Table S1. Summary statistics for meropenem and vaborbactam free-drug plasma AUC₀₋₂⁴ on day 1 and at steady state among simulated patients with cUTI or AP by renal function group for the U.S. FDA and EMA submissions

| Free-drug plasma AUC₀₋₂⁴ measure (mg•h/L) | US FDA submission | EMA submission |
|------------------------------------------|-------------------|----------------|
|                                          | Mean %CV Min Median Max | Mean %CV Min Median Max |
| eGFR (mL/min/1.73 m²)                   |                  |                |
| ≥0 to <15                               | 479.06 52.80 82.62 426.30 2600.51 | ≥0 to <10 496.9 51.25 66.38 444.0 2009 |
| ≥15 to <30                              | 638.85 53.22 93.61 569.41 2631.94 | ≥10 to <20 787.3 49.37 116.6 713.3 3105 |
| ≥30 to <50                              | 432.36 51.79 89.14 384.08 1612.30 | ≥20 to <40 690.4 58.10 115.5 606.6 3548 |
| ≥50 to <150                             | 675.07 56.92 113.26 601.98 4384.92 | ≥40 to <150 713.3 54.08 113.7 628.6 2943 |
| ≥150 to ≤200                            | 624.72 52.75 95.83 554.89 2089.70 | ≥150 to ≤200 631.8 55.60 90.37 551.5 2952 |

Day 1 free-drug plasma meropenem AUC₀₋₂⁴

| Day 1 free-drug plasma meropenem AUC₀₋₂⁴ | US FDA submission | EMA submission |
|------------------------------------------|-------------------|----------------|
|                                          | Mean %CV Min Median Max | Mean %CV Min Median Max |
| ≥0 to <15                               | 681.81 62.28 93.85 595.44 4135.80 | ≥0 to <10 735.3 57.80 92.68 626.2 2897 |
| ≥15 to <30                              | 748.55 58.51 94.92 653.14 3825.05 | ≥10 to <20 999.0 53.00 126.8 878.9 3736 |
| ≥30 to <50                              | 453.20 53.26 89.49 399.71 1684.04 | ≥20 to <40 808.2 66.35 115.7 696.3 4390 |
| ≥50 to <150                             | 693.80 58.02 95.89 614.17 3736    | ≥10 to <20 735.7 55.27 114.9 642.9 3140 |
| ≥150 to ≤200                            | 639.63 53.74 95.89 566.70 2292.44 | ≥150 to ≤200 647.2 56.67 91.53 560.9 3230 |

Steady-state free-drug plasma vaborbactam AUC₀₋₂⁴

| Steady-state free-drug plasma vaborbactam AUC₀₋₂⁴ | US FDA submission | EMA submission |
|-------------------------------------------------|-------------------|----------------|
|                                          | Mean %CV Min Median Max | Mean %CV Min Median Max |
| ≥0 to <15                               | 533.03 37.79 142.79 499.88 1539.74 | ≥0 to <10 562.7 36.65 146.8 532.4 1549 |
| ≥15 to <30                              | 699.37 37.67 146.42 627.10 2108.92 | ≥10 to <20 891.1 33.10 294.0 857.0 2420 |
| ≥30 to <50                              | 531.31 41.09 120.50 492.37 1417.95 | ≥20 to <40 737.2 38.29 172.1 695.6 2093 |
| ≥50 to <150                             | 605.15 44.69 147.58 559.30 1848.97 | ≥40 to <150 658.2 46.16 148.6 603.4 1860 |
| ≥150 to ≤200                            | 510.40 42.39 91.46 475.07 1810.01 | ≥150 to ≤200 514.1 41.97 92.57 479.3 1798 |

Day 1 free-drug plasma vaborbactam AUC₀₋₂⁴

| Day 1 free-drug plasma vaborbactam AUC₀₋₂⁴ | US FDA submission | EMA submission |
|-------------------------------------------------|-------------------|----------------|
|                                          | Mean %CV Min Median Max | Mean %CV Min Median Max |
| ≥0 to <15                               | 2868.31 71.53 300.76 2328.80 14508.97 | ≥0 to <10 3653 57.02 692.3 3297 15936 |
| ≥15 to <30                              | 1179.35 62.54 146.92 999.11 8029.06 | ≥10 to <20 2508 62.15 311.2 2146 16482 |
| ≥30 to <50                              | 673.72 53.52 121.92 590.38 2441.44 | ≥20 to <40 1195 63.66 177.9 989.1 7188 |
| ≥50 to <150                             | 656.29 51.32 147.97 593.58 2399.32 | ≥40 to <150 733.4 56.16 149.1 645.5 3519 |
| ≥150 to ≤200                            | 540.21 47.32 91.46 494.73 1925.72 | ≥150 to ≤200 544.9 47.03 92.57 499.1 1911 |

a. To assess the appropriateness of the steady-state free-drug plasma vaborbactam AUC₀₋₂⁴ values in simulated patients with low eGFR or absolute eGFR groups, steady-state free-drug plasma vaborbactam AUC₀₋₂⁴ values in patients with such low eGFR or absolute eGFR values from the TANGO II study included in the population PK dataset were examined. To facilitate comparisons between observed and simulated patients, individual post-hoc PK parameter estimates using baseline measures of renal function were used to generate the steady-state exposures for observed patients. Results of this comparison demonstrated similar trends for exposures in simulated and observed patients.
Table S2. Summary statistics for meropenem and vaborbactam free-drug plasma $\text{AUC}_{0-24}$ on day 1 and at steady state among simulated patients with cUTI/AP for the U.S. FDA and EMA submissions

| Drug and period or baseline renal function measure | US FDA submission | EMA submission |
|-------------------------------------------------|-------------------|----------------|
|                                                 | Mean | %CV | Min | Median | Max | Mean | %CV | Min | Median | Max |
| Meropenem Day 1                                 | 674  | 54.4| 94.7| 595     | 5039| 706  | 52.9| 94.7| 628     | 5039|
| Steady-state                                    | 701  | 55.3| 94.7| 616     | 5340| 739  | 54.9| 94.7| 652     | 5340|
| Vaborbactam Day 1                               | 606  | 45.4| 108 | 554     | 2368| 642  | 47.3| 108 | 581     | 2794|
| Steady-state                                    | 707  | 62.7| 108 | 600     | 5706| 771  | 75.8| 108 | 620     | 8300|
| Baseline eGFR (mL/min/1.73 m²)                  | 84.5 | 36.6| 4.3 | 83.8    | 207 |      |     |     |         |     |
| Baseline absolute eGFR (mL/min)                 |      |     |     |         |     | 87.9 | 36.0| 5.0 | 89.3    | 266 |

a. All simulated patients ($n=3,245$) received meropenem-vaborbactam dosing regimens by eGFR or absolute eGFR as described in Table 1. Simulated patients with cUTI or AP and eGFR or absolute eGFR > 200 mL/min were assigned the same meropenem-vaborbactam dosing regimen as those with eGFR or absolute eGFR ≥ 150 to ≤ 200 mL/min.
### Table S3. Meropenem and meropenem-vaborbactam MIC distributions for Enterobacterales, KPC-producing Enterobacterales, and *P. aeruginosa* isolates based on *in vitro* surveillance data collected from regions worldwide

| Drug                        | Number of isolates at MIC (µg/mL; cumulative %)\(^a\) | <0.03 | 0.03 | 0.06 | 0.12 | 0.25 | 0.50 | 1.00 | 2.00 | 4.00 | 8.00 | 16.00 | 32.00 | >32.00 | MIC\(_{50}\) | MIC\(_{90}\) |
|-----------------------------|------------------------------------------------------|-------|------|------|------|------|------|------|------|------|------|-------|-------|--------|--------|--------|
| **All Enterobacterales (n=11,559)\(^b\)** | **Meropenem**                                        | 5595  | 3799 | 1321 | 338  | 73   | 44   | 36   | 44   | 48   | 44   | 62    | 48    | 107    | 0.03   | 0.06   |
|                             |                                                     | (48.4)| (81.3)| (92.7)| (95.6)| (96.3)| (96.6)| (96.9)| (97.3)| (97.7)| (98.1)| (98.7)| (99.1)| (100)  |        |        |
|                             | **Meropenem-vaborbactam**                           | 4551  | 5193 | 1208 | 271  | 89   | 69   | 50   | 28   | 14   | 9    | 22    | 32    | 23     | 0.03   | 0.06   |
|                             |                                                     | (39.4)| (84.3)| (94.7)| (97.1)| (97.9)| (98.5)| (98.9)| (99.1)| (99.3)| (99.5)| (99.8)| (100)  |        |        |
| **All KPC-producing Enterobacterales (n=1,331)\(^b\)** | **Meropenem**                                        | –     | –    | –    | –    | –    | –    | –    | –    | –    | –    | –     | 5     | (0.40) | 116    | (85.0) |
|                             |                                                     | –     | –    | –    | –    | –    | –    | –    | –    | –    | –    | –     | (0.50)| (0.40) | (13.4) | (25.4) |
|                             | **Meropenem-vaborbactam**                           | 515   | 68   | 78   | 89   | 195  | 186  | 110  | 55   | 22   | 7    | 1     | 3     | 32     | 0.12   | 1      |
|                             |                                                     | (38.7)| (43.8)| (49.7)| (56.3)| (71.0)| (85.0)| (93.2)| (97.4)| (99.0)| (99.5)| (99.8)| (100)  |        |        |
| **All P. aeruginosa (n=2,806)\(^b\)** | **Meropenem**                                        | 15.0  | 47.0 | 194  | 321  | 540  | 477  | 293  | 193  | 170  | 189  | 173   | 64    | 130    | 0.50   | 16     |
|                             |                                                     | (0.50)| (2.20)| (9.10)| (20.6)| (39.8)| (56.8)| (71.2)| (74.1)| (80.2)| (86.9)| (93.1)| (95.4)| (100)  |        |        |
|                             | **Meropenem-vaborbactam**                           | 30    | 65   | 193  | 310  | 525  | 462  | 298  | 186  | 187  | 167  | 187   | 71    | 125    | 0.50   | 16     |
|                             |                                                     | (1.10)| (3.40)| (10.3)| (21.3)| (40.0)| (56.5)| (67.1)| (73.7)| (80.4)| (86.4)| (93.0)| (95.5)| (100)  |        |        |

\(^a\) Shaded cells represent the MIC values up to and/or including the MIC\(_{90}\) value.

\(^b\) Enterobacterales, KPC-producing Enterobacterales, and *P. aeruginosa* isolates were collected as part of the 2014-2015 SENTRY Antimicrobial Surveillance Program [1, 2, 3, 4].
Figure S1. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC on day 1 based on the assessment of the meropenem free-drug plasma %T>MIC ≥ 30% target and MIC data for collections of isolates among simulated patients with cUTI or AP by eGFR and absolute eGFR groups after administration of meropenem-vaborbactam dosing regimens for the U.S. FDA and EMA submissions, overlaid on the meropenem-vaborbactam MIC distributions for Enterobacterales (top), KPC-producing Enterobacterales (middle), and *P. aeruginosa* (bottom) isolates.
Figure S2. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC on day 1 based on the assessment of the meropenem free-drug plasma %T>MIC ≥ 35% target and MIC data for collections of isolates among simulated patients with cUTI or AP by eGFR and absolute eGFR groups after administration of meropenem-vaborbactam dosing regimens for the U.S. FDA and EMA submissions, overlaid on the meropenem-vaborbactam MIC distributions for Enterobacterales (top), KPC-producing Enterobacterales (middle), and *P. aeruginosa* (bottom) isolates.
Figure S3. Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC on day 1 based on the assessment of the meropenem free-drug plasma %T>MIC ≥ 45% target and MIC data for collections of isolates among simulated patients with cUTI or AP by eGFR and absolute eGFR groups after administration of meropenem-vaborbactam dosing regimens for the U.S. FDA and EMA submissions, overlaid on the meropenem-vaborbactam MIC distributions for Enterobacterales (top), KPC-producing Enterobacterales (middle), and *P. aeruginosa* (bottom) isolates.
Explanation for Figure S4

The steps of the algorithm, which were applied by using sets of meropenem and vaborbactam free-drug plasma PK-PD targets associated with net bacterial stasis and 1- and 2-log\(_{10}\) CFU reductions from baseline for the assessment of meropenem-vaborbactam dosing regimens, are described below.

- If the meropenem MIC value for the isolate was less than or equal to the meropenem-vaborbactam MIC value, then the given meropenem free-drug plasma %\(T>MIC\) was calculated using the meropenem MIC value and compared to the meropenem free-drug plasma %\(T>MIC\) target for the same bacterial reduction endpoint.
  - If the calculated meropenem free-drug plasma %\(T>MIC\) was at least equal to the meropenem free-drug plasma %\(T>MIC\) target, PK-PD target attainment was classified as achieved,
  - and if not, as not achieved.

- If the meropenem MIC value for the isolate was greater than the meropenem-vaborbactam MIC value, the given meropenem free-drug plasma %\(T>MIC\) was calculated using the meropenem MIC value and compared to the meropenem free-drug plasma %\(T>MIC\) target.
  - If the calculated meropenem free-drug plasma %\(T>MIC\) was at least equal to the meropenem free-drug plasma %\(T>MIC\) target, PK-PD target attainment was classified as achieved.
  - If not, the vaborbactam free-drug plasma AUC:MIC ratio (calculated using the meropenem-vaborbactam MIC value) was calculated in order to assess whether or not the meropenem-vaborbactam, MIC value can be used.
    - If the calculated vaborbactam free-drug plasma AUC:MIC ratio was at least equal to the vaborbactam free-drug plasma AUC:MIC ratio target for a given endpoint, the meropenem free-drug plasma %\(T>MIC\) (using the meropenem-vaborbactam MIC value) was calculated and compared to the meropenem free-drug plasma %\(T>MIC\) target.
      - If the calculated meropenem free-drug plasma %\(T>MIC\) was at least equal to the meropenem free-drug plasma %\(T>MIC\) target, PK-PD target attainment was classified as achieved,
      - and if not, as not achieved.
    - If the calculated vaborbactam free-drug plasma AUC:MIC ratio was less than the vaborbactam free-drug plasma AUC:MIC ratio target, PK-PD target attainment was classified as not achieved (given that the meropenem free-drug plasma %\(T>MIC\) target had not been achieved using the meropenem MIC value).
Figure S4. Algorithm to calculate percent probabilities of PK-PD target attainment for meropenem-vaborbactam dosing regimens evaluated
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