

Version Date: February 21, 2019

**Evaluation of Plazomicin, Tigecycline, and Meropenem Pharmacodynamic Exposure  
against Carbapenem-Resistant Enterobacteriaceae in Evaluable Patients from the  
CARE Study (ACHN-490-007)**

Supplementary Data

*Tigecycline and Meropenem Analytical Methods*

Remnant plasma from these samples was thawed and tested for tigecycline or meropenem concentration by Alturas Analytics, Inc. (Moscow, ID) using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) assay. Briefly, an aliquot of the extract was injected onto an HPLC/MS/MS triple quadrupole mass spectrometer (Sciex API5500 and API6500). A Discovery HS-C18, 3  $\mu$ m HPLC column (2.1 x 50 mm) from Supelco (Bellefonte, PA) was used to separate tigecycline, meropenem, and the stable labeled internal standards (IS), Meropenem-d6 and Tigecycline-d9, from interfering compounds that may have been present in the sample extract. The peak area of the product ion of tigecycline and meropenem was measured against the peak area of the product ion of the respective IS. The multiple reaction monitoring (MRM) transitions for tigecycline and the IS were  $m/z$  586.5  $\rightarrow$  513.2 and  $m/z$  595.1  $\rightarrow$  514.2, respectively. The MRM transitions for meropenem and the IS were  $m/z$  384.8  $\rightarrow$  114.0 and  $m/z$  391.0  $\rightarrow$  113.6, respectively. A calibration curve (eight concentrations in duplicate) ranging from 50 to 2000 ng/mL or 150 to 40,000 ng/mL was used to quantify tigecycline and meropenem in the samples, respectively.

**Table S1.** Raw concentration data for tigecycline and meropenem

| Patient Number | Visit       | Actual Sampling Date | Actual Sampling Time | Concentration (ng/mL) | Analyte     |
|----------------|-------------|----------------------|----------------------|-----------------------|-------------|
| 3              | Day 1       | 10-Sep-15            | 21:40:00             | 965                   | Tigecycline |
| 3              | Day 1       | 10-Sep-15            | 23:30:00             | 160                   | Tigecycline |
| 3              | Day 1       | 11-Sep-15            | 6:36:00              | 95.8                  | Tigecycline |
| 3              | Day 4       | 13-Sep-15            | 21:30:00             | 114                   | Tigecycline |
| 3              | Day 4       | 13-Sep-15            | 23:30:00             | 235                   | Tigecycline |
| 3              | Day 4       | 14-Sep-15            | 6:30:00              | 121                   | Tigecycline |
| 3              | Unscheduled | 15-Sep-15            | 21:30:00             | 150                   | Tigecycline |
| 3              | Unscheduled | 16-Sep-15            | 14:10:00             | 355                   | Tigecycline |
| 3              | Day 8       | 18-Sep-15            | 9:35:00              | 139                   | Tigecycline |
| 3              | Day 8       | 19-Sep-15            | 1:55:00              | 370                   | Tigecycline |
| 4              | Day 1       | 9-May-15             | 17:10:00             | 1820                  | Meropenem   |
| 4              | Day 1       | 9-May-15             | 17:55:00             | 1230                  | Meropenem   |
| 4              | Day 1       | 9-May-15             | 22:25:00             | 9250                  | Meropenem   |
| 4              | Day 1       | 10-May-15            | 2:25:00              | 10600                 | Meropenem   |
| 4              | Day 1       | 10-May-15            | 10:25:00             | 12800                 | Meropenem   |
| 4              | Day 1       | 10-May-15            | 16:28:00             | 5210                  | Meropenem   |
| 4              | EOT         | 22-May-15            | 20:30:00             | 79.2                  | Tigecycline |
| 4              | EOT         | 23-May-15            | 2:32:00              | 65.1                  | Tigecycline |
| 4              | EOT         | 23-May-15            | 15:40:00             | 303                   | Tigecycline |
| 5              | Day 1       | 22-Dec-15            | 13:30:00             | 742                   | Tigecycline |
| 5              | Day 1       | 22-Dec-15            | 16:00:00             | 711                   | Tigecycline |
| 5              | Day 1       | 22-Dec-15            | 22:00:00             | 424                   | Tigecycline |
| 6              | Day 1       | 25-Oct-14            | 21:30:00             | 701                   | Tigecycline |
| 6              | Day 1       | 26-Oct-14            | 2:00:00              | 109                   | Tigecycline |
| 6              | Day 1       | 26-Oct-14            | 5:00:00              | 102                   | Tigecycline |
| 6              | Day 1       | 26-Oct-14            | 13:00:00             | 134                   | Tigecycline |
| 6              | Day 1       | 26-Oct-14            | 19:00:00             | 217                   | Tigecycline |
| 6              | Day 7       | 31-Oct-14            | 20:30:00             | 187                   | Tigecycline |
| 6              | Day 7       | 1-Nov-14             | 5:00:00              | 267                   | Tigecycline |
| 6              | EOT         | 5-Nov-14             | 19:45:00             | 297                   | Tigecycline |
| 6              | EOT         | 5-Nov-14             | 20:30:00             | 280                   | Tigecycline |
| 6              | EOT         | 6-Nov-14             | 7:00:00              | 405                   | Tigecycline |
| 6              | EOT         | 6-Nov-14             | 13:00:00             | 307                   | Tigecycline |
| 6              | EOT         | 7-Nov-14             | 7:00:00              | 147                   | Tigecycline |
| 6              | EOT         | 7-Nov-14             | 19:00:00             | 140                   | Tigecycline |
| 7              | EOT         | 2-Dec-14             | 4:45:00              | 99.2                  | Tigecycline |
| 7              | EOT         | 2-Dec-14             | 5:30:00              | 85.6                  | Tigecycline |
| 7              | EOT         | 2-Dec-14             | 7:00:00              | 88.8                  | Tigecycline |
| 7              | EOT         | 2-Dec-14             | 12:00:00             | 69                    | Tigecycline |
| 7              | EOT         | 2-Dec-14             | 16:00:00             | 50.6                  | Tigecycline |
| 7              | Day 7       | 24-Nov-14            | 17:30:00             | 148                   | Tigecycline |
| 7              | Day 7       | 24-Nov-14            | 23:50:00             | 96.3                  | Tigecycline |
| 7              | Day 1       | 18-Nov-14            | 16:45:00             | 263                   | Tigecycline |
| 7              | Day 1       | 18-Nov-14            | 17:30:00             | 193                   | Tigecycline |
| 7              | Day 1       | 18-Nov-14            | 22:00:00             | 129                   | Tigecycline |
| 7              | Day 1       | 19-Nov-14            | 2:00:00              | 182                   | Tigecycline |
| 7              | Day 1       | 19-Nov-14            | 10:00:00             | 82.9                  | Tigecycline |
| 7              | Day 1       | 19-Nov-14            | 16:00:00             | 161                   | Tigecycline |
| 8              | Day 4       | 13-Sep-15            | 14:30:00             | 213                   | Tigecycline |
| 8              | Day 4       | 13-Sep-15            | 17:00:00             | 99.4                  | Tigecycline |
| 8              | Day 4       | 13-Sep-15            | 21:00:00             | 286                   | Tigecycline |
| 8              | Day 8       | 17-Sep-15            | 14:15:00             | 138                   | Tigecycline |
| 8              | Day 8       | 17-Sep-15            | 21:00:00             | 416                   | Tigecycline |

|    |             |           |          |      |             |
|----|-------------|-----------|----------|------|-------------|
| 8  | Day 1       | 10-Sep-15 | 22:50:00 | 203  | Tigecycline |
| 9  | Unscheduled | 4-Oct-15  | 20:00:00 | 106  | Tigecycline |
| 9  | Day 1       | 30-Sep-15 | 20:30:00 | 362  | Tigecycline |
| 9  | Day 1       | 1-Oct-15  | 2:15:00  | 194  | Tigecycline |
| 9  | Day 4       | 2-Oct-15  | 16:30:00 | 357  | Tigecycline |
| 9  | Day 4       | 2-Oct-15  | 19:00:00 | 273  | Tigecycline |
| 9  | Day 4       | 3-Oct-15  | 1:00:00  | 119  | Tigecycline |
| 9  | Unscheduled | 5-Oct-15  | 12:30:00 | 804  | Tigecycline |
| 9  | Unscheduled | 6-Oct-15  | 5:00:00  | 127  | Tigecycline |
| 9  | Unscheduled | 9-Oct-15  | 14:30:00 | 324  | Tigecycline |
| 9  | Unscheduled | 10-Oct-15 | 7:30:00  | 96.6 | Tigecycline |
| 9  | Day 8       | 7-Oct-15  | 14:30:00 | 209  | Tigecycline |
| 9  | Day 8       | 8-Oct-15  | 7:30:00  | 142  | Tigecycline |
| 10 | EOT         | 9-Oct-14  | 20:45:00 | 385  | Tigecycline |
| 10 | EOT         | 9-Oct-14  | 21:30:00 | 452  | Tigecycline |
| 10 | EOT         | 10-Oct-14 | 2:00:00  | 577  | Tigecycline |
| 10 | EOT         | 10-Oct-14 | 6:00:00  | 461  | Tigecycline |
| 10 | EOT         | 10-Oct-14 | 14:00:00 | 298  | Tigecycline |
| 10 | EOT         | 10-Oct-14 | 20:00:00 | 289  | Tigecycline |
| 10 | Day 1       | 27-Sep-14 | 2:00:00  | 284  | Tigecycline |
| 10 | Day 1       | 27-Sep-14 | 6:00:00  | 165  | Tigecycline |
| 10 | Day 1       | 27-Sep-14 | 14:00:00 | 199  | Tigecycline |
| 10 | Day 1       | 27-Sep-14 | 20:00:00 | 138  | Tigecycline |
| 10 | Day 7       | 2-Oct-14  | 21:30:00 | 174  | Tigecycline |
| 10 | Day 7       | 3-Oct-14  | 6:00:00  | 197  | Tigecycline |
| 11 | EOT         | 30-Apr-15 | 15:16:00 | 171  | Tigecycline |
| 11 | EOT         | 30-Apr-15 | 16:01:00 | 156  | Tigecycline |
| 11 | EOT         | 30-Apr-15 | 20:30:00 | 135  | Tigecycline |
| 11 | EOT         | 1-May-15  | 0:31:00  | 119  | Tigecycline |
| 11 | EOT         | 1-May-15  | 8:32:00  | 88.9 | Tigecycline |
| 11 | EOT         | 1-May-15  | 14:15:00 | 59   | Tigecycline |
| 11 | Day 1       | 19-Apr-15 | 15:16:00 | 182  | Tigecycline |
| 11 | Unscheduled | 21-Apr-15 | 16:07:00 | 143  | Tigecycline |
| 11 | Day 1       | 19-Apr-15 | 16:00:00 | 187  | Tigecycline |
| 11 | Day 1       | 19-Apr-15 | 20:31:00 | 498  | Tigecycline |
| 11 | Unscheduled | 22-Apr-15 | 0:25:00  | 154  | Tigecycline |
| 11 | Day 1       | 20-Apr-15 | 0:31:00  | 159  | Tigecycline |
| 11 | Day 1       | 20-Apr-15 | 8:43:00  | 888  | Tigecycline |
| 11 | Day 1       | 20-Apr-15 | 14:30:00 | 140  | Tigecycline |
| 11 | Unscheduled | 28-Apr-15 | 16:03:00 | 160  | Tigecycline |
| 11 | Unscheduled | 29-Apr-15 | 0:35:00  | 209  | Tigecycline |
| 11 | Day 7       | 25-Apr-15 | 16:03:00 | 135  | Tigecycline |
| 11 | Day 7       | 26-Apr-15 | 0:18:00  | 220  | Tigecycline |
| 12 | Unscheduled | 22-May-15 | 0:30:00  | 671  | Tigecycline |
| 12 | Day 1       | 19-May-15 | 0:34:00  | 1390 | Tigecycline |
| 12 | Day 1       | 19-May-15 | 5:10:00  | 250  | Tigecycline |
| 12 | Unscheduled | 22-May-15 | 9:00:00  | 151  | Tigecycline |
| 12 | Day 1       | 19-May-15 | 9:01:00  | 162  | Tigecycline |
| 12 | Day 1       | 19-May-15 | 17:01:00 | 206  | Tigecycline |
| 12 | Day 1       | 19-May-15 | 22:59:00 | 93.9 | Tigecycline |
| 12 | EOT         | 31-May-15 | 23:45:00 | 101  | Tigecycline |
| 12 | EOT         | 1-Jun-15  | 0:34:00  | 418  | Tigecycline |
| 12 | EOT         | 1-Jun-15  | 11:05:00 | 148  | Tigecycline |
| 12 | EOT         | 1-Jun-15  | 17:00:00 | 77.8 | Tigecycline |
| 12 | Unscheduled | 28-May-15 | 0:20:00  | 431  | Tigecycline |
| 12 | EOT         | 2-Jun-15  | 11:00:00 | 58.8 | Tigecycline |
| 12 | Unscheduled | 28-May-15 | 16:54:00 | 224  | Tigecycline |

|    |             |           |          |       |             |
|----|-------------|-----------|----------|-------|-------------|
| 12 | Day 7       | 24-May-15 | 0:27:00  | 630   | Tigecycline |
| 12 | Day 7       | 24-May-15 | 16:48:00 | 205   | Tigecycline |
| 15 | Unscheduled | 3-Sep-15  | 1:55:00  | 4930  | Meropenem   |
| 15 | Day 1       | 1-Sep-15  | 0:20:00  | 25700 | Meropenem   |
| 15 | Unscheduled | 3-Sep-15  | 4:25:00  | 53600 | Meropenem   |
| 15 | Day 1       | 1-Sep-15  | 3:00:00  | 27700 | Meropenem   |
| 15 | Unscheduled | 3-Sep-15  | 17:55:00 | 43100 | Meropenem   |
| 15 | Day 4       | 4-Sep-15  | 23:40:00 | 15300 | Meropenem   |
| 15 | Day 4       | 5-Sep-15  | 2:10:00  | 19800 | Meropenem   |
| 15 | Day 4       | 5-Sep-15  | 16:10:00 | 50100 | Meropenem   |
| 15 | Day 8       | 8-Sep-15  | 23:40:00 | 21500 | Meropenem   |
| 15 | Day 8       | 9-Sep-15  | 16:10:00 | 59400 | Meropenem   |
| 16 | Day 1       | 1-May-15  | 1:30:00  | 271   | Tigecycline |
| 16 | Day 1       | 1-May-15  | 5:30:00  | 259   | Tigecycline |
| 16 | Day 1       | 1-May-15  | 13:30:00 | 387   | Tigecycline |
| 16 | Day 1       | 1-May-15  | 19:30:00 | 500   | Tigecycline |

EOT, end of therapy

**Table S2.** Median individual Bayesian posterior parameter estimates for the 11 tigecycline patients compared with covariate-based clearance estimate

| Patient Number | Population Model Derived PK Estimates |        |                        |                        | Covariate Based<br>CL (L/hr) |
|----------------|---------------------------------------|--------|------------------------|------------------------|------------------------------|
|                | CL (L/h)                              | Vc (L) | kcp (h <sup>-1</sup> ) | kpc (h <sup>-1</sup> ) |                              |
| 3              | 22.3                                  | 118.9  | 5.688                  | 1.883                  | 14.6                         |
| 4              | 37.0                                  | 100.2  | 1.046                  | 0.375                  | 33.4                         |
| 5              | 19.0                                  | 89.1   | 1.945                  | 1.269                  | 18.6                         |
| 6              | 15.0                                  | 79.3   | 2.575                  | 0.299                  | 26.6                         |
| 7              | 37.0                                  | 100.3  | 1.045                  | 0.376                  | 30.6                         |
| 8              | 37.0                                  | 100.3  | 1.045                  | 0.375                  | 24.6                         |
| 9              | 22.5                                  | 149.0  | 3.583                  | 1.986                  | 17.0                         |
| 10             | 19.5                                  | 89.1   | 4.152                  | 1.268                  | 16.0                         |
| 11             | 24.2                                  | 26.1   | 7.885                  | 0.110                  | 66.8                         |
| 12             | 19.4                                  | 21.9   | 4.195                  | 0.490                  | 19.8                         |
| 16             | 19.2                                  | 88.6   | 3.540                  | 1.262                  | 18.6                         |

CL, clearance; Vc, volume of distribution of the central compartment; kcp and kpc, intercompartment transfer constants between central and peripheral compartments and vice versa, respectively

**Table S3.** Tigecycline total drug daily AUC exposure at steady-state based on population pharmacokinetic parameters (n=11 patients) and covariate-based parameter estimates (n=12 patients)

| Patient Number  | Population PK Parameter Based<br>Steady-state AUC <sub>24</sub> <sup>a</sup> | Covariate-Based<br>Steady-state AUC <sub>24</sub> <sup>b</sup> |
|-----------------|--|--|
| 3               | 4.48   | 6.83   |
| 4               | 2.70   | 2.99   |
| 5               | 10.53  | 10.72  |
| 6               | 6.67   | 3.75   |
| 7               | 2.70   | 3.27   |
| 8               | 5.41   | 8.14   |
| 9               | 4.44   | 5.89   |
| 10              | 5.13   | 6.26   |
| 11              | 4.13   | 1.50   |
| 12              | 5.15   | 5.05   |
| 16              | 5.20   | 5.37   |
| 17 <sup>c</sup> | N/A  | 5.86   |

N/A, not available

<sup>a</sup> AUC exposure at steady-state calculated as 24 hour maintenance dose divided by clearance (CL)

<sup>b</sup> Calculated from Rubino and colleagues, as 24 hour maintenance dose divided by CL, where  $CL = (19.6 + (10.2 \cdot BSA - 1.73)) + (0.0638 \cdot (CrCL - 100))$ , where BSA is body surface area (1.92 m<sup>2</sup> for 278001) and CrCL is baseline creatinine clearance.

<sup>c</sup> Patient 17 did not provide any concentration data, so clearance was estimated based on a covariate-based model only.

**Table S4.** Pharmacokinetic parameter estimates for the 4 patients receiving meropenem in the CARE Study, with the final population PK model using observed concentration data (Patients 4 and 15) presented on the left and estimates from a covariate-based population model on the right (all patients)

| Patient Number | Population PK Parameter Estimates |        |                        |                        | Covariate-based PK Parameter Estimates |                     |                                     |                                     |
|----------------|-----------------------------------|--------|------------------------|------------------------|--|---------------------|-------------------------------------|-------------------------------------|
|                | CL (L/h)                          | Vc (L) | kcp (h <sup>-1</sup> ) | kpc (h <sup>-1</sup> ) | CL (L/h) <sup>a</sup>                  | Vc (L) <sup>b</sup> | kcp (h <sup>-1</sup> ) <sup>c</sup> | kpc (h <sup>-1</sup> ) <sup>c</sup> |
| 4              | 22.0                              | 40.9   | 9.95                   | 4.41                   | 20.4                                   | 24.3                | 0.487                               | 0.647                               |
| 15             | 3.2                               | 49.7   | 9.95                   | 0.74                   | 6.3                                    | 14.3                | 0.487                               | 0.647                               |
| 1              | N/A                               | N/A    | N/A                    | N/A                    | 10.2                                   | 16.7                | 0.487                               | 0.647                               |
| 2              | N/A                               | N/A    | N/A                    | N/A                    | 9.5                                    | 16.5                | 0.487                               | 0.647                               |

PK, pharmacokinetic; CL, clearance; Vc, volume of distribution of the central compartment; kcp and kpc, intercompartment transfer constants between central and peripheral compartments and vice versa, respectively; N/A, not available

<sup>a</sup> Calculated from Crandon and colleagues,  $CL = (0.392 + 0.003 * CrCL) * Vc$

<sup>b</sup> Calculated from Crandon and colleagues,  $Vc = 0.239 * \text{Adjusted Body Weight}$ , where adjusted body weight =  $IBW + (0.4 * (ABW - IBW))$ . If adjusted body weight is <20% above ideal body weight (IBW), then use actual body weight (ABW).

<sup>c</sup> From Crandon and colleagues, median population estimates for kcp and kpc were 0.487 and 0.647 h<sup>-1</sup>. No covariates predicted estimates of kcp or kpc.