be high in patients with eGFR<20 mL/min/1.73m$^2$.*

## 4.3 Target Attainment Analysis

Results from the animal infection model identified PK/PD targets of meropenem to be percentage of time during the dosing interval that free-drug meropenem concentrations exceed the MIC ($\%T_{Cf>MIC}/\tau$) for meropenem with the presence of 8 µg/mLvaborbactam. The magnitude of free-drug plasma meropenem% $T_{Cf>MIC}/\tau$ targets associated with net bacterial stasis, and a 1- and 2- log10 CFU reduction from baseline was determined to be 30, 35 and 45%, respectively, for Gram-negative bacilli based on data for other carbapenems studied in neutropenic murine infection models. PK/PD target of vaborbactam was the ratio of free-drug plasma vaborbactam 24 hour AUC to meropenem-vaborbactam MIC (fAUC:MIC). A free-drug plasma vaborbactam AUC:MIC ratio target for efficacy of (b) (4), which was calculated using the meropenem-vaborbactam MIC value, was used to evaluate the target attainment for vaborbactam. This PK/PD target corresponds to net bacterial stasis of KPC-producing Enterobacteriaceae isolates at 24 hours in an in vitro hollow-fiber infection model based on studies using challenge panel of KPC-producing Enterobacteriaceae isolates and combination therapy with meropenem.

*Reviewer's comment: It is not appropriate to evaluate the target attainment based on vaborbactam AUC:MIC ratio of (b) (4). This PK/PD target was obtained using an in vitro hollow-fiber infection model. The in vitro hollow-fiber infection model can be used to determine an estimate of the type of PK/PD index that is most associated with the effect of bacteria reduction but is not a good model to predict the magnitude of the PK/PD target. We suggest the use of the 24h free vaborbactam AUC:MIC ratio of 38 as vaborbactam PK/PD target to evaluate the target attainment at the proposed dose since this value was determined from the neutropenic murine thigh infection model and based on a 1-log kill of target pathogens. Meropenem 2g and vaborbactam 2g q8h 3-hour infusion dose regimen produced high AUC of vaborbactam which results in the vaborbactam fAUC:MIC of 2,252 or higher in patients with baseline KPC-Producing Enterobacteriaceae, which is over 50-fold higher than vaborbactam AUC:MIC ratio target of 38. No specific analyses for vaborbactam target attainment are presented below.*

Using the previously-developed population PK models for meropenem and vaborbactam described in Section 4.2, non-clinical PK-PD targets for efficacy, *in vitro* surveillance data, and Monte Carlo simulation, percent probabilities of PK-PD target attainment were evaluated for the Applicant's proposed meropenem-vaborbactam dosing regimens administered to simulated patients with varying degrees of renal function (Table 4.2-7).

Two sets of simulations were performed. For the first simulation, a population of 4,000 simulated patients with varying degrees of renal function was generated. First, CrCL values were obtained using a uniform probability distribution for the following renal function groups, each of which contained 1,000 simulated patients:

- ≥40-150 mL/min
- ≥20 to 40 mL/min
- ≥10 to 20 mL/min
- ≥0 to 10 mL/min

*Reviewer's comment: It is not appropriate to assume a uniform probability distribution of CrCL in the wide range of ≥40 to 150 mL/min that covers subjects with normal renal function and mild renal impairment. However, this may not impact the target attainment assessment in patients with normal renal function. Target attainment in patients with normal renal function was assessed in a second simulation that was conducted based on 3000 simulated patients with cUTI by resampling the dataset from Study 505.*

Within each renal function group, the following methods and assumptions were utilized for the generation of patient covariate distributions:

- Age was simulated according to a uniform distribution between 18 to 90 years (n = 1,000) and applied to each renal function group in order to maintain the same age distribution.

- Weight, height, and BSA values were generated by applying a bootstrapping method in which 1,000 patients were randomly sampled with replacement from the Phase 3 PK analysis population. This set of demographic values was applied to each renal function group in order to maintain the same covariate distributions.

- The eGFR value for each simulated patient was set equal to their CrCL (in mL/min/1.73m$^2$).

Using a baseline measure of serum creatinine (Scr), creatinine clearance (CrCL) was calculated according to the method described by Cockcroft and Gault and was normalized by body surface area (BSA), as shown in the following equations:

Males: CrCL (mL/min/1.73 m$^2$) = (140 - age [yr]) × weight [kg] ÷ 72 × SCr [mg/dL] × (1.73 ÷ BSA [m$^2$])

Females: CrCL (mL/min/1.73 m$^2$) = male value × 0.85

For the second simulation, the PK-PD analysis population consisting of Phase 3 patients with cUTI and Enterobacteriaceae isolated at baseline was used to generate a simulated clinical population. The simulated patient population was generated by including multiple records for the demographics of each patient such that the total sample size for the simulated patient population was at least 3,000. The majority of patients in this simulated population represent patients with CrCL >50 mL/min since the simulated patients were created by resampling the demographic data of Phase 3 patients, where about 92% of patients had CrCL >50 mL/min. Hence, the distribution

of CrCL in the simulated patients is expected to follow the same pattern from the Phase 3 patients.

Using the population PK models for meropenem and vaborbactam, individual total-drug plasma concentration time profiles were generated for each drug at the Applicant's proposed dose regimens. Concentration time profiles were summarized from 0 to 24 hours after the first dose and over a 24-hr interval at steady-state conditions. Using a protein binding estimate of 2% for meropenem, free-drug plasma meropenem concentrations were determined by multiplying the individual predicted total-drug meropenem plasma concentrations by 0.98. Meropenem % $T_{Cf>MIC}/\tau$ was determined for each patient by counting the total number of free-drug concentrations that were above a given MIC value, multiplying this number by the time interval between simulated concentrations (0.1 hour), and then dividing this product by the 24 hours. Meropenem % $T_{Cf>MIC}/\tau$ was determined for fixed MIC values in the range of meropenem-vaborbactam MIC values for Enterobacteriaceae, KPC-producing Enterobacteriaceae, and *P. aeruginosa* based on recent *in vitro* surveillance data (Table 4.3-1). Using a protein binding estimate of 33% for vaborbactam, total-drug plasma vaborbactam AUC values were adjusted to free-drug plasma vaborbactam AUC values using a free fraction of 0.67. Vaborbactam fAUC values from 0 to 24 hours were used to estimate the probability of PK/PD target attainment analyses. Vaborbactam fAUC:MIC ratios were determined by dividing fAUC values by fixed meropenem-vaborbactam MIC values in the range of meropenem-vaborbactam MIC values for Enterobacteriaceae, KPC-producing Enterobacteriaceae, and *P. aeruginosa* based on recent *in vitro* surveillance data (Table 4.3-1).

**Table 4.3-1. Meropenem and meropenem-vaborbactam MIC distributions for Enterobacteriaceae, KPC-producing Enterobacteriaceae, and *P. aeruginosa* based on in vitro surveillance data collected from regions worldwide**

| Drug | Number of isolates at MIC (µg/mL; cumulative %) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <0.03 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | >32 | $MIC_{50}$ | $MIC_{90}$ |
| **All Enterobacteriaceae[a] (n=11,559)** | | | | | | | | | | | | | | | |
| Meropenem | 5595 (48.4) | 3799 (81.3) | 1321 (92.7) | 338 (95.6) | 73 (96.3) | 44 (96.6) | 36 (96.9) | 44 (97.3) | 48 (97.7) | 44 (98.1) | 62 (98.7) | 48 (99.1) | 107 (100) | 0.03 | 0.06 |
| Meropenem-vaborbactam | 4551 (39.4) | 5193 (84.3) | 1208 (94.7) | 271 (97.1) | 89 (97.9) | 69 (98.5) | 50 (98.9) | 28 (99.1) | 14 (99.3) | 9 (99.3) | 22 (99.5) | 32 (99.8) | 23 (100) | 0.03 | 0.06 |
| **All KPC-producing Enterobacteriaceae[b] (n=1,331)** | | | | | | | | | | | | | | | |
| Meropenem | – | – | – | – | – | – | 5 (0.40) | 58 (4.70) | 116 (13.4) | 159 (25.4) | 200 (40.4) | 179 (53.9) | 614 (100) | 32 | >32 |
| Meropenem-vaborbactam | 515 (38.7) | 68 (43.8) | 78 (49.7) | 89 (56.3) | 195 (71.0) | 186 (85.0) | 110 (93.2) | 55 (97.4) | 22 (99.0) | 7 (99.5) | 2 (99.7) | 1 (99.8) | 3 (100) | 0.12 | 1 |
| **All *P. aeruginosa*[a] (n=2,806)** | | | | | | | | | | | | | | | |
| Meropenem | 15.0 (0.50) | 47.0 (2.20) | 194 (9.10) | 321 (20.6) | 540 (39.8) | 477 (56.8) | 293 (67.2) | 193 (74.1) | 170 (80.2) | 189 (86.9) | 173 (93.1) | 64 (95.4) | 130 (100) | 0.50 | 16 |
| Meropenem-vaborbactam | 30 (1.10) | 65 (3.40) | 193 (10.3) | 310 (21.3) | 525 (40.0) | 462 (56.5) | 298 (67.1) | 186 (73.7) | 187 (80.4) | 167 (86.4) | 187 (93.0) | 71 (95.5) | 125 (100) | 0.50 | 16 |

a. Enterobacteriaceae, KPC-producing Enterobacteriaceae, and *P. aeruginosa* isolates were collected as part of the 2014-2015 SENTRY Antimicrobial Surveillance Program [14, 15, 16, 17].
b. Shaded cells represent the MIC values up to and/or including the $MIC_{90}$ value.

*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 47, Table 7*

For each meropenem % $T_{Cf>MIC}/\tau$ target and meropenem-vaborbactam MIC distribution for the three isolate collections evaluated, the overall percent probability of PK/PD target attainment was determined by multiplying the percent probability of PK/PD target attainment at a given MIC value with the probability of occurrence of that MIC value. The sum of these percentages was then determined.

Results of PK/PD target attainment analysis against Enterobacteriaceae, are presented below.

***Enterobacteriaceae***

*Renal Impairment Patient Simulation:* Percent probabilities of PK/PD target attainment by MIC and overall for meropenem-vaborbactam dosing regimens assigned by renal function group are shown in Table 4.3-2. These assessments were performed based on three meropenem PK/PD targets (i.e., 30, 35, and 45% $T_{Cf>MIC}/\tau$) for meropenem and meropenem-vaborbactam MIC distributions for Enterobacteriaceae, stratified by renal function group. Percent probabilities of PK/PD target attainment based on 45% $T_{Cf>MIC}/\tau$ , overlaid on meropenem-vaborbactam MIC distribution for Enterobacteriaceae isolates, is shown in Figure 4.3-1.

As shown in Table 4.3-2, percent probabilities of PK-PD target attainment based on the above-described three meropenem % $T_{Cf>MIC}/\tau$ targets ranged from 95.1 to 100% across simulated patients by renal function group at an MIC value of 8 µg/mL. At an MIC value of 16 µg/mL,

percent probabilities of PK-PD target attainment based meropenem % $T_{Cf>MIC}/\tau \geq$ of 30%, 35% and 45% ranged from 83 to 98.4%, 79.1 to 97.2%, and 67.9 to 91.3%, respectively, across simulated patients by renal function group.

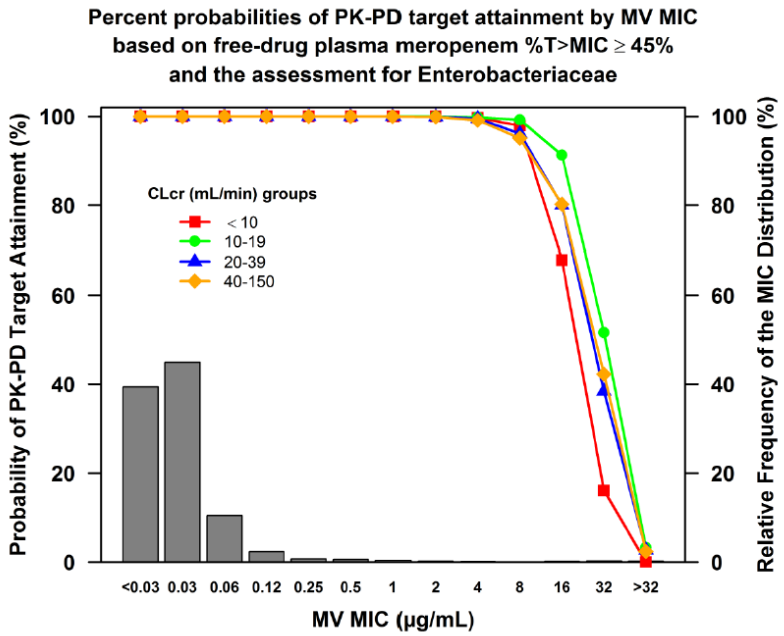
**Table 4.3-2. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall for meropenem-vaborbactam dosing regimens based on the assessment of three meropenem% $T_{Cf>MIC}/\tau$ targets and 11,559 Enterobacteriaceae isolates among simulated patients by renal function group**

| 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 defined by CLcr range (mL/min) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Free-drug plasma meropenem %T>MIC ≥ 30% | | | | Free-drug plasma meropenem %T>MIC ≥ 35% | | | | Free-drug plasma meropenem %T >MIC ≥ 45% | | | |
| | 0-10 | 10-20 | 20-40 | 40-150 | 0-10 | 10-20 | 20-40 | 40-150 | 0-10 | 10-20 | 20-40 | 40-150 |
| 0.12 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 0.25 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 0.5 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 1 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 99.9 | 99.9 |
| 4 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 99.7 | 99.8 | 99.5 | 99.1 |
| 8 | 99.6 | 100 | 100 | 100 | 99.4 | 99.9 | 99.7 | 99.9 | 97.9 | 99.2 | 96.1 | 95.1 |
| 16 | 83.0 | 98.4 | 94.0 | 98.4 | 79.1 | 97.2 | 90.0 | 95.9 | 67.9 | 91.3 | 80.0 | 80.2 |
| 32 | 23.0 | 70.5 | 52.2 | 72.3 | 20.7 | 64.9 | 47.2 | 62.2 | 16.1 | 51.6 | 38.4 | 42.3 |
| 64 | 0.2 | 6.6 | 5.0 | 7.6 | 0.1 | 5.1 | 4.3 | 5.4 | 0 | 3.3 | 2.7 | 2.4 |
| Overall[b] | 99.6 | 99.7 | 99.7 | 99.7 | 99.5 | 99.7 | 99.6 | 99.7 | 99.5 | 99.7 | 99.6 | 99.6 |

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

*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 67, Table 17*

**Figure 4.3-1. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for meropenem-vaborbactam dosing regimens based on meropenem% $T_{Cf>MIC}/\tau \geq 45\%$ among simulated patients by renal function group, overlaid upon the meropenem-vaborbactam MIC distribution for 11,559 Enterobacteriaceae isolates**




*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 70, Figure 5*

*cUTI Patient Simulation:* As shown in Table 4.3-3, percent probabilities of PK-PD target attainment based on the above-described three meropenem % $T_{Cf>MIC}/\tau$ targets for the population of simulated patients with cUTI ranged from 94.4 to 100% at an MIC value of 8 µg/mL. At an MIC value of 16 µg/mL, percent probabilities of PK-PD target attainment based on meropenem % $T_{Cf>MIC}/\tau$ of 30, 35, and 45% were 97.7, 94.3, and 78.1%, respectively. Overall percent probabilities of PK/PD target attainment based on the above-described three meropenem % $T_{Cf>MIC}/\tau$ targets and the meropenem-vaborbactam MIC distribution for Enterobacteriaceae isolates ranged from 99.6 to 99.7%. Percent probabilities of PK/PD target attainment by MIC based on the above described three % $T_{Cf>MIC}/\tau$ targets for simulated cUTI patients, overlaid upon the meropenem-vaborbactam MIC distribution for Enterobacteriaceae isolates, are shown in Figure 4.3-2.

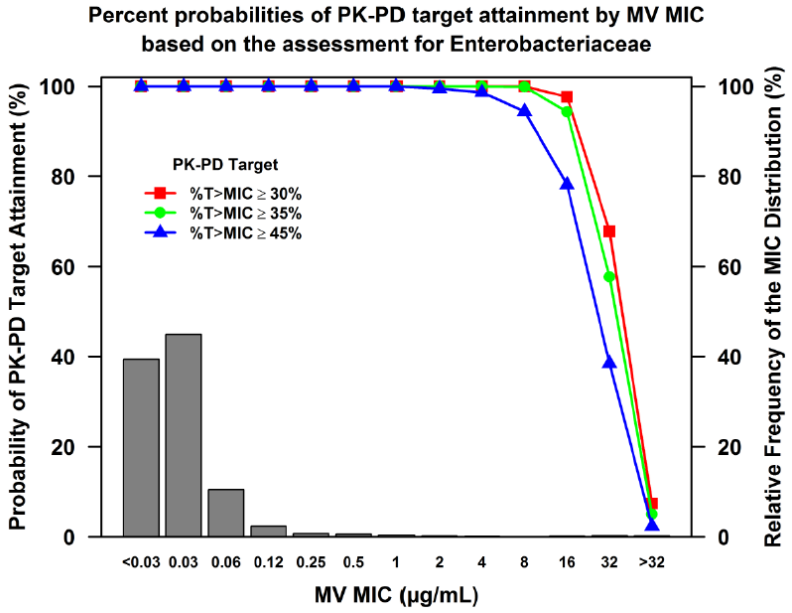
**Table 4.3-3. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall for meropenem-vaborbactam dosing regimens based on the assessment of three meropenem % $T_{Cf>MIC}/\tau$ targets and 11,559 Enterobacteriaceae isolates among simulated patients with cUTI**

| MV[a] MIC (µg/mL) | Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for free-drug plasma meropenem %T>MIC targets | | |
|---|---|---|---|
| | %T>MIC ≥ 30 | %T>MIC ≥ 35 | %T>MIC ≥ 45 |
| 0.12 | 100 | 100 | 100 |
| 0.25 | 100 | 100 | 100 |
| 0.5 | 100 | 100 | 100 |
| 1 | 100 | 100 | 100 |
| 2 | 100 | 100 | 99.5 |
| 4 | 100 | 100 | 98.6 |
| 8 | 100 | 99.9 | 94.4 |
| 16 | 97.7 | 94.3 | 78.1 |
| 32 | 67.8 | 57.7 | 38.4 |
| 64 | 7.40 | 4.97 | 2.34 |
| Overall[b] | 99.7 | 99.7 | 99.6 |

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

*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 71, Table 18*

**Figure 4.3-2. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for meropenem-vaborbactam dosing regimens based on meropenem % $T_{Cf>MIC}/\tau$ targets among simulated patients with cUTI, overlaid upon the meropenem-vaborbactam MIC distribution for 11,559 Enterobacteriaceae isolates**




*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 72, Figure 6*

***KPC-Producing Enterobacteriaceae***

*Renal Impairment Patient Simulation*: Table 4.3-4 shows the percent probabilities of PK/PD target attainment by MIC at meropenem-vaborbactam dosing regimens assigned by renal function group based on the assessment of three meropenem % $T_{Cf>MIC}/\tau$ targets, 30, 35, and 45%, and meropenem-vaborbactam MIC distributions for KPC-producing Enterobacteriaceae. Percent probabilities of PK-PD target attainment based on meropenem 45% $T_{Cf>MIC}/\tau$ , overlaid upon meropenem-vaborbactam MIC distribution for KPC-producing Enterobacteriaceae isolates, are shown in Figure 4.3-3. Percent probabilities of PK-PD target attainment based on meropenem % $T_{Cf>MIC}/\tau$ targets ranged from 95.1 to 100%, across simulated patients by renal function group at an MIC value of 8 µg/mL. At an MIC value of 16 µg/mL, percent probabilities of PK/PD target attainment based on free-drug plasma meropenem % $T_{Cf>MIC}/\tau$ of 30, 35, and 45% ranged from 80.6 to 98.2%, 76.1 to 96.9%, and 63.5 to 91.0%, respectively, across simulated patients by renal function group.

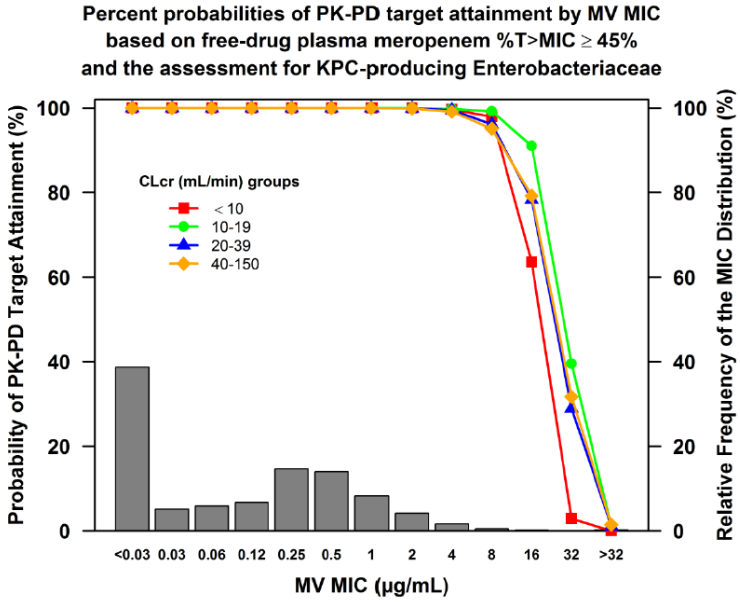
**Table 4.3-4. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall for meropenem vaborbactam dosing regimens based on the assessment of three meropenem % $T_{Cf>MIC}/\tau$ targets and 1,331 KPC-producing Enterobacteriaceae isolates among simulated patients by renal function group**

| 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 defined by CLcr range (mL/min) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Free-drug plasma meropenem %T>MIC ≥ 30% | | | | Free-drug plasma meropenem %T>MIC ≥ 35% | | | | Free-drug plasma meropenem %T>MIC ≥ 45% | | | |
| | 0-10 | 10-20 | 20-40 | 40-150 | 0-10 | 10-20 | 20-40 | 40-150 | 0-10 | 10-20 | 20-40 | 40-150 |
| 0.12 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 0.25 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 0.5 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 1 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 99.9 | 99.9 |
| 4 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 99.7 | 99.8 | 99.5 | 99.1 |
| 8 | 99.6 | 100 | 100 | 100 | 99.4 | 99.9 | 99.7 | 99.9 | 97.9 | 99.2 | 96.1 | 95.1 |
| 16 | 80.6 | 98.2 | 93.2 | 98.0 | 76.1 | 96.9 | 88.6 | 95.6 | 63.5 | 91.0 | 78.3 | 79.2 |
| 32 | 8.7 | 61.5 | 42.0 | 61.1 | 6.0 | 54.6 | 37.3 | 50.4 | 2.9 | 39.5 | 28.9 | 31.7 |
| 64 | 0 | 3.3 | 2.5 | 5.4 | 0 | 2.2 | 2.0 | 4.0 | 0 | 1.2 | 1.1 | 1.5 |
| Overall[b] | 99.7 | 99.8 | 99.7 | 99.8 | 99.7 | 99.7 | 99.7 | 99.7 | 99.6 | 99.7 | 99.7 | 99.7 |

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

*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 74, Table 19*

**Figure 4.3-3. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for meropenem-vaborbactam dosing regimens based on meropenem 45% $T_{Cf>MIC}/\tau$ among simulated patients by renal function group, overlaid upon the meropenem-vaborbactam MIC distribution for 1,331 KPC-producing Enterobacteriaceae isolates**




*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 77, Figure 9*

*cUTI Patient Simulation.* As shown in Table 4.3-5, percent probabilities of PK/PD target attainment based on the above-described three meropenem % $T_{Cf>MIC}/\tau$ targets for the population of simulated patients with cUTI ranged from 94.4 to 100% at an MIC value of 8 µg/mL. At an MIC value of 16 µg/mL, percent probabilities of PK/PD target attainment ranged from 76.3 to 97.0%. Percent probabilities of PK/PD target attainment by MIC based on the above described three free-drug plasma meropenem % $T_{Cf>MIC}/\tau$ targets for t simulated cUTI patients, overlaid upon meropenem vaborbactam MIC distribution for KPC-producing Enterobacteriaceae isolates, are shown in Figure 4.3-4.

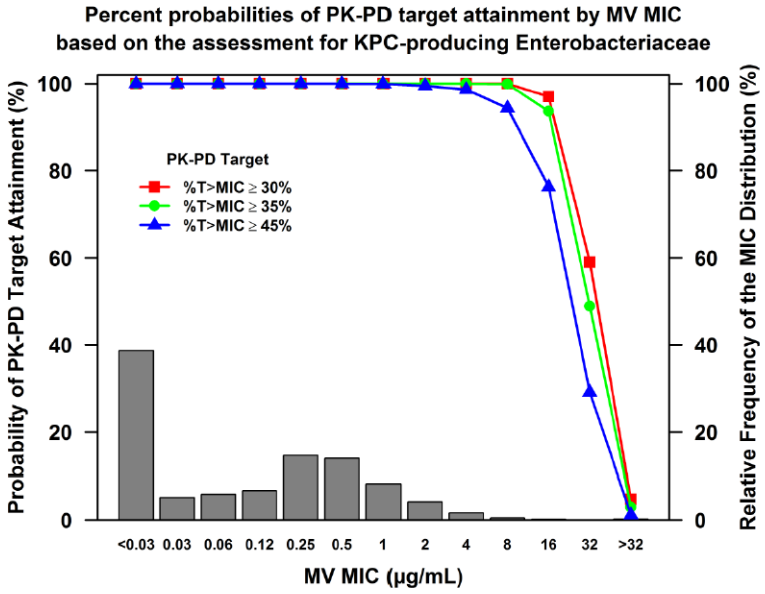
**Table 4.3-5. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall for meropenem-vaborbactam dosing regimens based on the assessment of three meropenem % $T_{Cf>MIC}/\tau$ targets and 1,331 KPC producing Enterobacteriaceae isolates among simulated patients with cUTI**

| MV[a] MIC (µg/mL) | Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for free-drug plasma meropenem %T>MIC targets | | |
|---|---|---|---|
| | %T>MIC ≥ 30 | %T>MIC ≥ 35 | %T>MIC ≥ 45 |
| 0.12 | 100 | 100 | 100 |
| 0.25 | 100 | 100 | 100 |
| 0.5 | 100 | 100 | 100 |
| 1 | 100 | 100 | 99.9 |
| 2 | 100 | 100 | 99.5 |
| 4 | 100 | 100 | 98.6 |
| 8 | 100 | 99.9 | 94.4 |
| 16 | 97.0 | 93.7 | 76.3 |
| 32 | 59.0 | 48.9 | 29.1 |
| 64 | 4.74 | 2.92 | 1.20 |
| Overall[b] | 99.7 | 99.7 | 99.6 |

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

*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 78, Table 20*

**Figure 4.3-4. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for meropenem-vaborbactam dosing regimens based on meropenem % $T_{Cf>MIC}/\tau$ targets among simulated patients with cUTI, overlaid upon the meropenem-vaborbactam MIC distribution for 1,331 KPC-producing Enterobacteriaceae isolates**




*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 79, Figure 10*

*Reviewer's comments: Regarding P. aeruginosa, vaborbactam does not increase the potency of meropenem against clinical isolates of P. aeruginosa and meropenem-vaborbactam in vitro activity against P. aeruginosa is similar to that of meropenem alone, probably because P. aeruginosa does not express Class A β-lactamase. Considering that the meropenem PK/PD target for P. aeruginosa is same as or lower than that for Enterobacteriaceae, the probability of target attainment for P. aeruginosa would be same as or greater than for Enterobacteriaceae.*

(b) (4)

*The Applicant did not perform a probability of target attainment analysis for vaborbactam. Instead, the Applicant made the following statement to claim that target attainment for vaborbactam was sufficient: Vaborbactam fAUC:MIC ratios in patients with baseline KPC-Producing Enterobacteriaceae were 2,252 or higher, which is over 50-fold higher than vaborbactam fAUC:MIC ratio target of 38 identified in mice thigh infection model to restore 1-log bacterial reduction effect of meropenem against KPC-Producing Enterobacteriaceae.*

*Even though vaborbactam exposure appears to be sufficient to achieve the PK/PD target at the proposed dose regimen, we would recommend the following method to evaluate the probability of target attainment for a β-lactamase inhibitor, e.g., vaborabactam: 1) conduct PK simulation in certain number of patients (e.g., 3000 cUTI patients) and obtain free vaborbactam $AUC_{0\text{-}24h}$; 2) then calculate the ratio $fAUC_{0\text{-}24h}$/MIC for each patient according to MIC distribution (e.g., 0.12-64 μg/mL) of KPC-producing Enterobacteriaceae; 3) determine the PTA at each MIC by calculating the percentage of patients who achieve the target $fAUC_{0\text{-}24h}$/MIC at that MIC.*

*In addition, the Reviewer conducted an independent analysis for assessing the probability of target attainment at the FDA recommended dose regimens. Briefly, using the Applicant's developed population PK model, a Monte Carlo simulation of meropenem plasma concentrations was conducted in 3540 patients according to the demographics from the two Phase 3 studies and the following renal function groups with eGFR 1) ≥50 mL/min/1.73m$^2$; 2) ≥40 to 50 mL/min/1.73m$^2$; 3) ≥30 to 40 mL/min/1.73m$^2$; 4) ≥20 to 30 mL/min/1.73m$^2$; 5) ≥10 to 20 mL/min/1.73m$^2$; 6) <10 mL/min/1.73m$^2$. A uniform probability distribution of eGFR values was generated in each renal function group. One hundred simulations were performed with the population PK model using NONMEM and the mean PK profile for each subject was calculated using R. Probability of PK/PD target attainment by meropenem-vaborbactam MIC range of 0.125 to 128 μg/mL in each renal function group was determined based on three meropenem % $T_{Cf>MIC}/\tau$ targets, 30, 35, and 45%, which are associated with net-stasis, 1-$\log_{10}$ and 2- $\log_{10}$ bacterial reduction in neutropenic mouse thigh infection model. Results of the probability of PK/PD target attainment are presented in Table 4.3-8. At the FDA recommended dose adjustment, percent probability of PK/PD target attainment based on the above-described three*

*meropenem PK/PD targets are all >97% across simulated patients in each renal function group at an MIC value of 8 μg/mL.*

***Table 4.3-8. Probability of PK/PD target attainment by meropenem-vaborbactam MIC at the FDA recommended dosing regimens based on three meropenem %*** $\mathbf{T_{Cf>MIC}/\tau}$ ***targets among simulated patients by renal function group*** **(by eGRF, mL/min/1.73m$^2$)**

| MIC (μg/ml) | eGFR ≥ 50 | | | eGFR 40-50 | | | eGFR 30-40 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Stasis | 1-log | 2-log | Stasis | 1-log | 2-log | Stasis | 1-log | 2-log |
| 0.12 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0.25 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 8 | 1 | 1 | 1 | 1 | 1 | 0.99 | 1 | 1 | 0.99 |
| 16 | 0.99 | 0.98 | 0.94 | 0.96 | 0.92 | 0.75 | 0.97 | 0.95 | 0.81 |
| 32 | 0.59 | 0.53 | 0.39 | 0.48 | 0.37 | 0.18 | 0.55 | 0.44 | 0.24 |
| 64 | 0.06 | 0.05 | 0.03 | 0.02 | 0.02 | 0.01 | 0.05 | 0.03 | 0.02 |

***Table 4.3-8. Probability of PK/PD target attainment by meropenem-vaborbactam MIC at the FDA recommended dosing regimens based on three meropenem % $T_{Cf>MIC}/\tau$ targets among simulated patients by renal function group* (by eGRF, mL/min/1.73m$^2$) (Continued)**

| MIC(µg/ml) | eGFR 20-30 | | | eGFR 10-20 | | | eGFR <10 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Stasis | 1-log | 2-log | Stasis | 1-log | 2-log | Stasis | 1-log | 2-log |
| 0.12 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0.25 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 8 | 1 | 1 | 0.99 | 0.99 | 0.99 | 0.97 | 0.99 | 0.99 | 0.97 |
| 16 | 0.93 | 0.90 | 0.81 | 0.86 | 0.83 | 0.75 | 0.87 | 0.84 | 0.79 |
| 32 | 0.41 | 0.36 | 0.27 | 0.37 | 0.34 | 0.27 | 0.35 | 0.31 | 0.28 |
| 64 | 0.04 | 0.03 | 0.03 | 0.04 | 0.03 | 0.03 | 0.03 | 0.02 | 0.02 |

## 4.4 Exposure-Response Analyses

Exposure-response analysis for efficacy was conducted by Applicant based on two Phase 3 studies (Study 505 and 506). Two analyses were carried out using data from the following populations:

- All patients with infections due to KPC-producing Enterobacteriaceae; all body sites and indications included.
- All patients with cUTIs in Study 505 and Study 506.

For each set of PK/PD analyses, univariable relationships between each of the efficacy endpoints and the percentage of the dosing interval that free-drug meropenem concentrations were above the MIC ($\%T_{Cf>MIC}/\tau$) were evaluated. The meropenem-vaborbactam MIC value of the baseline infecting pathogen was used to calculate meropenem $\%T_{Cf>MIC}/\tau$. Given that vaborbactam only potentiates the meropenem MIC value in KPC-producing isolates, the PK/PD index of interest for the PK/PD analyses for efficacy based on data from all patients with cUTI was meropenem $\%T_{Cf>MIC}/\tau$. For the PK/PD analyses based on data from all patients with KPC-producing Enterobacteriaceae, regardless of infection type, univariable relationships between each of the efficacy endpoints and the ratio of free-drug plasma vaborbactam area under the concentration-time curve (AUC) to meropenem-vaborbactam MIC (fAUC:MIC ratio) were also considered.

Univariable PK/PD relationships were examined using data from both study populations using chi-square or Fisher's exact tests for categorical independent variables. The thresholds used to define the PK/PD categorical independent variables were those that were optimally determined for a given efficacy endpoint. Multivariable analyses were considered for any efficacy endpoint for which a univariable relationship was identified.

Patients with KPC-Producing Enterobacteriaceae. For the Microbiologically Evaluable (ME) population of patients with CRE infection, only 11 patients had sufficient PK data and at least one carbapenemase-producing organism at baseline; of these, only 3 had KPC-producing Enterobacteriaceae and all had cUTIs or acute pyelonephritis. As shown in Table 4.4-1, the meropenem MICs for these isolates ranged from 8- >64 µg/ml; meropenem-vaborbactam MICs were < 0.25 µg/ml in these strains. Vaborbactam fAUC/MIC in these patients exceeded nonclinical targets; the vaborbactam fAUC:MIC ratio based upon the meropenem-vaborbactam MIC exceeded a value of 2,252, which is over 50-fold higher than the nonclinical targets for efficacy in mouse infection models. The corresponding meropenem plasma concentrations exceeded the meropenem-vaborbactam MIC for 100% of the dosing interval. All of these patients had a clinical response at early, EOIVT, and TOC endpoints. In view of the low number of patients and high PK/PD exposures, no further analyses were conducted to examine a statistical relationship between drug exposures and efficacy.

**Table 4.4-1: Listing of Three Patients from Studies 505 and 506 with KPC-producing Enterobacteriaceae at Baseline**

| Patient ID | Pathogen | Infection type | MIC[a] | | Carbapenamase | Day 1 free-drug plasma meropenem %T > MIC[a] | | Day 1 free-drug plasma vaborbactam AUC:MIC ratio | Clinical response[b] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | M | MV | | M | MV | | Day 3 | EOIVT | EOT | TOC | LFU |
| REMPEX-505-076-003-510 | *Providencia stuartii* | cUTI with removable source of infection | 8 | ≤0.06 | KPC-2 | 100 | 100 | 20,232 | S | S | S | | |
| REMPEX-506-300-001-608 | *Klebsiella pneumoniae* | cUTI | 32 | 0.06 | KPC-3 | 37.9 | 100 | 13,616 | S | | S | S | S |
| REMPEX-506-376-003-602 | *Klebsiella pneumoniae* | Acute pyelonephritis | >64 | 0.25 | KPC-3 | 0 | 100 | 2,252 | | | S | S | |

[a]: M=meropenem MIC, MV=meropenem-vaborbactam MIC
[b]:S=Success, F=Failure

*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 60, Table 14*

Patients with cUTIs. For patients with cUTIs, there were 175 patients within the ME population with sufficient PK data to enable post-hoc estimation of meropenem and vaborbactam PK parameters and exposures in the patients; of these, 154 patients had an Enterobacteriaceae as the baseline pathogen.

Table 4.4-2 shows the summary statistics for the PK/PD indices for meropenem and vaborbactam for all cUTI patients, and the subset with Enterobacteriaceae infection. Over 90% of patients with cUTI, including the subset of patients with Enterobactericeae, achieved 100% $T_{Cf>MIC}/\tau$ based on meropenem-vaborbactam MICs; 96.6 and 98.7% of patients with cUTI and the subset with Enterobacteriaceae, respectively, achieved a non-clinical meropenem PK/PD target for a 2-$\log_{10}$ CFU reduction from baseline (i.e., 45% $T_{Cf>MIC}/\tau$). The percentage of patients in these two populations that achieved successful responses for the efficacy endpoints assessed across study visits, including TOC, ranged from 93 to 100% for clinical response and 76.3 to 100% for microbiological response. Overall response at both EOIVT and TOC was 100 and 79% for patients with cUTI and the subset with Enterobacteriaceae, respectively. Accordingly, univariable PK/PD relationships for efficacy endpoints based on data for these analysis populations were not identified.

These analyses demonstrated that 97% of patients with cUTI achieved the plasma PK/PD target of meropenem for a 2-$\log_{10}$ CFU reduction from baseline (i.e., 45% $T_{Cf>MIC}/\tau$). Given the high urinary excretion of meropenem and vaborbactam, high urinary drug concentrations in addition to the high systemic exposures and relatively low MIC values likely contributed to the lack of identification of PK/PD relationships for efficacy. Together, these data support the proposed meropenem-vaborbactam dosing regimen.

**Table 4.4-2: Summary of Meropenem-Vaborbactam PK/PD Indices and Meropenem and Meropenem-Vaborbactam MICs for All cUTI Patients and Patients with Enterobacteriaceae**

| Exposure Measures | Analysis Populations | | | |
|---|---|---|---|---|
| | All patients (n=175) | | Patients with Enterobacteriaceae (n=154) | |
| | Mean (CV%) | Median (min, max) or $MIC_{50/90}$ (min, max) | Mean (CV%) | Median (min, max) or $MIC_{50/90}$ (min, max) |
| Meropenem MIC (µg/mL) | | ≤0.5/8 (≤0.12, >64) | | ≤0.5/≤0.5 (≤0.5, >64) |
| Free meropenem %T> meropenem MIC | 94.3 (20.6) | 100 (0, 100) | 96.9 (15.4) | 100 (0, 100) |
| Meropenem-vaborbactam MIC (µg/mL) | | ≤0.06/0.25 (≤0.06, >64) | | ≤0.06/0.12 (≤0.06, >64) |
| Free meropenem %T> meropenem-vaborbactam MIC | 96.0 (17.3) | 100 (0,100) | 98.9 (9.6) | 100 (0,100) |
| Free plasma vaborbactam Day 1 24h$AUC_{0-24}$ | 524.4 (44.7) | 468.3 (125.0, 1562) | 528.3 (43.5) | 468.6 (145.3, 1,562) |
| Free plasma vaborbactam Day 1 24h $AUC_{0-24}$:MIC ratio[a] | 7,290 (61.7) | 6,975 (4.22, 26,033) | 8,171 (49.4) | 7,567 (17.2, 26,033) |

Source: Study 00373-2, Table 12
[a] Calculated using a meropenem-vaborbactam MIC value for the baseline pathogen.
CV% = percent coefficient of variation; MIC = minimum inhibitory concentration; T = time; $AUC_{0-24}$:MIC = ratio of area under the concentration-time curve from time 0 to 24 hours to the MIC

*Source: Applicant's PK/PD Target Attainment Report (Study 00373-2 Report), Page 59, Table 13*

*Reviewer's comment: Studies from murine thigh infection model identified 30% to 45% $T_{Cf>MIC}/\tau$ to be the PK/PD target for meropenem and the free drug area under the concentration-time curve of vaborbactam:meropenem-vaborbactam MIC ratio (fAUC/MIC) of at least 38 to be the PK/PD target for vaborbactam. Analysis of probability of target attainment showed that 97% of patients with cUTI achieved the plasma meropenem PK/PD target of 45% $T_{Cf>MIC}/\tau$. The vaborbactam fAUC/MIC is also over 50-fold higher than the nonclinical vaborbactam PK/PD target (i.e., 38 of fAUC/MIC). In addition, overall response at EOIVT was 100% and 79% for patients with cUTI and the subset with Enterobacteriaceae, respectively.*

*Given the high target attainment rates for both meropenem and vaborbactam, along with high clinical or microbiological responses in these patients, meropemen and vaborbactam exposure in Phase 3 studies may have reached a plateau of the exposure-response curve for efficacy for the Enterobacteriaceae MICs included in the analysis. We agree that no apparent relationship*

*between clinical or microbiological response rates and PK/PD targets could be identified from the available data.*

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## 4.5 Review of Individual Study Reports

The following clinical pharmacology related individual studies were reviewed.

| Section | Study No. | Study information |
|---|---|---|
| 4.5.1 | | Animal models to determine the PK/PD targets |
| 4.5.2 | 402 | Single and multiple ascending dose study for vaborbactam |
| 4.5.3 | 501 | Single and multiple ascending dose study for meropenem and vaborbactam |
| 4.5.4 | 503 | PK; plasma, human epithelial lining fluid, alveolar macrophage |
| 4.5.5 | 504 | PK; renal impairment |

### 4.5.1 Animal Models to Determine the PK/PD Targets of Meropenem and Vaborbactam

**Meropenem**

*PK/PD of Meropenem against Enterobacteriaceae and Pseudomonas aeruginosa*

As meropenem has been used in patients for decades, the PK/PD relationship for meropenem has been studied extensively *in vitro*, in animals, and in humans. The relationship that best describes the antibacterial activity of meropenem is the proportion of the dosing interval for which the free drug levels exceed the MIC, or $\%T_{Cf>MIC}/\tau$; the magnitude of meropenem $\%T_{Cf>MIC}/\tau$ associated with net bacterial stasis, and a 1- and 2- $\log_{10}$ CFU reduction from baseline was determined to be 30, 35 and 45%, respectively, for Gram negative bacilli based on data from studies in neutropenic murine infection models.

**Vaborbactam**

*Identification of the Critical Concentration of Vaborbactam*

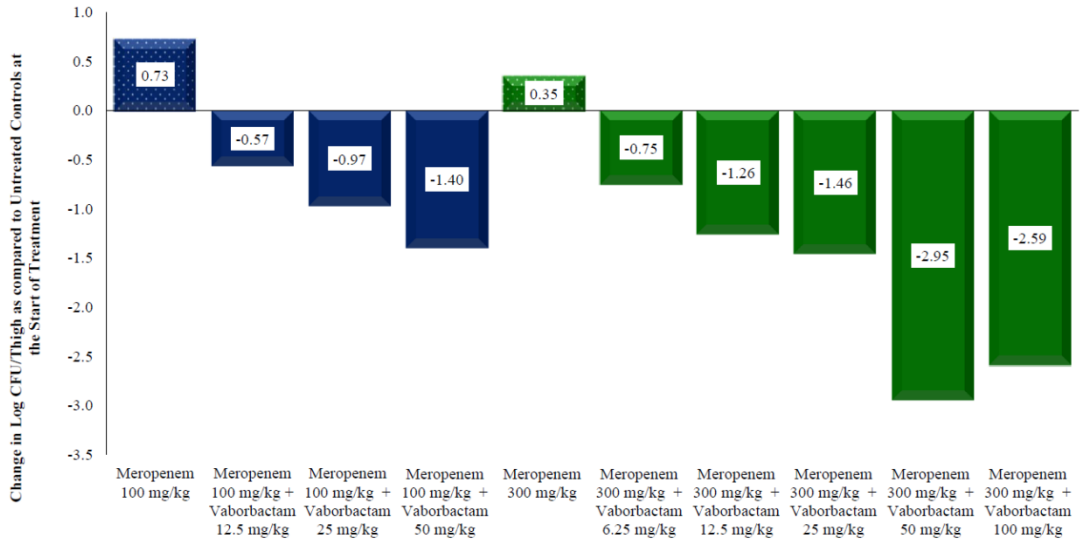
Meropenem activity was determined alone and in combination with vaborbactam at fixed concentrations of 4 μg/mL or 8 μg/mL against KPC-producing Enterobacteriaceae using 991 isolates collected worldwide in 2014-2015. The study demonstrated that 96.2% and 99.5% of KPC producing strains were inhibited by 8 μg/mL of meropenem in the presence of 4 μg/mL and 8 μg/mL of vaborbactam, respectively. In other studies using multiple strains of KPC-producing Enterobacteriaceae in the presence of a fixed 8 μg/mL of meropenem and varying concentrations of vaborbactam, the critical concentration of vaborbactam was determined for its effect in either reducing the frequency of resistance emergence to $<10^{-8}$ or preventing regrowth of pathogens at 24 hours. In both studies, the critical concentration of vaborbactam was found to be 8 μg/mL.

*Vaborbactam PK/PD in the Mouse Thigh Infection Model with Carbapenem-Resistant Enterobacteriaceae*

The antibacterial effects of meropenem in combination with vaborbactam were compared to those of meropenem alone in a neutropenic mouse thigh infection model using humanized dosage regimens against carbapenem-resistant KPC-producing strains. Dose-ranging of meropenem and vaborbactam was also explored in the neutropenic mouse thigh infection model against four carbapenem resistant *K. pneumonia* strains and one carbapenem resistant *E. cloacae* strain. Meropenem administered at 100 mg/kg, 200 mg/kg or 300 mg/kg every 2 hours over a 24 hour period in mice produced an exposure equivalent to 1 g, 1.5 g or 2 g of meropenem administered q8h by 3 hour infusion in humans, respectively. Vaborbactam administered at 6.25 mg/kg, 12.5 mg/kg, 25 mg/kg, 50 mg/kg and 100 mg/kg every 2 hours over a 24 hour period in mice produced an exposure equivalent to 0.25 g, 0.5 g, 1 g, 2 g, or 4 g of vaborbactam

administered q8h by 3 hour infusion in humans, respectively. Figure 4.5.1-1 shows the activity of meropenem alone and in combination with different doses of vaborbactam against a carbapenem-resistant *K. pneumoniae* strain with a meropenem-vaborbactam (in the presence of vaborbactam at fixed 8 µg/mL) MIC of 4 µg/mL. Using fixed doses of meropenem, the amount of bacterial killing increased with increasing doses of vaborbactam. These data show that vaborbactam potentiates the *in vivo* activity of meropenem against KPC-producing strains at drug exposures that are obtainable in humans.

**Figure 4.5.1-1: Activity of Meropenem Alone and in Combination with Vaborbactam against Carbapenem-resistant *K. pneumoniae* KP1094 in a 24 h Neutropenic Mouse Thigh Infection Model**




MIC for *K. pneumoniae* KP109: Meropenem: alone ≥64 µg/mL; with 4 µg/mL Vaborbactam = 32 µg/mL; with 8 µg/mL Vaborbactam = 4 µg/mL

The following relationships between each PK and PD parameter were explored to identify the PK/PD target of vaborbactam in neutropenic mouse thigh infection model: 1) the percentage of the time over 24 h that free vaborbactam concentrations were greater than 4 ($\%T_{C>4\mu g/mL}/\tau$) or 8 µg/mL ($\%T_{C>8\mu g/mL}/\tau$); 2) the 24 h area under the free vaborbactam concentration-time curve [fAUC]: and 3) free vaborbactam AUC/meropenem-vaborbactam MIC ratio (fAUC/MIC) versus the reduction in the log number of CFU per thigh or per mL between time zero and 24 h after the start of treatment. The above PK and PD relationships were analyzed by using the sigmoid maximum reduction ($E_{max}$) PD model:

Reduction in log CFU/thigh or mL = $[(E_{max} \times X^g)/(EC_{50}{}^g + X^g)] - E_0$;

where $E_{max}$ is the maximum reduction in the log number CFU/thigh or mL, X is the PK/PD parameter being examined (e.g., AUC/MIC), $EC_{50}$ is the X value corresponding to 50% of the $E_{max}$, $E_0$ is the effect when X is equal to 0 (untreated control animals), and g is a sigmoidicity factor which controls the steepness of the curve. The best model for each data set was established by using the Akaike criterion. The data for the four *K. pneumoniae* isolates and the single *E. cloacae* isolate tested in the neutropenic mouse thigh infection model were pooled for the analysis. These pooled data were used to determine the relationship between the change in Log CFU/thigh and vaborbactam $\%T_{C>4\mu g/mL}/\tau$, $\%T_{C>8\mu g/mL}/\tau$, fAUC, and fAUC/MIC. The relationships between each parameter and change in Log CFU are shown in Figure 4.5.1-2.

The goodness of fit and the relationship required to achieve stasis, 1-log of bacterial killing (1-log kill) and 2-logs of bacterial killing (2-log kill) are provided in Table 4.5.1-1. Overall, none of the indices described the neutropenic mouse thigh infection model data very well. However, of the PK/PD indices evaluated, the ratio of vaborbactam fAUC/ MIC appears to provide the best overall fit to the data. The magnitude of fAUC/MIC required for bacteriastasis or for 1-log of bacterial killing is 9 and 38, respectively.

**Figure 4.5.1-2: Vaborbactam PK/PD Relationships in the Neutropenic Mouse Thigh Infection Model**

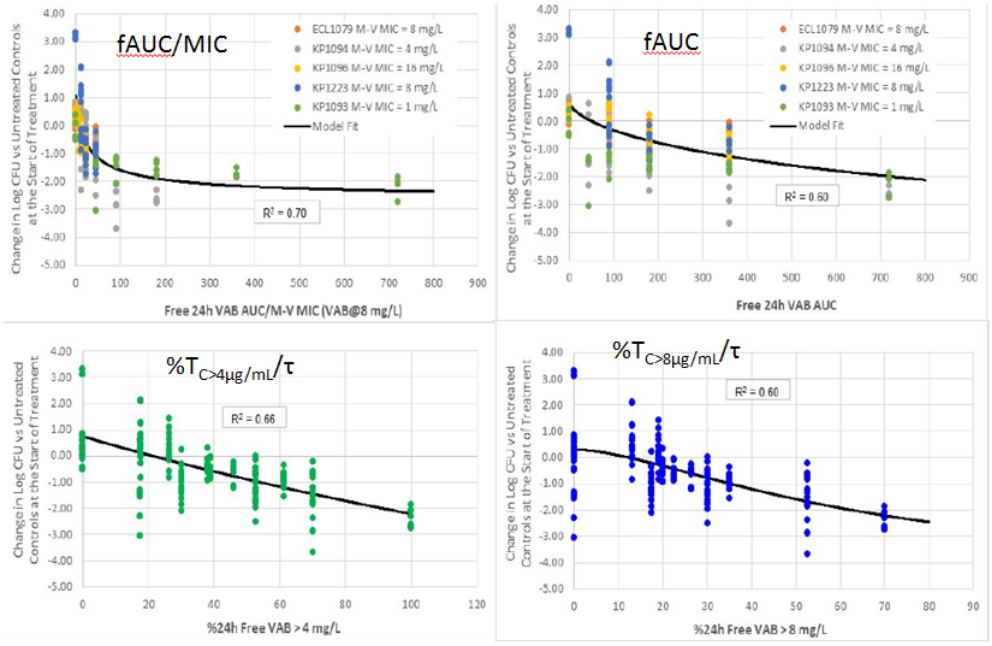


**Table 4.5.1-1: PK/PD Indices, Goodness of Fit, and Magnitude Required for Effect in the Neutropenic Mouse Thigh Infection Model**

| PK-PD Index | Goodness of Fit ($R^2$) | Magnitude Required for | | |
|---|---|---|---|---|
| | | Stasis | 1-log kill | 2-log kill |
| %Free >4 µg/mL | 0.66 | 21 | 54 | 95 |
| %Free>8 µg/mL | 0.60 | 12 | 35 | 62 |
| Free 24h AUC | 0.60 | 50 | 267 | 720 |
| Free 24h AUC/M-V MIC | 0.70 | 9 | 38 | 220 |

*Reviewer's comments: For approved β-lactamase inhibitors (BLI), the PK/PD targets are usually described as % time of the dosing interval that free BLI concentration are above a threshold concentration for restoring the antibacterial activity of the combined β-lactam anti-bacterial agent. Results from the Applicant's study using mouse thigh infection model with carbapenem-resistant Enterobacteriaceae showed that fAUC/meropenem-vaborbactam MIC appears to provide a slightly better fit to the data than other PK/PD parameters. Using the ratio of the vaborbactam fAUC/meropenem-vaborbactam MIC as the PK/PD index can be explained with an assumption that a higher AUC of vaborbactam is needed to restore the activity of meropenem against a pathogen with a higher meropenem-vaborbactam MIC, or a lower AUC of vaborbactam is reqired to restore the activity of meropenem against a pathogen with a lower meropenem-vaborbactam MIC . The caveat in selecting vaborbactam fAUC/meropenem-vaborbactam MIC as the PK/PD index is the lack of sufficient data in the range of more than 2-log kill (Figure 4.5.1-2). However, since high exposures of free vaborbactam ($10^{th}$ percentile of free $AUC_{0\text{-}24,\ steady\text{-}state}$ = 369 µg•h/mL, Study 506) were observed in the most of the infected patients at the Applicant's proposed dose regimens, it is expected that targets of 1-$log_{10}$ kill by all tested four PK/PD indices could be achieved at the Applicant's proposed dose regimens.*

*Pharmacodynamics of Vaborbactam in an In Vitro Hollow Fiber Pharmacodynamic Model*

The PD of vaborbactam were studied in combination with a fixed exposure of meropenem in an *in vitro* hollow-fiber PD model using humanized dosage regimens against KPC-producing strains including thirteen clinical isolates of *K. pneumoniae*, three clinical isolates of *E. cloacae*, and one *E.coli* isolate. The dosage regimen for meropenem was designed to simulate the exposure equivalent to a human dose of 2 g administered by a 3 hour infusion q8h.

The relationship between each PK and PD parameter (i.e., $\%T_{C>4\mu g/mL}/\tau$ or $\%T_{C>8\mu g/mL}/\tau$, the fAUC, and the fAUC/MIC) and the reduction in the log number of CFU per mL between time zero and 24 h after the start of treatment were analyzed by using the sigmoid maximum reduction ($E_{max}$) PD model:

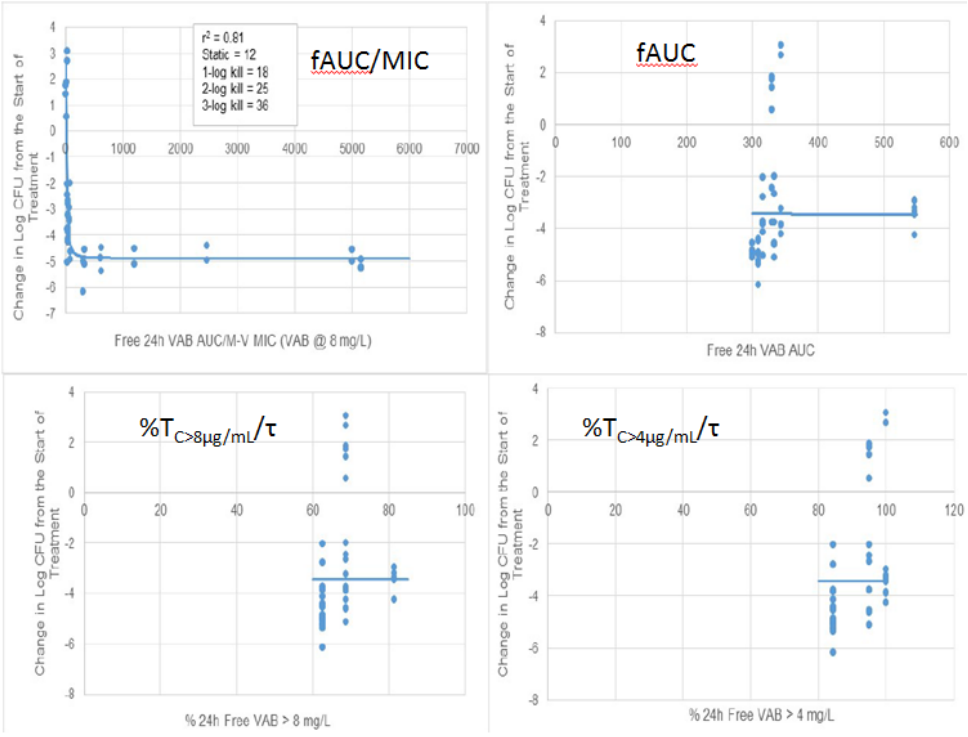
Reduction in log CFU/thigh or mL = $[(E_{max} \times X^g)/(EC_{50}{}^g + X^g)] - E_0$;

where $E_{max}$ is the maximum reduction in the log number CFU/thigh or mL, X is the PK/PD parameter being examined (e.g., fAUC/MIC), $EC_{50}$ is the X value corresponding to 50% of the $E_{max}$, $E_0$ is the effect when X is equal to 0 (untreated control animals), and g is a sigmoidicity factor which controls the steepness of the curve. The best model for each data set was established by using the Akaike criterion.

The data for the 13 *K. pneumoniae* isolates, the three *E. cloacae* isolates, and the single *E. coli* isolate tested in the *in vitro* hollow fiber PK/PD model were pooled for the analysis. As with the animal model data, these pooled data were used to determine the relationship between the change in log CFU/mL and $\%T_{C>4\mu g/mL}/\tau$, $\%T_{C>8\mu g/mL}/\tau$, vaborbactam fAUC, and vaborbactam fAUC/MIC.

The starting inocula used in all of the in vitro hollow-fiber PK/PD model studies was ~$10^8$ CFU/mL. Using high inocula, the objective was not only to determine the linked PK/PD parameter, but to also determine the magnitude of that parameter required to suppress resistance development/regrowth in the model. As shown in the Figure 4.5.1-3, fitting of $E_{max}$ model could only be accomplished when fit to the fAUC/MIC. This PK/PD parameter correlates very well with bacterial killing in the model with an $R^2$ of 0.81.

**Figure 4.5.1-3: Vaborbactam PK/PD in the *In Vitro* Hollow Fiber Model**



*Vaborbactam PK/PD Modeling Summary*

Based on data generated from 5 strains of carbapenem-resistant, KPC-containing Enterobacteriaceae in the neutropenic mouse thigh infection model and 17 strains of carbapenem-resistant, KPC-containing Enterobacteriaceae in the *in vitro* hollow fiber PK/PD model, 24 h free vaborbactam AUC/meropenem-vaborbactam MIC ratio best correlated with bacteriostasis and antibacterial killing in the mouse and *in vitro* models. As shown in Table 4.5.1-2, the magnitude of the ratio of the 24 h free vaborbactam AUC to the meropenem-vaborbactam MIC required for bacteriostasis in the neutropenic mouse thigh infection model and in the *in vitro* hollow fiber PK/PD model are 9 and 12, respectively.

**Table 4.5.1-2: Summary of the 24h Free Vaborbactam AUC/Meropenem-Vaborbactam MIC ratio in the Neutropenic Mouse Thigh Infection and In Vitro Hollow Fiber Models**

| Model | Ratio of the 24h Free Vaborbactam AUC:Meropenem-Vaborbactam MIC | | | | |
|---|---|---|---|---|---|
| | Stasis | 1-log kill | 2-log kill | 3-log kill | Regrowth Suppression |
| In Vitro Hollow Fiber Model | 12 | 18 | 25 | 36 | >24 |
| Neutropenic Mouse Thigh Infection Model | 9 | 38 | 220 | Not Observed | Not Observed |

*Reviewer's comments: The in vitro hollow-fiber infection model can provide an estimate of the type of PK/PD index that is most associated with the effect of bacterial reduction but is not a good model to predict the PK/PD target (i.e., the magnitude of PK/PD needed for specific reduction of bacterial load). We recommend using the magnitude of vaborbactam fAUC:MIC required for bacteriostasis or 1-log kill from the neutropenic mouse thigh infection model, i.e., 9 or 38, respectively, to select dose regimens of meropemen-vaboractam and to conduct the target attainment analysis.*

### *4.5.2 Study 402: Single and Multiple Ascending Dose - Vaborbactam*

**Title:** A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Ascending Single- and Multiple-Dose Study of the Safety, Tolerability, Pharmacokinetics of Intravenous RPX7009 (Vaborbactam) in Healthy Adult Subjects

**Information Regarding the Clinical Trial Site and Duration of the Trial:** The trial was conducted by Rempex Pharmaceuticals, Inc. from December 03, 2012 to August 16, 2013 with the final report date of June 5, 2014.

**Objectives:**

The primary objective was to assess the safety and tolerability of single and multiple intravenous doses of vaborbactam when administered to healthy adult subjects.

The secondary objectives were to assess the PK of single and multiple intravenous doses of vaborbactam when administered to healthy adult subjects.

**Trial Design:**

This was a first-in-human, randomized, placebo-controlled, double blind, sequential single-ascending dose (SAD) and multiple-ascending dose (MAD) study evaluating the PK and safety of vaborbactam in 80 adult healthy subjects. A total of 10 dose cohorts were enrolled in the study, with 6 subjects randomized to receive vaborbactam and 2 subjects randomized to receive placebo in each cohort. Subjects randomized to vaborbactam in the first 6 cohorts received the following single doses of vaborbactam administered as a 3-hour constant rate IV infusion: 250, 500, 750, 1000, 1250 mg and 1500 mg. The remaining 4 cohorts (Cohorts 7 to 10) received the following doses of vaborbactam as a 3-hour infusion, first as a single dose and subsequently every 8 hours for 7 days: 250 mg, 1000, 1500 and 2000 mg. Subjects could only participated in one cohort.

In MAD cohorts 7-9, each subject received a single IV dose of vaborbactam or placebo on Day 1, followed by multiple IV doses of vaborbactam starting on Day 2 at 24 hours after the start of infusion on Day 1, with the last dose in the morning of Day 8. In SAD/MAD cohort 10, each subject received a single IV dose of vaborbactam or placebo on Day 1, followed by multiple IV doses of vaborbactam or placebo starting on Day 4 at 72 hours after the start of infusion on Day 1, with the last dose on the morning of Day 10. For Cohort 10, a longer period of observation was implemented prior to the initiation of the multiple dosing since the 2000 mg dose was not included in the SAD phase.

Dose levels for single dose cohorts were as follows:

Cohort 1: 250 mg vaborbactam or matching placebo
Cohort 2: 500 mg vaborbactam or matching placebo
Cohort 3: 750 mg vaborbactam or matching placebo
Cohort 4: 1000 mg vaborbactam or matching placebo
Cohort 5: 1250 mg vaborbactam or matching placebo
Cohort 6: 1500 mg vaborbactam or matching placebo

Dose levels for multiple dose cohorts were as follows:

Cohort 7: 250 mg vaborbactam or matching placebo
Cohort 8: 1000 mg vaborbactam or matching placebo
Cohort 9: 1500 mg vaborbactam or matching placebo
Cohort 10: 2000 mg vaborbactam or matching placebo

**Excluded Medications, Restrictions:**

- Use of any prescription medication (with the exception of hormonal contraceptives or hormone replacement therapy for females) within 14 days prior to Day 1.
- Documented hypersensitivity reaction or anaphylaxis to any medication.
- Use of any over-the-counter (OTC) medication, including herbal products and vitamins, within the 7 days prior to Day 1. Up to 2 grams per day of acetaminophen was allowed for acute events at the discretion of the PI.
- Calculated creatinine clearance less than 80 mL/min (Cockcroft-Gault method) at screening or check-in (Day -1).
- Consumption of foods and beverages containing the following substances were prohibited as indicated:
    - Xanthines/caffeine 24 hours prior to Day 1 until the end-of-study (Day 4)
    - Alcohol 48 hours prior to Day 1 until the end-of-study (Day 4)

**Rationale for Doses Used in the Trial:**

For vaborbactam, the NOAEL in dogs was 300 mg/kg/day, and the NOAEL in rats was 1000 mg/kg/day. The corresponding human equivalent doses (HEDs) for the NOAEL in dogs and rats were calculated to be 167 and 161 mg/kg/day, respectively (approximately the same for both dogs and rats). The maximum recommended starting dose (1/10th the human equivalent dose) would be 16.7 mg/kg, approximately 1000 mg, for a 60 kg male. A conservative safe human starting dose was chosen at a lower level of 250 mg, which provides a safety factor of approximately 40. The doses were to be escalated until the maximum upper clinical dose of 2000 mg was reached in order to provide a broad range of doses available for the subsequent studies in healthy volunteers in a combination Phase 1 study with meropenem.

In the multiple dose cohorts (Cohorts 7-10), the initial dose of 250 mg (Cohort 7) was supported by the adverse effect profile of single doses of vaborbactam up to 1500 mg in the SAD portion. The subsequent dose could be escalated only if safety and tolerability from the previous cohort was acceptable.

**Drugs Used in the Trial:** A frozen solution form of vaborbactam (Lot No. 1-FIN-1521) was used in the single dose phase of the study (Cohorts 1-6).

A (b) (4) form of vaborbactam (Lot No. CL3-001) was used in the multiple dose phase of the study (Cohorts 7-10).

**Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis:**

Pharmacokinetic blood sampling performed on Day 1 (all Cohorts), Day 8 (Cohorts 7-9 only) and Day 10 (Cohort 10 only) was done at the following time points: pre-dose, 1.5, 3, 3.167, 3.333, 3.5, 3.75, 4, 5, 6, 7, 8, 12 and 24 hours post-dose. In addition, blood samples for steady-state analysis were collected at pre-dose on Days 3, 5, and 7 for Cohorts 7-9 and at pre-dose on Days 5, 7, and 9 for Cohort 10.

Pharmacokinetic urine sampling was performed on Day 1 for all cohorts, and following the last dose of the multiple dose phase for Cohorts 7-10, before dosing and during the following intervals: 0-4, 4-8, 8-12, 12-24, 24-48 hours after dosing.

On Day 1, urine was obtained from the 24-hour urine interval to measure creatinine clearance.

*Bioanalytical method (see Section 4.1 for details for the methods and method validation data):* Drug concentrations of vaborbactam in plasma and urine were determined with validated high-performance liquid chromatography with mass spectrometric detection.

| Analyte | Matrix | Validation Report | Bioanalytical Report |
|---|---|---|---|
| Vaborbactam | Plasma | # MC12B-0022 | # MC12B-0025 |
| Vaborbactam | Urine | #MC12B-0023 | #MC12B-0025 |

*Reviewer's Comment: Based on results from method validation and bioanalytical reports, both analytical methods met the acceptable criteria specified in the FDA Guidance to Industry: Bioanalytical Method Validation.*

*Pharmacokinetic Assessments:* PK parameters include: $C_{max}$, $T_{max}$, $AUC_{0-□}$, $AUC_{0-T}$, $AUC_{0-inf}$, $T_{1/2}$, $CL_t$, $CL_{t,ss}$, $V_{ss}$, $V_d$, $Ae_{(0-24)}$, $Ae_{(0-□□)}$, %Excreted in the urine and $CL_R$.

*Statistical Analysis:* Dose proportionality was examined using AUC and $C_{max}$ values of vaborbactam on Day 1 and Day 7 by linear regression model and an ANOVA model. The equation for linear regression model fit is: AUC or $C_{max} = \mu + \beta \times dose$

An ANOVA model was applied on the dose-normalized AUC and the dose-normalized AUC between dose cohorts – statistically different from zero was used (no significant group means difference indicates a proportionality; p-value ≥ 0.05). An ANOVA model was also used to investigate the effect of dose on CL and $V_d$ for both the single and the multiple doses.

**Results:**

*Subject Demographics and Disposition:* There was a total of 80 subjects enrolled in the study, with 79 subjects completing the study. One subject in Cohort 8 (randomized to vaborbactam) terminated the study prior to completion as follows:

- Subject 02261: Participant withdrew consent due to personal reasons following the first dose of vaborbactam (1000 mg).

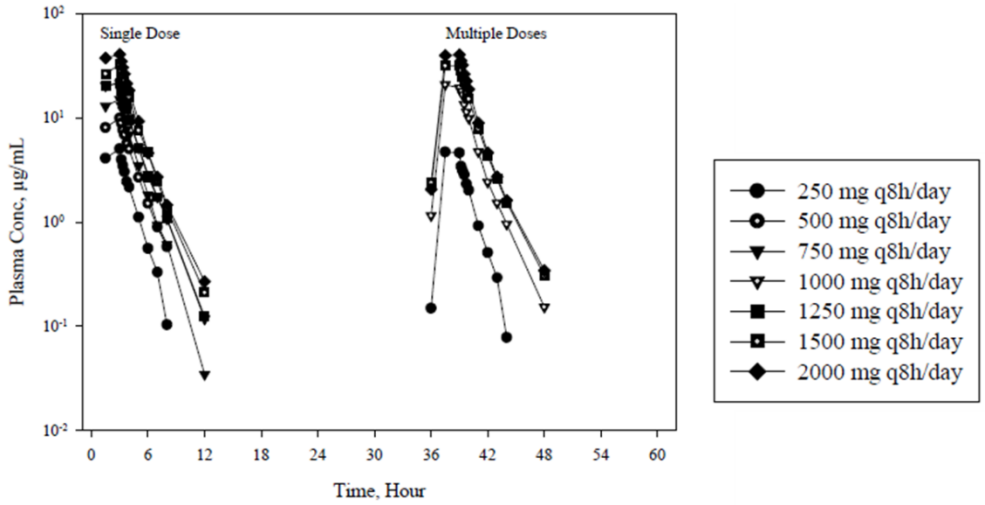
*Pharmacokinetic and Statistical Analysis:* The key PK parameters for the multiple-dose cohorts are shown in Table 1. Maximum concentrations ($C_{max}$) for vaborbactam were achieved at the end of the 3-hour infusion. Vaborbactam exposure [$C_{max}$ and area under the plasma concentration-time curve from 0 to 8 hours ($AUC_{0-8}$)] increased in a dose-proportional manner with increasing dose (Table 1 and Figure 1). There was no evidence of accumulation with multiple doses, consistent with the short terminal half-life (<2 hours). Both the volume of distribution ($V_d$) and plasma clearance ($CL_t$) were independent of dose. The mean percent of vaborbactam excreted in the urine within 48 hours of dosing was greater than 79% across all dose groups.

**Table 1: Mean (SD) Vaborbactam PK Parameters Following Multiple IV Infusions of Vaborbactam – Study 402**

| Parameter | 250 mg q8h | 1000 mg q8h | 1500 mg q8h | 2000 mg q8h |
|---|---|---|---|---|
| $C_{max}$ (µg/mL) | 4.81 (1.04) | 21.3 (6.63) | 33.4 (4.48) | 40.9 (4.68) |
| $AUC_{0-8}$ (µg•h/mL) | 16.3 (3.56) | 74.6 (17.9) | 118 (15.3) | 145 (15.8) |
| $t_{1/2}$ (h) | 1.17 (0.131) | 1.43 (0.359) | 1.65 (0.262) | 1.66 (0.0965) |
| CLt (L/h) | 15.2 (2.56) | 14.1 (3.42) | 12.9 (1.71) | 14.0 (1.78) |
| $V_d$ (L) | 25.7 (5.57) | 28.0 (5.66) | 30.3 (3.48) | 33.4 (4.52) |
| $fe_{0-8}$ (%) | 79.9 (16.3) | 82.8 (10.3) | 86.8 (2.48) | 91.6 (5.36) |
| $CL_R$ (L/h) | 12.7 (3.68) | 11.7 (3.75) | 11.2 (1.72) | 12.8 (2.05) |

Source: MC13R-0009, Table 3 and 4
Abbreviations: SD=standard deviation; $C_{max}$=maximum concentration; $AUC_{0-8}$=area under the concentration-time curve from 0 to 8 hours; $t_{1/2}$=half-life; CLt=clearance; $V_d$=volume of distribution; $fe_{0-8}$=percentage of dose excreted in the urine over 8 hours; $CL_R$=renal clearance

**Figure 1: Mean (± SD) Vaborbactam Plasma Concentration-Versus-Time Profiles Following a Single and Multiple 3 Hour Intravenous Infusion of 250 to 2000 mg in Normal Volunteers (Semi- Logarithmic Scale)**




*Safety Analysis:* Intravenous vaborbactam administered as 3-hour infusions as single doses (250, 500, 750, 1000, 1250 and 1500 mg) and as a single dose followed by multiple doses every 8 hours for 7 days (250, 1000, 1500 and 2000 mg) was well tolerated in healthy adult subjects. There were no deaths or serious adverse events (AE). In the SAD cohorts, the most common treatment-emergent AE was headache, however there was no evidence of increasing incidence with increasing dose of vaborbactam and the overall incidence was similar to placebo. In the MAD cohorts, catheter site complications, unrelated to study drug dosing, were the most common AEs reported. Infusion site reactions (associated with IV dosing catheters) were reported with a similar incidence in subjects who received active treatment and in subjects who received placebo. Commonly occurring AEs, other than catheter and infusion site AEs, were headache, lethargy and contact dermatitis. There were no apparent dose-related trends in safety assessments in subjects who received vaborbactam. There were also no differences in safety assessments between single and multiple dosing cohorts.

**Applicant's Conclusions:** Following vaborbactam single and multiple doses ranging from 250 to 2000 mg, the exposure of vaborbactam ($C_{max}$ and AUC) increased proportionately with vaborbactam dose. The volume of distribution for vaborbactam did not change with repeated dosing. There was no evidence of accumulation of vaborbactam in plasma following 7 days of repeated q8h 3-hour IV infusion of 250 to 2000 mg doses of vaborbactam. Plasma vaborbactam concentrations achieved pharmacokinetic steady state conditions after 1 to 2 days of 3-hour IV infusion q8h of vaborbactam, which is consistent with the plasma half-life of vaborbactam.

Vaborbactam was measurable at high concentrations in the urine for both single and repeated dosing. The % of the dose excreted unchanged in urine was ~ 80-90% of the administered dose and did not change with increasing dose.

Intravenous vaborbactam administered as 3-hour infusions as single doses (250, 500, 750, 1000, 1250 and 1500 mg) and as a single dose followed by multiple doses every 8 hours for 7 days (250, 1000, 1500 and 2000 mg) was well tolerated in healthy adult subjects. No safety concerns were identified and there was no evidence of increasing incidence or severity of AEs with increasing doses of vaborbactam up to 2 g q8h for 7 days.

**Reviewer's Assessment:** Study 402 evaluated the safety, tolerability and PK of single and multiple intravenous doses of vaborbactam when administered to healthy adult subjects. We concur with the Applicant's general conclusions on the PK results from Study 402.

### *4.5.3 Study 501: Single and Multiple Ascending Dose - Meropenem and Vaborbactam*

**Title:** A Phase 1, Randomized, Double-blind, Placebo Controlled, Single- and Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Intravenous Meropenem (RPX2014) and vaborbactam (RPX7009) Alone and in Combination in Healthy Adult Subjects

**Information Regarding the Clinical Trial Site and Duration of the Trial:** The trial was conducted by Rempex Pharmaceuticals, Inc. from June 24, 2013 to February 18, 2014 with the final report date of October 01, 2015.

**Objectives:**
The primary objective was to assess the safety and tolerability of ascending doses of meropenem and vaborbactam when administered alone and in combination as a single dose and in multiple doses to healthy adult subjects.

The secondary objective was to assess the PK of ascending doses of meropenem and vaborbactam when administered alone and in combination as a single dose and in multiple doses to healthy adult subjects.

**Trial Design:** This was a double-blind, randomized, placebo-controlled, single and multiple ascending dose study of meropenem and vaborbactam alone and in combination conducted in healthy adult subjects. A total of 90 subjects were enrolled and assigned to one of six cohorts. Each dose cohort consisted of placebo, meropenem, and vaborbactam/meropenem groups. The first cohort also included a vaborbactam 250 mg treatment group, and the sixth cohort included an vaborbactam 2 gram (g) treatment group. The following doses of vaborbactam /meropenem in combination were evaluated: 250 mg/1 g; 1 g/1 g; 1.5 g/1g; 2 g/1 g; and 2 g/2 g. The dosing schemes for each cohort are provided in Table 1, Table 2, and Table 3. Each dose in Cohorts 1 through 5 was to be infused over 3 hours and the multiple-dose infusions were to be given q8h. Cohort 6 was added to study the PK of meropenem and vaborbactam infused over 1 hour.

**Table 1: Dosing Schemes for Cohort 1 – Study 501 (all drugs infused over 3h)**

| Treatment Arm | Day 1 Single dose | | Day 4 Single dose | Day 7 Single dose | Day 8 to 14 Multiple dose |
|---|---|---|---|---|---|
| Treatment Arm A: meropenem 1000 mg | 8 subjects | | 8 subjects | 8 subjects | 8 subjects |
| Treatment Arm B: vaborbactam 250 mg | 8 subjects | | 8 subjects | 8 subjects | 8 subjects |
| Treatment Arm C: placebo | 6 subjects | | 6 subjects | 6 subjects | 6 subjects |
| Treatment Arm D: meropenem/vaborbactam in combination[a] | 4 subjects meropenem 4 subjects vaborbactam | ✕ | 4 subjects meropenem 4 subjects vaborbactam | 8 subjects | 8 subjects |

[a] Subjects in Treatment Arm D received single-IV dose of 250 mg vaborbactam or 1000 mg meropenem randomized to treatment sequence on Days 1 and 4, and then combination of 250 mg vaborbactam and 1000 mg meropenem on Day 7 and Days 8 to 14.

**Table 2: Dosing Schemes for Cohorts 2 through 5 – Study 501 (all drugs infused over 3h)**

| Cohort | Day 1 Single dose | | Day 4 Single dose | | Day 7 Single dose | | Days 8 to 14 Multiple dose |
|---|---|---|---|---|---|---|---|
| 2 | 4 subjects: meropenem (1 g) | → | Vaborbactam (1 g) | → | Combination of meropenem (1 g)/ vaborbactam (1 g) | → | Combination of meropenem (1 g)/ vaborbactam (1 g) |
| | 4 subjects: vaborbactam (1 g) | → | Meropenem (1 g) | | | | |
| | 3 subjects: placebo | → | Placebo | → | Placebo | → | Placebo |
| | 3 subjects meropenem (1 g) | → | Meropenem (1 g) | → | Meropenem (1 g) | → | Meropenem (1 g) |
| 3 | 4 subjects: meropenem (1 g) | → | Vaborbactam (1.5 g) | → | Combination of meropenem (1 g)/ vaborbactam (1.5 g) | → | Combination of meropenem (1 g)/ vaborbactam (1.5 g) |
| | 4 subjects: vaborbactam (1.5 g) | → | Meropenem (1 g) | | | | |
| | 3 subjects: placebo | → | Placebo | → | Placebo | → | Placebo |
| | 3 subjects meropenem (1 g) | → | Meropenem (1 g) | → | Meropenem (1 g) | → | Meropenem (1 g) |
| 4 | 4 subjects: meropenem (1 g) | → | Vaborbactam (2 g) | → | Combination of meropenem (1 g)/ vaborbactam (2 g) | → | Combination of meropenem (1 g)/ vaborbactam (2 g) |
| | 4 subjects: vaborbactam (2 g) | → | Meropenem (1 g) | | | | |
| | 3 subjects: placebo | → | Placebo | → | Placebo | → | Placebo |
| | 3 subjects meropenem (1 g) | → | Meropenem (1 g) | → | Meropenem (1 g) | → | Meropenem (1 g) |
| 5 | 4 subjects: meropenem (2 g) | → | Vaborbactam (2 g) | → | Combination of meropenem (2 g)/ vaborbactam (2 g) | → | Combination of meropenem (2 g)/ vaborbactam (2 g) |
| | 4 subjects: vaborbactam (2 g) | → | Meropenem (2 g) | | | | |
| | 3 subjects: placebo | → | Placebo | → | Placebo | → | Placebo |
| | 3 subjects meropenem (2 g) | → | Meropenem (2 g) | → | Meropenem (2 g) | → | Meropenem (2 g) |

**Table 3: Dosing Schemes for Cohort 6 – Study 501**

| Cohort | Day 1 Single dose | | Days 2 to 8 Multiple dose |
|---|---|---|---|
| 6 | 2 subjects: meropenem (2 g) | → | Meropenem (2 g) |
| | 2 subjects: vaborbactam (2 g) | → | vaborbactam (2 g) |
| | 8 subjects: combination of meropenem (2 g)/vaborbactam (2 g)[a] | → | Combination of meropenem (2 g)/vaborbactam (2 g)[a] |
| | 2 subjects: placebo | → | Placebo |

[a] Subjects in Cohort 6 received meropenem-vaborbactam doses infused over 1 hour

**Excluded Medications, Restrictions:**

- Hypersensitivity or idiosyncratic reaction to β-lactam antibiotics (e.g., penicillins, cephalosporins, carbapenems, etc.).
- Use of any prescription medication (with the exception of hormonal contraceptives or hormone replacement therapy for females) within 14 days prior to Day 1.
- Use of any over-the-counter (OTC) medication, including herbal products and vitamins, within the 7 days prior to Day 1. Up to 2 grams per day of acetaminophen was allowed for acute events at the discretion of the PI.
- Calculated creatinine clearance less than 50 mL/min (Cockcroft-Gault method) at Screening or check-in (Day -1).

**Rationale for Doses Used in the Trial:**

*Meropenem:* Meropenem has been used in clinics at doses up to 2 g q8h. Based on the literature data of safety, PK and pharmacodynamics for meropenem, a dose of up to 2 g q8h was chosen for this combination study.

*Vaborbactam:* The PK of vaborbactam administered as 3-hour infusions at doses of 250 mg, 500 mg, 750 mg, 1000 mg, 1250 mg, 1500 mg, and 2000 mg were evaluated in a total of 42 healthy subjects in Study 402. Vaborbactam plasma concentrations and PK parameters increased dose-proportionally. Intravenous vaborbactam administered as 3-hour infusions as single doses and as a single dose followed by multiple doses every 8 hours for 7 days up to 2000 mg was well tolerated in healthy adult subjects. In the neutropenic mouse thigh infection model, the addition of vaborbactam to biapenem at a 1:1 or 1:0.5 ratio was able to restore the biapenem activity at the doses of the biapenem that were ineffective when the biapenem was used alone. These data suggest that vaborbactam would likely be given at an approximately 1:1 or 1:0.5 ratio with biapenem and meropenem. Therefore, the proposed starting dose of 250 mg of vaborbactam in this study was supported by the PK and safety data from single and multiple dose cohorts of vaborbactam alone in Study 402, and lack of a drug-drug PK interaction in animals.

**Drugs Used in the Trial:** Meropenem was supplied in single-use vials as a pyrogen-free white to pale yellow crystalline powder containing 1000 mg of meropenem trihydrate (b) (4) sodium carbonate. Meropenem was manufactured, packaged, and labeled in accordance with current Good Manufacturing Practices at AstraZeneca, S.P.S. Via F. Sforza Palazzo Volta, 20080 Basiglio (MI), Italy. The meropenem lot number used for this study was 13062D.

Vaborbactam was supplied in single-use vials at two dosage strengths (500 mg/vial and 1000 mg/vial) (b) (4). Vaborbactam was manufactured, packaged, and labeled in accordance with current Good Manufacturing Practices (b) (4). The vaborbactam lot

number used for this study was 1-FIN-1521.

Placebo was 0.9% sterile saline for infusion.

**Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis:**

In Cohorts 1 through 5, blood samples were obtained pre –dose and at 1.5 (mid-point of the infusion), 3, 3.167, 3.333, 3.5, 3.75, 4, 5, 6, 7, 8, 12, and 24 hours after the start of the 3-hour infusion on Days 1, 4, 7, and 14. Blood samples were also collected pre-dose and at the end-of-infusion in the morning on Days 9, 11, and 13. Urine for PK analysis was obtained at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours on Days 1, 4, 7, and 14. Additionally, urine was collected over the 24 to 48 h post-dose on Days 1, 4, and 14.

In Cohort 6, blood samples were obtained pre-dose and at 0.5 (mid-point of the infusion), 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, and 24 hours after the start of the 1-hour infusion on Days 1 and 8. Blood samples were also collected pre-dose and at the end-of-infusion in the morning on Days 2, 3, 5, and 7. Urine samples for PK analysis were not obtained in Cohort 6.

*Bioanalytical method (see Section 4.1 for details for the methods and method validation data):* Drug concentrations of meropenem, vaborbactam, and meropenem open-lactam metabolite concentrations in plasma and urine were determined with validated high-performance liquid chromatography with mass spectrometric detection.

| Analyte | Matrix | Validation Report | Bioanalytical Report |
|---|---|---|---|
| Meropenem | Plasma | # MC13B-0105 | # MC13B-0162 |
| Meropenem | Urine | #MC13B-0106 | #MC13B-0163 |
| Meropenem Open-Lactam | Plasma | # MC13B-0105 | # MC13B-0162 |
| Meropenem Open-Lactam | Urine | #MC13B-0106 | #MC13B-0163 |
| Vaborbactam | Plasma | # MC13R-0016 | # MC13B-0162 |
| Vaborbactam | Urine | #MC13R-0017 | #MC13B-0163 |

*Reviewer's Comment: Based on results from method validation and bioanalytical reports, all above-mentioned analytical methods met the acceptable criteria specified in the FDA Guidance to Industry: Bioanalytical Method Validation.*

*Pharmacokinetic Assessments:* PK parameters include: $C_{max}$, $T_{max}$, $AUC_{0-□}$, $AUC_{0-t}$, $AUC_{0-inf}$, $T_{1/2}$, $K_{el}$, $A_e$ (cumulative amount of unchanged drug excreted in the urine), $f_e$ (fraction of administered dose excreted in the urine) and $CL_R$.

*Statistical Analysis*
Statistical comparisons of the potential for an interaction between meropenem and vaborbactam (comparison of alone versus combination treatment) were done for $C_{max}$, $AUC_{0\text{-}t}$, and $AUC_{0–inf}$ (single-dose comparisons only) using analysis of variance (ANOVA) using mixed model analyses based on the ln-transformed data. The ANOVA model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The statistical comparisons of the PK parameters were assessed based on whether the 90% confidence interval (CI) for the geometric mean ratios for the defined comparisons was within the 80% to 125% interval.

**Results:**
*Subject Demographics and Disposition:* Ninety-four subjects were enrolled in the study as follows: 30 subjects in Cohort 1, 9 subjects in Cohort 2, 13 subjects in Cohort 3, and 14 subjects each in Cohorts 4, 5, and 6.
A total of four subjects, two subjects in Cohort 1, one subject in Cohort 3, and one subject in Cohort 4, prematurely withdrew from the study. Reasons for premature withdrawal included:

- Withdrawal of consent: Subject 02413 in Cohort 1 (1 g meropenem alone) and Subject 02449 in Cohort 3 (1.5 g vaborbactam /1 g meropenem)
- AE: Subject 02460 in Cohort 4 (2 g vaborbactam /1 g meropenem) because of thrombophlebitis
- Principle investigator withdrawal: Subject 02421 in Cohort 1 (1 g meropenem alone) with ongoing forearm cellulitis and lack of venous access in the opposite arm

Eighteen of the 90 subjects received placebo and were not included in the PK analyses.

*Pharmacokinetic and Statistical Analysis:* Summary statistics for select PK parameters are provided in Table 4, Table 5, and Table 6 for meropenem, its inactive open lactam metabolite, and vaborbactam, respectively.

In general, $C_{max}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ were similar regardless of treatment administration (alone versus combination) suggesting that concomitant administration of meropenem and vaborbactam does not affect the PK of either drug. There appeared to be little accumulation with multiple dosing, which is consistent with the half-life observed for meropenem and vaborbactam (geometric means consistently below 1.5 h, regardless of dose). Similar to previous studies with meropenem alone, the open lactam metabolite of meropenem was also detected and tended to accumulate with multiple doses.

The results of ANOVA models constructed to test for a drug-drug interaction between meropenem and vaborbactam indicated that the 90% CI for the least squares (LS) geometric mean ratios for every PK parameter ($C_{max}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$) were completely contained

within the bioequivalence window of 0.8 to 1.25 for both meropenem and vaborbactam. The results of these statistical comparisons indicate that the plasma exposure to either meropenem or vaborbactam is not different when the drugs are given alone or in combination.

Comparison of meropenem and vaborbactam PK parameters in subjects enrolled in Cohorts 1 through 5 (3-h infusion duration) with those in Cohort 6 (1-h infusion duration) showed some differences. As expected, $C_{max}$ was higher for both drugs with the 1-h infusion; however, plasma clearance of both drugs was noted to be reduced in Cohort 6 compared to the others; these clearance differences resulted in higher plasma drug AUCs in Cohort 6 compared to Cohort 5. The reasons for this difference were not explored but are likely due to differences in plasma sampling times relative to the time of highest drug concentrations..

In general, 40 to 60% of the meropenem dose was excreted in the urine over 24 to 48 h as the parent (active) drug while 75 to 95% of the vaborbactam dose was excreted in the urine as vaborbactam over 24 to 48 h after a dose. Although there was a trend for the median renal clearance to be lower with combination therapy, the overall range of values was similar across all treatments (single- versus multiple-dose, alone or in combination).

**Table 4: Geometric Mean (Geometric CV%) for Select Plasma PK Parameters — Meropenem (Study 501)**

| Cohort / Dose[a] | Treatment | N | $C_{max}$ (µg/mL) | | $AUC_{0-inf}$ (µg•h/mL) | $AUC_{0-t}$ (µg•h/mL) | CLt (L/h) | | $t_{1/2}$ (h) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Single dose | Multiple dose | Single dose | Multiple dose | Single dose | Multiple dose | Single dose | Multiple dose |
| 1 1:0.25 | Meropenem | 32 | 16.8 (44.7%) | 16.5 (58.0%) | 51.6 (43.3%) | 49.2 (55.7%) | 19.4 (43.3%) | 20.3 (55.6%) | 1.02 (42.8%) | 0.967 (55.5%) |
| | Combination | 16 | 18.6 (32.4%) | 15.7 (34.5%) | 56.1 (30.5%) | 47.1 (32.5%) | 17.8 (30.5%) | 21.2 (32.8%) | 0.952 (28.8%) | 0.974 (33.4%) |
| 2 1:1 | Meropenem | 13 | 18.6 (47.4%) | 16.4 (38.4%) | 58.1 (47.7%) | 49.9 (39.2%) | 17.2 (47.7%) | 20.1 (39.2%) | 0.963 (35.3%) | 0.892 (20.3%) |
| | Combination | 10 | 19.9 (46.6%) | 17.0 (32.1%) | 64.1 (51.0%) | 53.9 (36.5%) | 15.6 (51.0%) | 18.5 (36.2%) | 1.14 (45.2%) | 0.943 (24.1%) |
| 3 1:1.5 | Meropenem | 19 | 20.9 (34.8%) | 23.3 (59.1%) | 64.6 (38.2%) | 67.0 (55.9%) | 15.5 (38.2%) | 14.9 (55.9%) | 0.892 (31.5%) | 0.872 (33.2%) |
| | Combination | 14 | 20.4 (48.3%) | 19.9 (50.3%) | 64.2 (48.4%) | 64.5 (48.0%) | 15.6 (48.4%) | 15.5 (48.0%) | 1.02 (44.4%) | 0.882 (28.9%) |
| 4 1:2 | Meropenem | 19 | 17.3 (37.4%) | 15.9 (43.9%) | 53.7 (43.0%) | 50.7 (32.7%) | 18.6 (43.0%) | 19.7 (32.7%) | 1.01 (47.5%) | 0.976 (52.6%) |
| | Combination | 14 | 17.5 (23.7%) | 15.8 (29.2%) | 55.0 (27.0%) | 47.9 (20.7%) | 18.2 (27.0%) | 20.9 (20.7%) | 0.910 (45.5%) | 1.07 (39.8%) |
| 5 2:2 | Meropenem | 20 | 40.9 (53.6%) | 46.0 (59.6%) | 126 (48.9%) | 134 (56.4%) | 15.9 (48.9%) | 15.0 (56.4%) | 1.06 (54.9%) | 1.00 (46.0%) |
| | Combination | 16 | 45.7 (35.7%) | 42.5 (48.5%) | 139 (45.8%) | 136 (46.8%) | 14.4 (45.8%) | 14.9 (45.8%) | 1.30 (82.6%) | 1.18 (56.4%) |
| 6[b] 2:2 | Meropenem | 4 | 92.3 (13.6%) | 88.9 (4.89%) | 188 (10.9%) | 179 (17.2%) | 10.6 (10.9%) | 11.2 (17.2%) | 1.03 (31.1%) | 1.29 (62.7%) |
| | Combination | 16 | 90.1 (28.3%) | 94.0 (21.6%) | 206 (32.8%) | 203 (34.1%) | 9.72 (32.8%) | 9.90 (33.5%) | 1.02 (35.5%) | 1.12 (40.8%) |

Source: Study 00371, Appendix 3

a. Expressed as meropenem (g):vaborbactam (g).

b. Administered as 1-hour infusion (other cohorts used 3-hour infusion).

CV% = percent coefficient of variation; $C_{max}$ = maximum concentration; $AUC_{0-t}$ = area under the concentration-time curve from 0 to the end of the dosing interval; $AUC_{0-inf}$ = area under the concentration-time curve from 0 to infinity; CLt = clearance; $t_{1/2}$ = half-life

**Table 5: Geometric Mean (Geometric CV%) for Select Plasma PK Parameters — Meropenem Open Lactam Metabolite (Study 501)**

| Cohort/ Dose[a] | Treatment | N | $C_{max}$ (µg/mL) | | $AUC_{0\text{-}inf}$ (µg•h/mL) | $AUC_{0\text{-}t}$ (µg•h/mL) | $t_{1/2}$ (h) | |
|---|---|---|---|---|---|---|---|---|
| | | | Single dose | Multiple dose | Single dose | Multiple dose | Single dose | Multiple dose |
| 1 1:0.25 | Meropenem | 32 | 1.87 (44.7%) | 1.89 (50.4%) | 8.31 (43.1%) | 9.02 (55.6%) | 2.13 (52.6%) | 2.92 (54.9%) |
| | Combination | 16 | 1.87 (41.2%) | 1.91 (43.4%) | 8.28 (44.1%) | 8.75 (49.3%) | 1.96 (66.8%) | 2.89 (54.1%) |
| 2 1:1 | Meropenem | 13 | 1.98 (36.0%) | 2.05 (31.2%) | 8.94 (31.2%) | 11.2 (6.95%) | 2.02 (38.0%) | 4.15 (27.1%) |
| | Combination | 10 | 2.19 (42.3%) | 2.27 (39.8%) | 9.67 (44.8%) | 11.5 (42.5%) | 2.16 (41.4%) | 3.08 (55.3%) |
| 3 1:1.5 | Meropenem | 19 | 2.20 (53.7%) | 2.16 (67.3%) | 9.91 (56.5%) | 12.0 (74.2%) | 2.13 (50.4%) | 3.83 (167%) |
| | Combination | 14 | 2.22 (40.3%) | 2.27 (41.1%) | 9.73 (45.7%) | 11.4 (52.4%) | 2.03 (49.8%) | 2.84 (55.4%) |
| 4 1:2 | Meropenem | 19 | 1.88 (48.4%) | 1.98 (50.1%) | 8.30 (50.4%) | 10.1 (35.3%) | 1.96 (58.1%) | 3.38 (64.6%) |
| | Combination | 14 | 1.73 (37.6%) | 1.73 (35.0%) | 7.80 (46.7%) | 8.00 (45.8%) | 2.17 (58.8%) | 2.87 (60.7%) |
| 5 2:2 | Meropenem | 20 | 4.44 (46.7%) | 6.29 (80.4%) | 19.6 (46.0%) | 35.8 (65.2%) | 2.44 (58.5%) | 5.56 (69.2%) |
| | Combination | 16 | 4.57 (42.2%) | 6.14 (35.4%) | 21.9 (35.6%) | 42.6 (48.1%) | 3.01 (68.4%) | 6.08 (44.9%) |
| 6[b] 2:2 | Meropenem | 4 | 4.27 (51.2%) | 5.45 (45.1%) | 17.9 (55.0%) | 27.4 (4.03%) | 2.39 (38.8%) | 4.84 (87.6%) |
| | Combination | 16 | 4.88 (47.5%) | 6.35 (32.2%) | 22.2 (45.6%) | 33.3 (43.0%) | 2.52 (40.6%) | 6.38 (78.1%) |

Source: Study 00371, Appendix 4

a. Expressed as doses of meropenem (g): vaborbactam (g).

b. Administered as 1-hour infusion (other cohorts used 3-hour infusion).

CV% = percent coefficient of variation; $C_{max}$ = maximum concentration; $AUC_{0\text{-}t}$ = area under the concentration-time curve from 0 to the end of the dosing interval; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from 0 to infinity; CLt = clearance; $t_{1/2}$ = half-life

**Table 6: Geometric Mean (Geometric CV%) for Select Plasma PK Parameters — Vaborbactam (Study 501)**

| Cohort/ Dose[a] | Treat | N | $C_{max}$ (µg/mL) | | $AUC_{0-inf}$ (µg•h/mL) | $AUC_{0-t}$ (µg•h/mL) | CLt (L/h) | | $t_{1/2}$ (h) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Single dose | Multiple dose | Single dose | Multiple dose | Single dose | Multiple dose | Single dose | Multiple dose |
| 1 1:0.25 | Vab | 40 | 5.18 (41.8%) | 4.87 (37.0%) | 17.2 (42.7%) | 16.2 (46.8%) | 14.5 (42.7%) | 15.3 (45.9%) | 1.09 (57.2%) | 1.12 (50.3%) |
| | Combin | 16 | 5.28 (40.2%) | 4.57 (39.5%) | 17.0 (38.3%) | 14.6 (39.7%) | 14.7 (38.3%) | 16.9 (39.4%) | 1.06 (52.0%) | 1.16 (38.6%) |
| 2 1:1 | Vab | 5 | 21.7 (42.3%) | — | 75.4 (48.0%) | — | 13.3 (48.0%) | — | 1.46 (69.6%) | — |
| | Combin | 10 | 23.3 (46.1%) | 19.9 (29.6%) | 79.4 (46.2%) | 68.4 (39.0%) | 12.6 (46.2%) | 14.8 (37.4%) | 1.50 (49.8%) | 1.32 (61.9%) |
| 3 1:1.5 | Vab | 7 | 36.2 (41.0%) | — | 118 (36.6%) | — | 12.7 (36.6%) | — | 1.19 (49.3%) | — |
| | Combin | 14 | 36.9 (37.0%) | 32.6 (32.5%) | 124 (40.4%) | 115 (38.4%) | 12.1 (40.4%) | 13.3 (37.3%) | 1.33 (44.7%) | 1.43 (61.2%) |
| 4 1:2 | Vab | 7 | 38.0 (28.8%) | — | 126 (35.0%) | — | 15.9 (35.0%) | — | 1.27 (54.8%) | — |
| | Combin | 14 | 40.0 (22.7%) | 34.7 (34.6%) | 133 (29.2%) | 113 (29.8%) | 15.1 (29.2%) | 17.9 (28.7%) | 1.37 (46.7%) | 1.51 (56.3%) |
| 5 2:2 | Vab | 8 | 49.5 (57.4%) | — | 152 (54.5%) | — | 13.2 (54.5%) | — | 1.38 (37.6%) | — |
| | Combin | 16 | 50.1 (42.6%) | 54.7 (47.1%) | 165 (45.2%) | 193 (45.0%) | 12.1 (45.2%) | 10.7 (43.1%) | 1.88 (61.9%) | 1.64 (50.5%) |
| 6[b] 2:2 | Vab | 4 | 95.5 (20.0%) | 115 (19.4%) | 192 (11.1%) | 210 (9.48%) | 10.4 (11.0%) | 9.68 (6.51%) | 1.18 (36.0%) | 1.64 (46.3%) |
| | Combin | 16 | 94.0 (42.6%) | 116 (35.8%) | 207 (43.1%) | 226 (42.4%) | 9.67 (43.1%) | 9.01 (42.4%) | 1.36 (40.1%) | 1.59 (39.2%) |

Source: Study 00371, Appendix 5

a. Expressed as doses of meropenem (g): vaborbactam (g).

b. Administered as 1-hour infusion (other cohorts used 3-hour infusion).

CV% = percent coefficient of variation; $C_{max}$ = maximum concentration; $AUC_{0-t}$ = area under the concentration-time curve from 0 to the end of the dosing interval; $AUC_{0-inf}$ = area under the concentration-time curve from 0 to infinity; CLt = clearance; $t_{1/2}$ = half-life; vab = vaborbactam; Combin = combination

*Safety Analysis:* During the single-dose administration period, 68% of subjects had at least one AE across the treatment groups as follows: 67% in the placebo group, 60% in the pooled vaborbactam group, 90% in the pooled meropenem group, and 60% in the pooled vaborbactam /meropenem combination group. There was no evidence for an increasing incidence of AEs, related AEs, or moderate or severe AEs with increasing single doses of meropenem or vaborbactam, or the combination of vaborbactam/meropenem.

During the multiple-dose administration period, 89% of subjects had at least one AE across the treatment groups as follows: 83% in the placebo group, 80% in the pooled vaborbactam group, 95% in the pooled meropenem group, and 91% in the pooled vaborbactam/meropenem combination group. With the exception of nausea (which was reported in subjects receiving 2 g meropenem either alone or in combination with vaborbactam), there was no evidence for an increasing incidence of overall AEs, related AEs, or moderate or severe AEs with increasing dose of meropenem, vaborbactam, or the vaborbactam/meropenem combination. Nausea is an expected AE with meropenem administration (Merrem® US Prescribing Information [USPI], December 2013), and all episodes of nausea reported were mild, resolved without treatment, and did not result in study drug discontinuation.

AEs with a higher incidence (≥ 5%) with the vaborbactam /meropenem combination compared with meropenem alone during the multiple-dose administration period included infusion site pain (36% and 19%, respectively), vessel puncture site hematoma (16% and no subjects, respectively), vessel puncture site pain (7% and no subjects, respectively), infusion site hematoma (11% and no subjects, respectively), and nausea (16% and 10%, respectively).

The majority of AEs were mild and moderate in severity with two subjects reporting severe AEs of infusion site phlebitis. No SAEs were reported.

Two subjects, one who received meropenem alone and one who received vaborbactam /meropenem in combination, had ALT elevations > 3x the upper limit of the normal range, which were reported as mild AEs. These were asymptomatic, resolved after study drug dosing was completed, and were not associated with bilirubin elevations. ALT elevations are an expected adverse reaction observed with meropenem.

AEs in the one-hour infusion cohort were similar to the three-hour infusion cohort of the same dose except for temperature elevations observed in some patients. These elevations were observed in the one-hour infusion cohort only, and in both the meropenem and meropenem/vaborbactam subjects. The temperature elevations were short-lived, resolved without treatment, and did not result in any study drug discontinuation.

**Applicant's Conclusions:**

- The PK of meropenem and vaborbactam in this population of healthy subjects were qualitatively similar. Both drugs exhibited a rapid terminal elimination half-life and, although some PK parameters were similar, vaborbactam exposures ($C_{max}$ and AUC) were slightly higher than those for meropenem.
- Although there was a trend for the median renal clearance to be lower with combination therapy, the overall range of values was similar across all treatments (single- versus multiple-dose, alone or in combination) for both meropenem and vaborbactam.
- Meropenem and vaborbactam PK were consistent regardless of infusion duration (1-h versus 3-h). As expected, $C_{max}$ was higher in subjects who received the 1-h infusions. The differences in clearance and AUC are likely due to the sampling scheme employed and the small sample size in Cohort 6.
- Concomitant administration of meropenem and vaborbactam did not affect the plasma or urine PK of either drug.
- Perhaps due to the lack of cross-over and the small sample size in some cohorts, dose proportionality could not be confirmed for vaborbactam.

Overall, IV infusions of vaborbactam (250 mg, 1 g, 1.5 g, and 2 g), meropenem (1 g and 2 g), and the combination of various doses of vaborbactam and meropenem were generally well

tolerated in healthy adult subjects, especially as three-hour infusions, with no evidence that vaborbactam changed the known safety profile of meropenem.

**11. Reviewer's Assessment**

Study 501 evaluated the safety, tolerability and PK of ascending doses of meropenem and vaborbactam when administered alone and in combination as a single dose and in multiple doses to healthy adult subjects. The following results are valid:

- There appeared to be little accumulation for both meropenem and vaborbactam following multiple dosing.
- Concomitant administration of meropenem and vaborbactam did not affect the plasma or urine PK of either drug, indicating no drug-drug interaction between meropenem and vaborbactam.
- 40 to 60% of the meropenem dose was excreted in the urine over 24 to 48 h as the parent (active) drug while 75 to 95% of the vaborbactam dose was excreted in the urine as vaborbactam over 24 to 48 h after a dose.

When comparing meropenem PK in subjects enrolled in Cohorts 1 through 5 (3-h infusion duration) to those in Cohort 6 (1-h infusion duration), meropenem and vaborbactam half-life estimates are similar regardless of duration. As expected, $C_{max}$ estimates are higher after the 1-h infusion. The differences seen with AUC, whereby the AUC in subjects receiving the 1-h infusions was approximately 50% higher than that in subjects receiving the 3-h infusion, was somewhat unexpected but is likely a consequence of the difference in PK sampling scheme at the early sampling times. Clearance of meropenem and vaborbactam is relatively rapid such that having the first PK sample at 1.5 h for 3-h infusion versus at 0.5 h for 1-h infusion may result in an underestimation of AUC in subjects receiving the 3-h infusion.

### *4.5.4 Study 503: Multiple Dose, Epithelial Lining Fluid and Alveolar Macrophage Penetration Study - Meropenem and Vaborbactam*

**Title:** A Phase 1, Randomized, Open-Label Trial Evaluating the Plasma, Epithelial Lining Fluid, and Alveolar Macrophage Concentrations of Intravenous meropenem/vaborbactam in Healthy Adult Subjects

**Information Regarding the Clinical Trial Site and Duration of the Trial:** The trial was conducted by Rempex Pharmaceuticals, Inc. from February 24, 2014 to April 24, 2014 with the final report date of May 13, 2015.

**Objectives:**
The primary objective of the study was to determine and compare plasma, epithelial lining fluid (ELF), and alveolar macrophage (AM) concentrations of intravenous (IV) meropenem/ vaborbactam in healthy adult subjects.

The secondary objective of the study was to assess the safety and tolerability of IV meropenem/ vaborbactam in healthy adult subjects.

**Trial Design:** This was a Phase 1, randomized, open-label, multiple dose study evaluating the plasma, ELF, and AM concentrations of meropenem and vaborbactam after administration of meropenem 2 g – vaborbactam 2 g to healthy adults. The study included an up to 28-day Screening Period, a 2-day Treatment Period, and an End-of-Study Assessment occurring immediately after completion of the Treatment Period. Approximately 25 subjects were planned to be enrolled. Subjects were administered 2 g meropenem/2 g vaborbactam as 3-hour IV infusion every 8 hours (ie, at 0, 8, and 16 hours) for a total of 3 doses.

**Excluded Medications, Restrictions:**

- Had hypersensitivity or idiosyncratic reaction to beta-lactam antibiotics (eg, penicillins, cephalosporins, carbapenems, etc.).
- Had a history of allergic or other serious adverse reactions to lidocaine.
- Used of any prescription medication (with the exception of hormonal contraceptives or hormone replacement therapy for females) within 14 days prior to Day 1.
- Use of any over-the-counter (OTC) medication, including herbal products and vitamins, within the 7 days prior to Day 1. Up to 2 grams per day of acetaminophen was allowed for acute events at the discretion of the Principal Investigator.
- Calculated creatinine clearance less than 80 mL/min (Cockcroft-Gault method) at Screening.

**Rationale for Doses Used in the Trial:** The dose of vaborbactam administered in the study was based on safety and PK data observed in Phase 1 single-ascending and multiple-ascending dose studies. Intravenous vaborbactam administered in 3-hour infusions as single doses (250, 500, 750, 1000, 1250 and 1500 mg) and as a single dose followed by multiple doses (250, 1000, 1500, and 2000 mg) q8h for 7 days was well tolerated in healthy adult subjects. No safety concerns were identified and there was no evidence of increasing incidence or severity of adverse events with increasing doses of vaborbactam up to 2 g q8h for 7 days. In another Phase 1 clinical study (Study 501), cohorts that received multiple IV infusions of 2 g meropenem with 2 g vaborbactam showed no evidence of any alteration of the well-established safety profile of meropenem in comparison to the placebo cohort. Furthermore, there was no evidence of any PK interaction between the two agents.

**Drugs Used in the Trial:** Meropenem was supplied as sterile powder (b) (4) with sodium carbonate. Vaborbactam was supplied as (b) (4) powder. Both meropenem and vaborbactam were reconstituted in 0.9% sterile saline for infusion. Lot numbers for the study drug used in the study are listed in Table 1.

**Table 1: Study Drug**

| Study Drug | Dose and Mode of Administration | Lot Number |
|---|---|---|
| Meropenem | 2 g meropenem/2 g RPX7009 given intravenously as Carbavance | 0016D31 |
| RPX7009 | | CL3-402 |

RPX7009=vaborbactam

**Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis:** Plasma samples for PK assessments were collected prior to (time 0), and 1.5, 2.95, 3.083, 3.25, 3.5, 4, 6, and 8 hours after the start of the third meropenem/ vaborbactam infusion. In addition, each subject was randomized to 1 of 5 bronchoscopy sampling time points after the start of the third meropenem/vaborbactam infusion (i.e., 1.5, 3.25, 4, 6, or 8 hours)

Urea has been commonly used as an endogenous marker to estimate the apparent volume of ELF. Blood samples to determine plasma urea concentrations were obtained just prior to scheduled bronchoscopy. Aliquots of bronchoalveolar lavage (BAL) were obtained to determine urea concentrations in BAL and differential cell count.

*Bioanalytical method:* Drug concentrations of meropenem, vaborbactam, and meropenem open-lactam concentrations in plasma, ELF, and AM were determined with validated high-performance liquid chromatography with mass spectrometric detection. The urea concentrations in plasma and BAL were performed with a microplate-based method with an O-phthalaldehyde chromogenic solution. See table below and Section 4.1 for details for the methods and method validation data.

| Analyte | Matrix | Validation Report | Bioanalytical Report |
|---|---|---|---|
| Meropenem | Plasma | # MC13B-0105 | # MC14B-0013 |
| | ELF | #MC14B-0020 | # MC14B-0014 |
| | AM | #MC14B-0021 | # MC14B-0015 |
| Meropenem Open-Lactam | Plasma | # MC13B-0105 | # MC14B-0013 |
| | ELF | #MC14B-0020 | # MC14B-0014 |
| | AM | #MC14B-0021 | # MC14B-0015 |
| Vaborbactam | Plasma | # MC13R-0016 | # MC14B-0013 |
| | ELF | #MC14R-0007 | # MC14B-0014 |
| | AM | #MC14R-0008 | # MC14B-0015 |
| Urea | Plasma | # MC14I-0022 | # MC14I-0011 |
| | ELF | # MC14I-0023 | # MC14I-0012 |

*Reviewer's Comment: Based on results from method validation and bioanalytical reports, all above-mentioned analytical methods met the acceptable criteria specified in the FDA Guidance to Industry: Bioanalytical Method Validation.*

*Pharmacokinetic Assessments:* Plasma PK parameters include: $C_{max}$, $T_{max}$, $AUC_{0-□}$, $T_{1/2}$, CL, $V_{ss}$.

Drug Concentrations in ELF and AM:
The concentration of drug ($ABX_{ELF}$) in the epithelial lining fluid (ELF) was determined as follows: $ABX_{ELF} = ABX_{BAL} \times (V_{BAL} / V_{ELF})$,
where $ABX_{BAL}$ is the measured concentration of meropenem, vaborbactam or meropenem open-lactam in BAL fluid, $V_{BAL}$ is the volume of aspirated BAL fluid, and $V_{ELF}$ is the volume of ELF sampled by the BAL. $V_{ELF}$ is derived from the following: $V_{ELF} = V_{BAL}$ x $Urea_{BAL} / Urea_P$ where $Urea_{BAL}$ is the concentration of urea in BAL fluid and $Urea_P$ is the concentration of urea in plasma.
The concentration of drug ($ABX_{AM}$) in the alveolar cells (AC) was determined as follows: $ABX_{AM} = ABX_M / V_{AC,}$
where $ABX_M$ is the measured concentration of meropenem, vaborbactam or meropenem open-lactam in the 1- mL cell suspension, and $V_{AC}$ is the volume of alveolar cells in the 1-mL cell suspension. Differential cell count was performed to determine the number of macrophages present. A mean macrophage cell volume of 2.42 µl/$10^6$ cells was used in the calculations for volume of alveolar cells in the pellet suspension.

The ratios of ELF and AM concentrations to the simultaneous plasma concentrations were calculated for each subject and summarized for each group at each BAL sampling time. The concentrations at the 8 h (trough) sampling time were also used as a time zero value for determining the AUC in ELF relative to plasma. Penetration of meropenem and vaborbactam was estimated from the ratios of the $AUC_{0–8}$ for ELF or AM to the corresponding $AUC_{0–8}$ in plasma.

*Statistical Analysis:* The area under the concentration-time curve (AUC) from 0 to 8 hours ($AUC_{0-8}$) was determined for the comparison of systemic exposure within the three matrices of each dosing regimen. Compartmental and/or noncompartmental pharmacokinetic parameters based on plasma concentrations was determined for each individual subject using the microcomputer programs such as WinNonlin (version 5.2; Pharsight Corporation, Cary, N.C.), ADAPT II or S-ADAPT.

**Results:**

*Subject Demographics and Disposition:* Twenty-six healthy adult subjects were enrolled into this study. One subject was discontinued from the study due to an adverse event and the pharmacokinetic phases for this subject (e.g., blood sample collection to measure drug concentrations in plasma and a bronchoscopy with BAL at the scheduled sampling time [4-hour]) were not performed.

*Pharmacokinetic and Statistical Analysis:* The mean (SD) PK parameters for meropenem and vaborbactam in plasma are provided in Table 2. The mean (SD) meropenem and vaborbactam Concentrations in plasma (total), epithelial lining fluid, and alveolar macrophages at sampling time of bronchoscopy and bronchoalveolar lavage are shown in Table 3. The mean (SD) concentrations of meropenem in plasma and ELF at the bronchopulmonary lavage sampling times are illustrated in Figure 1.

**Table 2: Mean (SD) Plasma PK Parameters Following Administration of 2 g Meropenem/2 g Vaborbactam as 3-hour IV Infusion q8h for a Total of 3 Doses (Study 503)**

| | N | $C_{max}$ (µg/mL) | $AUC_{0-8}$ (µg*h/mL) | Vss (L) | CLt (L/h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| Meropenem | 25 | 58.2 (10.8) | 186 (33.6) | 16.3 (2.6) | 11.1 (2.1) | 1.03 (0.15) |
| Vaborbactam | 25 | 59.0 (8.4) | 204 (34.6) | 17.6 (2.6) | 10.1 (1.9) | 1.27 (0.21) |

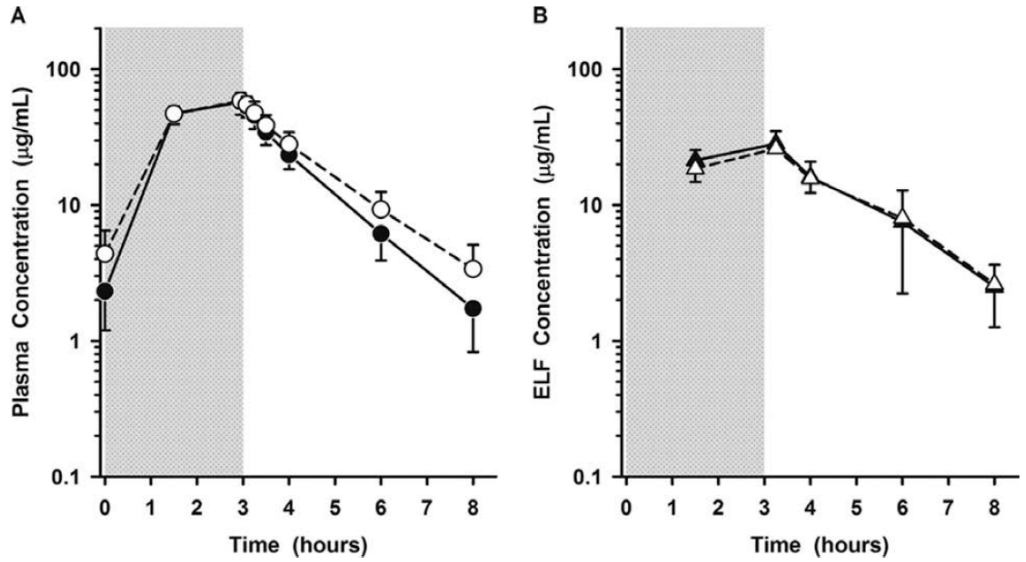
SD = standard deviation; N = Count of subjects; $C_{max}$ = maximum concentration; $AUC_{0-8}$ = area under the concentration-time curve from 0 to 8 hours; $V_{ss}$ = steady-state volume of distribution; $CL_t$ = clearance; $t_{1/2}$ = half-life

**Table 3: Meropenem and Vaborbactam Concentrations (µg/mL) in Plasma (Total), Epithelial Lining Fluid, and Alveolar Macrophages at Sampling Time of Bronchoscopy and Bronchoalveolar Lavage (Study 503)**

| BAL Sampling Time (h) | Meropenem | | | Vaborbactam | | |
|---|---|---|---|---|---|---|
| | Plasma | ELF | AM | Plasma | ELF | AM |
| 1.5 | 41.2 ± 5.02 | 21.4 ± 3.96 | BQL | 42.1 ± 5.00 | 18.6 ± 3.76 | 2.28 (1.29–4.69) |
| 3.25 | 47.7 ± 7.28 | 28.3 ± 6.69 | BQL | 51.1 ± 6.78 | 26.1 ± 7.12 | 4.68 (2.08–25.1) |
| 4 | 23.8 ± 4.30 | 16.1 ± 4.77 | BQL | 28.2 ± 5.32 | 15.7 ± 3.36 | 6.94 (1.26–8.36) |
| 6 | 7.24 ± 2.79 | 7.51 ± 5.29 | BQL | 10.8 ± 2.82 | 8.04 ± 5.81 | 3.85 (2.32–95.9) |
| 8 | 1.36 ± 0.51 | 2.51 ± 1.13 | BQL | 2.74 ± 1.12 | 2.61 ± 1.35 | 2.35 (2.22–11.7) |

Values reported as mean ± standard deviation or median (minimum – maximum)
BAL = bronchoalveolar lavage; h = hours; ELF = epithelial lining fluid; AM = alveolar macrophage; BQL = below the limit of quantitation

**Figure 1: Mean (±SD) Concentration-Versus-Time Profile of Meropenem and Vaborbactam in Plasma (A) and Epithelial Lining Fluid (B) Before and After The Third Dose of Meropenem (2 g) and vaborbactam (2 g) Administered as a 3-h IV infusion**




Note: In panel A, meropenem is illustrated by the filled circles and a solid line, and vaborbactam is illustrated by open circles and a dashed line. In panel B, meropenem is illustrated by the filled triangles and a solid line, and vaborbactam is illustrated by open triangles and a dashed line. Shaded region represents the 3-h infusion period. The y axis is in the log scale.

*Safety Analysis:* Only 2 subjects experienced adverse events. One subject experienced adverse events of headache and vomiting, which were considered by the Investigator to be not related to

study drug. One subject experienced adverse events of chest discomfort (2 events), dizziness (2 events), and dyspnea, which were considered by the Investigator to be possibly related to study drug; an adverse event of chest discomfort resulted in discontinuation of study drug and discontinuation from the study. No subjects had an SAE. No meaningful laboratory, vital sign, ECG, or physical examination findings were observed during the study.

**Applicant's Conclusions:** Meropenem and vaborbactam achieved a similar time course and magnitude of concentrations in plasma and ELF. The intrapulmonary penetrations of meropenem and vaborbactam were calculated as 63 and 53%, respectively based upon ratio of $AUC_{0-8}$ for ELF compared to the corresponding $AUC_{0-8}$ in plasma. When unbound plasma concentrations were considered, ELF penetrations were 65 and 79% for meropenem and vaborbactam, respectively. Meropenem concentrations in AM were below the quantitative limit of detection, whereas mean concentrations of vaborbactam in AM ranged from 2.35 to 6.94 μg/mL. Overall, meropenem/ vaborbactam was well tolerated in this study.

**Reviewer's Assessment:** Study 503 determined and compared plasma epithelial lining fluid and alveolar macrophage concentrations of intravenous (IV) meropenem/ vaborbactam in healthy adult subjects. We concur with the Applicant's conclusions. However, we noticed a slightly higher $AUC_{0-8}$ of meropenem in plasma from this study (mean [CV%]: 186 μg·h/mL [18.1%]) than that from Cohort 5 in Study 501 (mean [CV%]:136 μg·h/mL [20.1%]) when meropenem is administer in the combination with vaborbactam. Such difference may be due to the variability across studies.

### *4.5.5 Study 504: Renal Impairment PK Study*

**Title:** A Phase 1, Open-Label, Single Dose Study to Determine the Safety and Pharmacokinetics of Meropenem/Vaborbactam (Formerly RPX2014/RPX7009) in Subjects with Renal Insufficiency

**Information Regarding the Clinical Trial Site and Duration of the Trial:** The trial was conducted by Rempex Pharmaceuticals, Inc. from January 27, 2014 to September 03, 2014 with the final report date of June 14, 2016.

**Objectives:**
The objectives of this study are:

- To assess the pharmacokinetics (PK) of meropenem/vaborbactam in subjects with renal insufficiency and in subjects receiving hemodialysis (HD) therapy.
- To evaluate the safety and tolerability of meropenem/vaborbactam in subjects with renal insufficiency and in subjects receiving HD therapy.

**Trial Design:**
This was a Phase 1 open-label, single-dose study to assess the safety, tolerability, and PK of intravenous (IV) meropenem and vaborbactam given in combination to adults with varying degrees of renal insufficiency and in adult subjects receiving HD therapy as compared to subjects with normal renal function. Additionally, the clearance of IV meropenem and vaborbactam was determined in subjects with end-stage renal disease (ESRD) both before and after dialysis.

Renal function was determined once at the Screening Visit, calculated using both the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault equations for each subject. Renal insufficiency was categorized by MDRD equation calculations and normal renal function was identified by Cockcroft-Gault equation calculations. Subjects who received HD therapy were admitted to the study based on receiving HD therapy 3 times a week for at least 3 months prior to Day 1.

A total of 41 subjects were enrolled and assigned to one of five groups based on renal function. Subjects were classified as having mild, moderate, or severe renal impairment (Groups 1, 2, and 3, respectively) if they had an estimated glomerular filtration rate (eGFR) of 60 to 89, 30 to <60, or <30 mL/min/1.73m$^2$, respectively, by MDRD equation calculations. Normal renal function (Group 4) was defined as a creatinine clearance (CrCL) ≥90 mL/min by Cockcroft-Gault equation calculations. Group 5 enrolled subjects with end stage renal disease (ESRD) who were receiving hemodialysis therapy 3 times a week for at least 3 months prior to Day 1 of the study.

All subjects received a single IV dose of meropenem 1 g - vaborbactam 1 g in combination as a

3-hour infusion. Subjects in Groups 1 to 4 were dosed on Day 1. Subjects enrolled in Group 5 received two doses separated by a washout. On Day 1, IV infusion of meropenem-vaborbactam ended approximately 2 hours before the start of hemodialysis ("on dialysis"). On Day 8, the dose was administered within 2 hours after the completion of a hemodialysis session ("off dialysis").

**Excluded Medications, Restrictions:**

- Hypersensitivity or idiosyncratic reaction to β-lactam antibiotics (eg, penicillins, cephalosporins, carbapenems, etc.) determined by Investigators' discretion.
- Previously received any dose of meropenem/ vaborbactam.
- Received any investigational drug within 30 days or 5 half-lives, whichever was longer, of Day 1 for the current clinical study.
- Any acute illness that required antibiotic drug therapy within 30 days prior to Day 1 or a febrile illness within 7 days prior to Day 1.
- Positive drug test at the Screening Visit or Day -1 unless results were explained by a prescription medication. Recent history (i.e., within 6 months prior to Day -1) of abuse of prescription or illicit drugs. Subjects with positive cannabinoid results could have participated in the study provided that the subject was counseled and agreed to refrain from using cannabinoids for the duration of study participation.
- Positive alcohol breath test at the Screening Visit or Day -1. Recent history (i.e., within 6 months prior to Day -1) of excessive alcohol intake, defined as an average daily intake greater than 3 units (maximum weekly intake greater than 21 units) where 1 unit equaled half a pint of beer or 1 measure of spirits.
- Concurrent use of medications known to affect the elimination of serum creatinine (e.g., trimethoprim/sulfamethoxazole [Bactrim®] or cimetidine [Tagamet®]) and competitors of renal tubular secretion (e.g., probenecid) within 30 days prior to the first dose of study drug or anticipated need for these therapies through the last PK sample.
- Use of products containing alcohol, caffeine, xanthine, or ephedrine within 48 hours before dosing.

**Rationale for Doses Used in the Trial:** The 1 g meropenem dose was co-administered with 1 g vaborbactam via IV infusion. These doses were selected for subject safety, to mitigate the possibility of drug accumulation in renal insufficiency subjects, and consistent with clinical evidence.

**Drugs Used in the Trial:**

Meropenem for injection was purchased commercially (APP Pharmaceuticals, LLC, Schaumburg, IL) and came packaged in 20-mL, single-use vials each containing 1 g meropenem. The lot number of meropenem is 0023D31.

Vaborbactam was provided by the Applicant's manufacturer (b) (4) (b) (4) as a (b) (4) white to off-white powder presented in 20-mL, single-use

vials each containing 525 mg of vaborbactam to deliver 500 mg vaborbactam when constituted as instructed. The lot number of vaborbactam is CL3-402.

**Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis:** Blood samples for assay of meropenem, meropenem open lactam metabolite and/or vaborbactam concentrations were to be collected pre-dose, and at 1.5 (mid-point of the infusion), 3, 3.25, 3.50, 3.75, 4, 5, 6, 8, 10, 12, and 24 hours after the start of the 3-hour infusion. Voided urine was also collected at 0-4, 4-8, 8-12, 12-24, 24-38, and 48-72 hours after dose administration.

*Bioanalytical method (see Section 4.1 for details for the methods and method validation data):* Plasma/urine samples were assayed for meropenem, its open-lactam metabolite or vaborbactam concentrations using validated high-performance liquid chromatography with mass spectrometric detection. Samples that were expected to be outside of the validated range were appropriately diluted using blank biological fluid prior to sample analysis.

| Analyte | Matrix | Validation Report | Bioanalytical Report |
|---|---|---|---|
| Meropenem | Plasma | # MC13B-0105 | # MC14B-0003 |
| | Urine | #MC13B-0106 | # MC14B-0004 |
| | Dialysis | #MC14B-0172 | # MC14B-0004 |
| Meropenem Open-Lactam | Plasma | # MC13B-0105 | # MC14B-0003 |
| | Urine | #MC13B-0106 | # MC14B-0004 |
| | Dialysis | #MC14B-0172 | # MC14B-0004 |
| Vaborbactam | Plasma | # MC13R-0016 | # MC14B-0003 |
| | Urine | #MC13R-0017 | # MC14B-0004 |
| | Dialysis | #MC14R-0034 | # MC14B-0004 |

*Reviewer's Comment: Based on results from method validation and bioanalytical reports, all above-mentioned analytical methods met the acceptable criteria specified in the FDA Guidance to Industry: Bioanalytical Method Validation.*

*Pharmacokinetic Assessments:* Plasma PK parameters for meropenem and vaborbactam include: $C_{max}$, $T_{max}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $T_{1/2}$, $CL_t$ (total clearance), $CL_{NR}$ (non-renal clearance), $V_{ss}$, $V_z$. Urine PK parameters for meropenem and vaborbactam include: $A_e$ (cumulative amount of drug excreted), $f_e$ (Fraction of dose excreted in the urine over collection interval), $CL_R$ (renal clearance), $CL_{dialysis}$ (dialysis clearance).

*Statistical Analysis:* Summary statistics (N, mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum) were tabulated by group and day for the PK parameters.

The relationship between drug clearance and renal function was quantified using linear regression. For the linear regression analyses, the dependent variables were weight-normalized $CL_R$ (Groups 1 through 4 only) and weight-normalized $CL_t$ (Groups 1 through 4 and Group 5, Day 8). Meropenem and vaborbactam parameters were analyzed separately. Using the data from Group 5 alone, the impact of dialysis on the PK of meropenem and vaborbactam was quantified using the ratio of $CL_t$ on Day 1 to $CL_t$ on Day 8. The probability that the sample mean ratio differed significant from unity (1.0) was tested using a single-sample t-test.

**Results:**

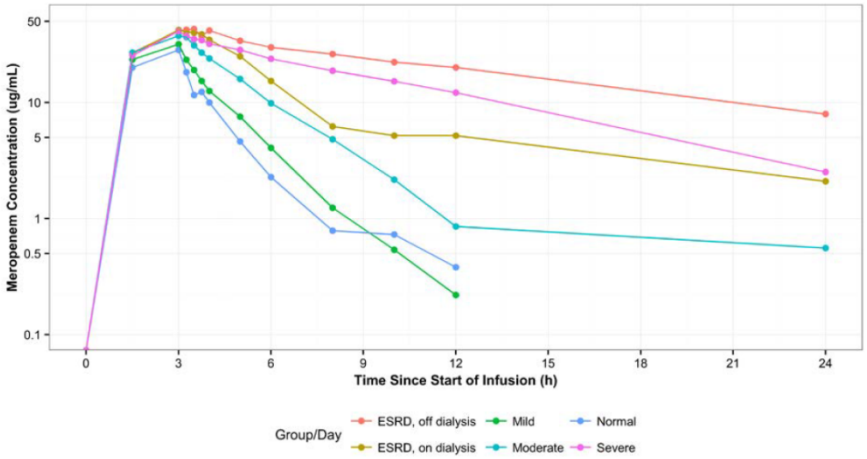
*Subject Demographics and Disposition:* Eight subjects were assigned to each of the normal, mild, moderate, and severe renal function groups, and all of these subjects completed the study. Nine subjects were assigned to the ESRD group, and 1 subject (Subject 05-637) discontinued study participation due to an SAE (prostate cancer metastatic).

*Pharmacokinetic and Statistical Analysis:* Each of the subjects in Groups 1 through 4 (n=32 combined) contributed 1 sampling profile to the PK analysis dataset while the 8 of the 9 subjects from Group 5 contributed two profiles (Days 1 and 8); 1 subject in Group 5 did not have a Day 8 profile.

Plots of the median concentration-time profiles on a semi-log scale for Groups 1 to 5 are provided in Figure 1, Figure 2, and Figure 3 for meropenem, its open lactam metabolite, and vaborbactam, respectively. Summary statistics for selected PK parameters are provided in Table 1, Table 2, and Table 3 for meropenem, its open lactam metabolite, and vaborbactam, respectively.

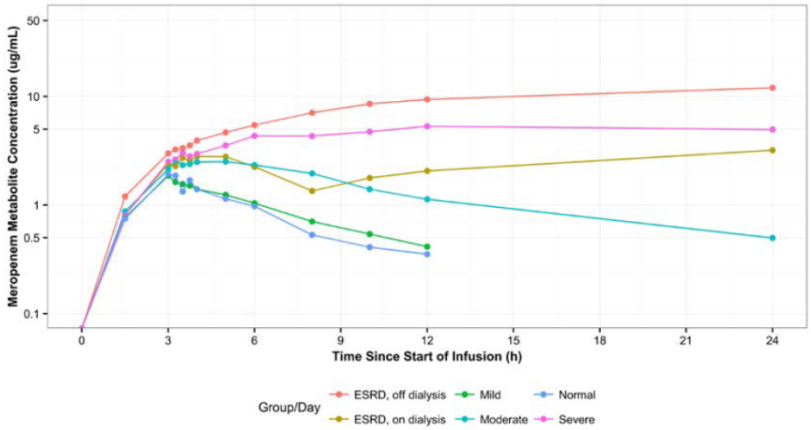
Concentrations of all three analytes increased over time with decreasing renal function. In Group 5, the concentrations fell slightly faster with time when the drugs were administered just before dialysis (Day 1) than when the drugs were administered after the completion of a hemodialysis session, consistent with the expectation that all three analytes are removed by dialysis.

**Figure 1: Plots of Median Meropenem Concentration-Time Profiles, Stratified by Renal Impairment Group and Timing Relative to Dialysis (ESRD only)**



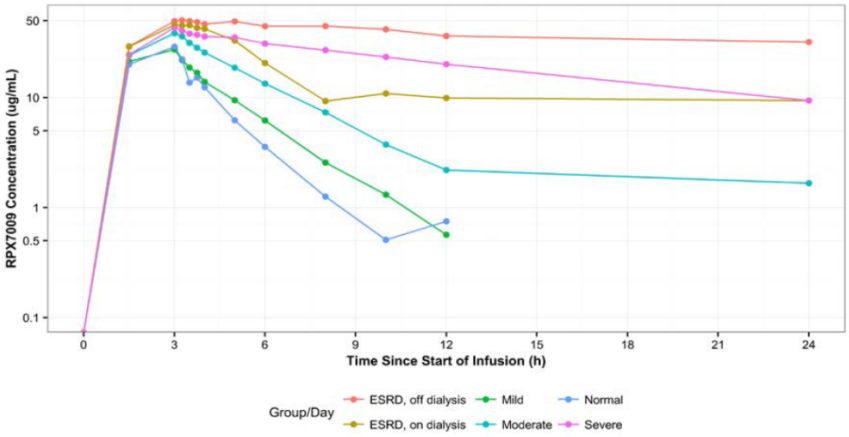

ESRD = end-stage renal disease

**Figure 2: Plots of Median Meropenem Open Lactam Metabolite Concentration-Time Profiles, Stratified by Renal Impairment Group and Timing Relative to Dialysis (ESRD only)**




ESRD = end-stage renal disease

**Figure 3: Plots of Median Vaborbactam Concentration-Time Profiles, Stratified by Renal Impairment Group and Timing Relative to Dialysis (ESRD only)**




RPX7009 = vaborbactam; ESRD = end-stage renal disease

**Table 1: Geometric Mean (Geometric CV%) for Select Plasma PK Parameters for Meropenem Following Single IV Dose of Meropenem 1 g - Vaborbactam 1 g as a 3-hour Infusion (Study 504)**

| Group | N | $C_{max}$ (µg/mL) | $AUC_{0-t}$ (µg*h/mL) | $AUC_{0-inf}$ (µg*h/mL) | CLt (L/h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 1: Mild impairment | 8 | 31.7 (26.3%) | 106 (30.4%) | 107 (30.5%) | 9.33 (30.5%) | 1.42 (12.3%) |
| 2: Moderate impairment | 8 | 40.1 (15.4%) | 169 (32.0%) | 173 (32.9%) | 5.80 (32.9%) | 2.06 (37.1%) |
| 3: Severe impairment | 8 | 44.2 (25.8%) | 355 (21.2%) | 387 (24.3%) | 2.59 (24.3%) | 5.71 (38.6%) |
| 4: Normal | 8 | 26.7 (26.1%) | 82.8 (31.9%) | 83.5 (31.9%) | 12.0 (31.9%) | 1.28 (20.2%) |
| 5: ESRD on dialysis (Day 1) | 9 | 44.1 (18.0%) | 268 (20.9%) | 274 (21.1%) | 3.65 (21.1%) | 9.11 (25.2%) |
| 5: ESRD off dialysis (Day 8) | 8 | 46.6 (22.6%) | 580 (32.0%) | 603 (31.6%) | 1.66 (31.6%) | 9.28 (21.8%) |

CV% = percent coefficient of variation; $C_{max}$ = maximum concentration; $AUC_{0-t}$ = area under the concentration-time curve from 0 to the end of the dosing interval; $AUC_{0-inf}$ = area under the concentration-time curve from 0 to infinity; $CL_t$ = clearance; $t_{1/2}$ = half-life

**Table 2: Geometric Mean (Geometric CV%) for Select Plasma PK Parameters for Meropenem Open-Lactam Metabolite Following Single IV Dose of Meropenem 1 g - Vaborbactam 1 g as a 3-hour Infusion (Study 504)**

| Group | N | $C_{max}$ (µg/mL) | $AUC_{0-t}$ (µg*h/mL) | $AUC_{0-inf}$ (µg*h/mL)[a] | $t_{1/2}$ (h)[a] |
|---|---|---|---|---|---|
| 1: Mild impairment | 8 | 1.90 (22.7%) | 10.7 (38.9%) | 12.7 (42.5%) | 3.39 (21.4%) |
| 2: Moderate impairment | 8 | 2.84 (27.4%) | 27.0 (67.9%) | 32.4 (76.6%) | 5.74 (55.9%) |
| 3: Severe impairment | 8 | 5.78 (21.5%) | 103 (25.8%) | — | — |
| 4: Normal | 8 | 1.79 (27.1%) | 8.67 (39.4%) | 9.87 (40%) | 2.76 (22.4%) |
| 5: ESRD with dialysis (Day 1) | 9 | 3.80 (19.5%) | 132 (25.5%) | 892 (—) | 291 (—) |
| 5: ESRD between dialysis (Day 8) | 8 | 12.4 (55.2%) | 473 (47.7%) | — | — |

[a]Only calculable for one subject in Groups 3 or 5. The remainder of subjects in those groups did not exhibit asufficient terminal elimination phase for meropenem open lactam metabolite. CV% = percent coefficient of variation; $C_{max}$ = maximum concentration; $AUC_{0-t}$ = area under the concentration-time curve from 0 to the end of the dosing interval; $AUC_{0-inf}$ = area under the concentration-time curve from 0 to infinity; $CL_t$ = clearance; $t_{1/2}$ = half-life

**Table 3: Geometric Mean (Geometric CV%) for Select Plasma PK Parameters for Vaborbactam Following Single IV Dose of Meropenem 1 g - Vaborbactam 1 g as a 3-hour Infusion (Study 504)**

| Group | N | $C_{max}$ (µg/mL) | $AUC_{0-t}$ (µg*h/mL) | $AUC_{0-inf}$ (µg*h/mL) | CLt (L/h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 1: Mild impairment | 8 | 29.2 (25.8%) | 110 (25.9%) | 112 (26.3%) | 8.94 (26.3%) | 1.86 (14.8%) |
| 2: Moderate impairment | 8 | 41.8 (17.4%) | 212 (42.5%) | 219 (44.2%) | 4.56 (44.2%) | 3.11 (50.3%) |
| 3: Severe impairment | 8 | 45.1 (25.9%) | 524 (18.8%) | 740 (36.1%) | 1.35 (36.1%) | 11.7 (58.3%) |
| 4: Normal | 8 | 27.1 (24.9%) | 93.5 (34.0%) | 94.7 (34.3%) | 10.6 (34.3%) | 1.62 (22.1%) |
| 5: ESRD with dialysis (Day 1) | 9 | 49.2 (20.0%) | 519 (25.6%) | 966 (62.7%) | 1.04 (62.7%) | 45.7 (78.7%) |
| 5: ESRD between dialysis (Day 8) | 8 | 55.0 (24.7%) | 1550 (36.3%) | 3550 (127%)[a] | 0.282 (127%)[a] | 54.3 (121%)[a] |

[a]n=7 for $AUC_{0-inf}$, $CL_t$, and $t_{1/2}$ on Day 8 in Group 5 (Subject 05-642 did not have a sufficient terminal elimination phase for calculation of the elimination rate constant)
CV% = percent coefficient of variation; $C_{max}$ = maximum concentration; $AUC_{0-t}$ = area under the concentration-time curve from 0 to the end of the dosing interval; $AUC_{0-inf}$ = area under the concentration-time curve from 0 to infinity; $CL_t$ = clearance; $t_{1/2}$ = half-life

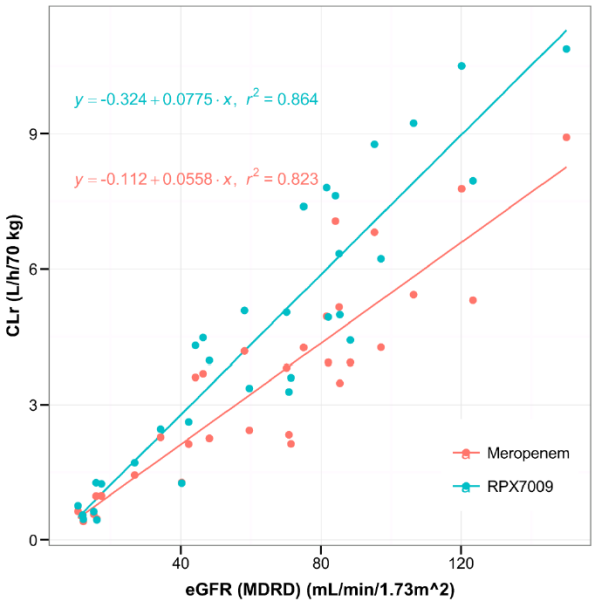
For meropenem, the mean $AUC_{0-inf}$ increased from a low of 87.1 µg•h/mL in subjects with normal renal function to 112, 181, 397, and 629 µg•h/mL in subjects with mild, moderate, and severe renal impairment, and ESRD in between dialysis sessions (Day 8), respectively. A similar trend was seen for $AUC_{0-t}$ for meropenem open lactam metabolite. The trend was also similar for vaborbactam but the magnitude of increase in $AUC_{0-inf}$ was more pronounced as renal function decreased (from 99.4 µg•h/mL in subjects with normal renal function to 781 and 5220 µg•h/mL in subjects with severe renal impairment and ESRD between dialysis sessions, respectively). For both meropenem and vaborbactam, the amount of drug excreted via the urine over the 48-hour

sampling period decreased with decreasing renal function. For all three analytes, AUC was larger and $t_{1/2}$ was longer with decreasing renal function.

In Group 5, the increase in drug clearance with dialysis is illustrated in the comparison of the AUC estimates from Day 1 (on dialysis) and Day 8 (off dialysis). The differences were most pronounced for vaborbactam; the mean $AUC_{0\text{-}inf}$ was nearly 5-times higher after Day 8 administration compared to Day 1 administration. For meropenem, the mean $AUC_{0\text{-}inf}$ was 2.24-times higher on Day 8 relative to Day 1. $AUC_{0\text{-}inf}$ could not be calculated for meropenem open lactam metabolite but the ratio of Day 8 to Day 1 $AUC_{0\text{-}t}$ was 3.77 indicating that the meropenem open lactam metabolite is also significantly cleared by dialysis. Based upon the recovery of drug in dialysate, 38% of the meropenem dose and 53% of the vaborbactam dose can be removed by dialysis.

The relationships between weight-normalized $CL_R$ or $CL_t$ and eGFR are shown in Figure 4 and Figure 5, respectively. The slope of the relationship between vaborbactam $CL_R$ and eGFR was steeper than that for the meropenem $CL_R$ to eGFR relationship (Figure 4), which may be due to the fact that vaborbactam $CL_{NR}$ is very low, which results in a closer correlation between eGFR and $CL_R$. The slopes of the lines for the $CL_t$ to eGFR relationships were nearly identical (Figure 5). The difference between the two figures in regards to meropenem is likely due to the fact that meropenem non-renal clearance increases with increasing eGFR. Changes in the relationship of $CL_t$ to eGFR for both drugs were parallel to one another, indicating that dose adjustments based on renal function would be expected to be proportional and result in a consistent ratio of meropenem and vaborbactam doses and plasma exposures.

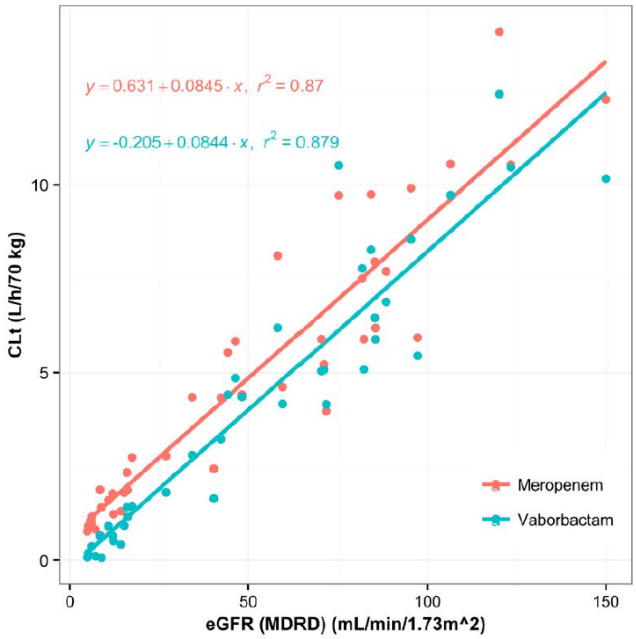
**Figure 4: Relationship between eGFR and $CL_R$ of Meropenem and Vaborbactam – Study 504**




Note: linear regression analyses conducted separately for the two drugs. Data from Groups 1 through 4 only

RPX7009=vaborbacam, CLr = renal clearance; eGFR = glomerular filtration rate as estimated by the Modification of Diet in Renal Disease (MDRD) equation

**Figure 5: Relationship between eGFR and $CL_t$ of Meropenem and Vaborbactam – Study 504**




Note: linear regression analyses conducted separately for the two drugs. Data from Groups 1 through 4 and Group 5, Day 8 only.
RPX7009=vaborbacam, $CL_t$ = clearance; eGFR = glomerular filtration rate as estimated by the Modification of Diet in Renal Disease (MDRD) equation

***Reviewer's Comments:*** *$AUC_{0\text{-}inf}$ of vaborbactam increased to a greater degree than meropenem in subjects with severe renal impairment and in ESRD patients with or without hemodialysis. Therefore, we don't agree with the Applicant's statement of "dose adjustments based on renal function would be expected to be proportional and result in a consistent ratio of meropenem and vaborbactam doses and plasma exposures". The comparison of the slopes of the regression lines over the entire range of eGFR does not inform that the proportional dose adjustments would result in consistent ratio of meropenem and varbobactam exposure in patients with severe renal impairment or ESRD.*

*Safety Analysis:* Overall, for the full study population, 14 subjects (34.1%) reported a total of 20 TEAEs during conduct of the study. The most frequently reported TEAEs were diarrhea, headache, abdominal pain, and dermatitis contact with the SOCs of Gastrointestinal Disorders and Nervous System Disorders having the highest frequency of TEAEs. All TEAEs were mild in severity except 1 moderate TEAE (abdominal pain) and 2 severe TEAEs (1 prostate cancer metastatic and 1 diarrhea hemorrhagic).

A similar proportion of subjects reported at least 1 TEAE in the mild (2 subjects [25.0%]), moderate (3 subjects [37.5%]), severe (1 subject [12.5%]), and normal (2 subjects [25.0%]) renal

function groups. In contrast, in the ESRD group, a larger proportion of subjects in the Period 2 group (5 subjects [62.5%]) reported TEAEs (i.e., when dialysis occurred prior to study drug administration) as compared to the Period 1 group (2 subjects [22.2%]; i.e., when dialysis occurred after study drug administration); however, the type and severity of these AEs in the ESRD group were similar to those AEs observed in the other renal function groups.

Eight of the 20 TEAEs reported in the study were either "possibly" or "probably" related to study treatment and were reported by 7 subjects (17.1%). Only 1 TEAE (prostate cancer metastatic) was ongoing at study completion.

Two SAEs were reported (1 prostate cancer metastatic and 1 diarrhea hemorrhagic) in subjects with ESRD. The event of prostate cancer metastatic resulted in an interruption to study drug dose administration, and the subject did not receive the second dose. No AEs resulted in death. There were no clinically significant trends in 12-lead ECG data, vital signs data, clinical laboratory results, or physical examination data.

**Applicant's Conclusions:**

PK conclusions:

- After single-dose administration of the combination of meropenem 1 g and vaborbactam 1 g to subjects with varying degrees of renal impairment, the clearance of meropenem, meropenem metabolite, and vaborbactam decreased with decreasing renal function.
- The slopes of the relationship between eGFR and meropenem or vaborbactam plasma clearance were similar, indicating a similar proportional reduction in clearance with decreasing renal function. These data suggest that dose reduction in subjects with renal impairment should be similar for both meropenem and vaborbactam.
- While the clearance of meropenem and vaborbactam were similar for normal, mild, and moderate renal impairment, the non-renal clearance and metabolism of meropenem contributed to a greater total clearance in subjects with severe renal impairment.
- Administration of the combination just prior to dialysis in subjects with ESRD resulted in an increase in the clearance of all analytes relative to administration between dialysis sessions.
- Both meropenem and vaborbactam are removed by hemodialysis.

Safety conclusions:

- A single, 3-hour infusion of meropenem/vaborbactam, containing 1 g meropenem and 1 g vaborbactam, was safe and well tolerated in subjects with mild, moderate, severe, and normal renal function, and there was no evidence of increasing incidence or severity of AEs with decreasing renal function.
- In ESRD subjects, the same dose of meropenem/vaborbactam was safe and well tolerated whether administered before or after hemodialysis therapy; however, a greater number of AEs was observed when meropenem/vaborbactam was administered after dialysis

(Period 2) as opposed to when meropenem/vaborbactam was administered prior to dialysis during Period 1 (62.5% versus 22.5%). The AEs occurring during Period 2 were mild in severity except for the single event of diarrhea haemorrhagic which was classified as severe.

**Reviewer's Assessment:** Study 504 assessed the pharmacokinetics (PK) of meropenem/vaborbactam in subjects with renal insufficiency and in subjects receiving hemodialysis (HD) therapy.

Based on the PK results reported by the Applicant, the following conclusions are valid:

- The clearance of meropenem, meropenem metabolite, and vaborbactam decreased with decreasing renal function.
- Both meropenem and vaborbactam are removed by hemodialysis. Based upon the recovery of drug in dialysate, 38% of the meropenem dose and 53% of the vaborbactam dose can be removed by dialysis.
- Administration of the combination just prior to dialysis in subjects with ESRD resulted in an increase in the clearance of all analytes relative to administration between dialysis sessions.

In addition, for meropenem, the $AUC_{0\text{-}inf}$ ratios to subjects with normal renal function are 1.28, 2.07, and 4.63 for subjects with mild, moderate, and severe renal impairment, respectively. In ESRD patients maintained on hemodialysis, the ratio increased to 3.28 when completing infusion of meropenem-vaborbactam  2 hours before the start of dialysis and to 7.22 when dosing meropenem-vaborbactam 2 hours after the end of dialysis. The $AUC_{0\text{-}inf}$ ratios to subjects with normal renal function for vaborbactam are 1.18, 2.31, and 7.8, for subjects with mild, moderate, and severe renal impairment. In ESRD patients maintained on hemodialysis, the ratio increased to 10.2 when completing infusion of meropenem-vaborbactam  2 hours before the start of dialysis and to 37.5 when dosing meropenem-vaborbactam 2 hours after the end of dialysis. . $AUC_{0\text{-}inf}$ of vaborbactam increased in a greater degree than meropenem in subjects with severe renal impairment and in ESRD patients with or without hemodialysis. Accordingly, unlike the Applicant's conclusion, a proportional dose adjustment (dictated by fixed combination product) of meropenem and vaborbactam in patients with severe renal impairment and in ESRD patients would not result in a consistent ratio of meropenem and vaborbactam systemic exposure. The systemic exposure ratio of varborbactam:merepenem will be higher in patients with severe renal impairment and in ESRD patients than in patients with less impaired renal function.

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/s/

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