Ceftazidime-Avibactam Susceptibility Breakpoints Against Enterobacteriaceae and Pseudomonas aeruginosa

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Running header: Ceftazidime-avibactam MIC breakpoints

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ABSTRACT

Clinical susceptibility breakpoints against *Enterobacteriaceae* and *Pseudomonas aeruginosa* for the ceftazidime-avibactam dosage regimen of 2000-500 mg every 8 hours (q8h) by 2-h intravenous infusion (adjusted for renal function) have been established by the FDA, CLSI and EUCAST as susceptible, MIC ≤8 mg/L, and resistant, MIC >8 mg/L. The key supportive data from PK/PD analyses, *in vitro* surveillance including molecular understanding of relevant resistance mechanisms, and efficacy in regulatory clinical trials, are collated and analyzed here.

Word count: 75
Ceftazidime-avibactam is active in vitro against ESBL-, AmpC- and serine-carbapenemase- (e.g. KPC-) producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*, but not metallo β-lactamase (MBL) producers (1-6). Ceftazidime-avibactam clinical breakpoints of susceptible/resistant, MIC ≤8/>8 mg/L (tested with a fixed avibactam concentration of 4 mg/L (7)) have been assigned to both *Enterobacteriaceae* and *P. aeruginosa* by the United States (US) Food and Drug Administration (FDA), Clinical and Laboratory Standards Institute (CLSI), and European Committee on Antimicrobial Susceptibility Testing (EUCAST) for ceftazidime-avibactam 2000-500 mg q8h (8-10) based on three key data sources (11-13): probabilities of pharmacokinetic/pharmacodynamic (PK/PD) target attainment (PTA) analyses; multinational surveillance; and clinical trials.

PK/PD targets were derived from non-clinical studies for avibactam, and from non-clinical and clinical studies for ceftazidime. An established target for ceftazidime, used previously to support ceftazidime breakpoint determinations, is 50% $fT>MIC$ per dosing interval (13-18). For avibactam to render bacteria functionally β-lactamase-negative (19), it must maintain a critical threshold concentration ($C_T$) for 50% of the dosing interval (20). Conservative $C_T$ values for avibactam in combination with ceftazidime considered to correlate with clinical efficacy have been determined as 0.5 mg/L for up to 3 log$_{10}$ CFU reduction in an *Enterobacteriaceae* hollow-fiber model and 1 mg/L for bacteriostasis in a *P. aeruginosa* neutropenic mouse thigh infection model and 2 log$_{10}$ killing in a *P. aeruginosa* neutropenic mouse lung infection model (20-22). PTA analyses for both *Enterobacteriaceae* and *P. aeruginosa* used ‘joint’ PK/PD targets,
defined as simultaneous attainment of 50% $fT>MIC$ for ceftazidime and 50% $C_T>1\text{ mg/L}$ for avibactam in each patient (20).

Population PK models for ceftazidime and avibactam were developed using PK data from Phase I, II and III trials (23-25). As both drugs are excreted predominantly via the kidney, the primary covariate affecting exposure is creatinine clearance (CrCL), necessitating dosage adjustments for patients with CrCL <50 mL/min (8, 9). Exposure simulations for each compound in 5000 paired patients per indication (complicated intra-abdominal infections [cIAI], complicated urinary tract infections [cUTI], and nosocomial pneumonia [NP] including ventilator-associated pneumonia [VAP]) and renal function group, incorporated Phase III patient covariate distributions appropriate to each patient population and between-subject variability; exposure for both ceftazidime and avibactam was simulated in the same (virtual) patients to evaluate joint PTA (25, 26). Representative PTA curves in cIAI patients (the most conservative indication for PTA) with normal renal function (Figures 1A and 1B) were overlaid with MIC distributions from the International Network for Optimal Resistance Monitoring (INFORM) surveillance program. The simulations yielded PTA >94% against bacteria with ceftazidime-avibactam MICs ≤8 mg/L; lower PTA values were associated with MICs of 16 mg/L or ≥32 mg/L. Sensitivity analyses for higher PK-PD targets produced PTAs >90% at joint exposure targets up to 60% $fT>MIC$ (for ceftazidime-avibactam MICs ≤8 mg/L) and 60% $C_T>1\text{ mg/L}$ (Figure 1C). Ceftazidime-avibactam dosage adjustments for varying degrees of renal impairment also demonstrated high (>98%) PTA at MICs ≤8 mg/L (27).

Individual predicted exposures in Phase III patients showed no clinically relevant impact on joint target attainment associated with disease severity, obesity, advanced age, or
CrCL >150 mL/min (25, 26). Hence, a susceptible breakpoint of ≤8 mg/L is consistent with PTA values yielded by the recommended dosage regimens.

A key consideration in setting the clinical breakpoint for an antibacterial agent tested against a particular species or group of species is where the putative breakpoint is located on the MIC frequency distribution. The breakpoint should encompass the great majority of the MICs of the drug against contemporary isolates (11) and should not fall on a “peak” in the MIC distribution (13). The clinical breakpoint of ≤8 mg/L for ceftazidime-avibactam vs *P. aeruginosa* straightforwardly fit these criteria as follows. Against 7,062 *P. aeruginosa* isolates collected globally (ex-US) in INFORM 2012–14 (Figure 1B), 92.0% were susceptible to ceftazidime-avibactam (MIC$_{90}$ 8 mg/L) (5); more recent analyses, including from the US, have reported equivalent susceptibility rates (28-34). Of note, 8 mg/L is at the upper end of the ceftazidime-avibactam MIC distribution, which (as stated above) is an important attribute for the clinical breakpoint (12, 35).

In the case of *Enterobacteriaceae*, the analysis was not as straightforward, because the breakpoint of ≤8 mg/L supported by PK/PD target attainment analyses was higher than the MIC$_{90}$ (0.5 mg/L) by several doubling dilutions. The global (excluding the US) INFORM program analyzed 34,062 *Enterobacteriaceae* isolates collected during 2012–14 (Figure 1A); 99.5% were inhibited by ≤8 mg/L ceftazidime-avibactam (MIC$_{90}$ 0.5 mg/L) (3), with equivalent susceptibility rates reported from recent analyses, including the US (29, 31-34, 36). The argument might be made therefore that a breakpoint of ≤0.5 or ≤1 mg/L at the upper end of the mode of MICs would be suitable for the *Enterobacteriaceae*. However, the following analyses of ceftazidime-avibactam MICs
against genotypically- and phenotypically-characterized antibiotic-resistant sub-
populations among the *Enterobacteriaceae* countered that idea. Figure 1A includes
meropenem-nonsusceptible isolates (3), and multi-drug-resistant (MDR: resistant to ≥3
classes of antibacterial agent) isolates (6), including 816 MBL-negative meropenem-
nonsusceptible isolates. The 90th percentile ceftazidime-avibactam MIC for these
isolates was 4 mg/L, with 97.7% inhibited by ≤8 mg/L (3), and the MIC distribution was
right-shifted compared to the whole distribution, with an upper cut-off of 4–8 mg/L i.e.,
the susceptible breakpoint was at the upper end of, and did not divide, the MIC
distribution against this critical phenotypically- and genotypically-defined sub-population.

The 34,062 *Enterobacteriaceae* isolates (Figure 1A) also included 2,739 MDR *Klebsiella
pneumoniae* and 82 MDR *Klebsiella oxytoca*. The ceftazidime-avibactam MIC was ≤2
mg/L against 90% of these isolates, and ≤8 mg/L against 96.6% (6); again, the MIC
distribution was right-shifted compared with the overall distribution, and the susceptible
breakpoint was at the upper end of, but did not divide, that distribution. From these
analyses, it is clear that a breakpoint of ≤8 mg/L is necessary to encompass important
antibiotic resistant sub-populations such as carbapenem-resistant or MDR strains.

Phenotypical/genotypical sub-population analyses of *P. aeruginosa* were less helpful
than analyses of *Enterobacteriaceae* sub-populations, possibly because in
approximately 30% of ceftazidime-non-susceptible *P. aeruginosa* the ceftazidime-
resistance was not β-lactamase-mediated, not being reversed by combination with
avibactam (5).
Ceftazidime-avibactam MIC distributions against *Enterobacteriaceae* and *P. aeruginosa* isolates from clinical trials in cIAI, cUTI or NP patients (Figure 2) were consistent with global INFORM data, apart from a greater proportion of ceftazidime-avibactam-resistant *P. aeruginosa*, possibly because a relatively high proportion of trial patients were in Eastern Europe, where MBL-producing *P. aeruginosa* are comparatively common (37, 38). Across the trials, clinical and microbiological response rates were generally comparable, and similar for ceftazidime-avibactam and comparator treatments. Per-pathogen responses were generally similar across indications (39-44); against *P. aeruginosa*, clinical cure (but not favorable microbiological response) rates were notably lower for ceftazidime-avibactam vs meropenem in the NP trial (44). Among patients who received ceftazidime-avibactam, favorable microbiological response rates were generally high for infections by *Enterobacteriaceae* and more variable for *P. aeruginosa* with ceftazidime-avibactam MICs ≤8 mg/L, including ceftazidime non-susceptible isolates (Tables 1 and 2). However, consistent with other investigations (45, 46), response rates by MIC did not reveal any trends, possibly because few clinical trial isolates had ceftazidime-avibactam MICs >8 mg/L, and because MIC:outcome correlations may be complicated in cIAI through surgical intervention, and in cUTI because of the concentration of some drugs (including ceftazidime and avibactam) in urine.

The low rate of clinical failures is a key limitation in interpreting the PK/PD targets used for PTA analyses; however, the overall high clinical/microbiological success rates are broadly consistent with the PK/PD analyses using joint target attainment criteria in supporting the assigned ceftazidime-avibactam susceptible breakpoint (≤8 mg/L).
against both *Enterobacteriaceae* and *P. aeruginosa*. Moreover, surveillance data confirm that the MIC cutoff of \( \leq 8 \text{ mg/L} \) separates ceftazidime-avibactam resistant MBL-carrying isolates from those without known ceftazidime-avibactam resistance mechanisms (3, 47, 48). These breakpoints define \( \geq 90\% \) of *Enterobacteriaceae* and *P. aeruginosa* from contemporary global surveillance, including key antibiotic resistant sub-populations, as susceptible to ceftazidime-avibactam (3-6, 28-34).
ACKNOWLEDGMENTS

The authors would like to thank all investigators and patients involved in the ceftazidime-avibactam clinical trial program. Thanks also to Boudewijn L. M. de Jonge for providing additional INFORM Enterobacteriaceae data. Medical writing support was provided by Mark Waterlow BSc, CMPP, of Prime, Knutsford, Cheshire, UK, and funded by AstraZeneca and Pfizer.

FUNDING

The ceftazidime-avibactam Phase II and Phase III clinical studies (clinicaltrials.gov identifiers NCT00752219, NCT01499290, NCT01500239, NCT01726023, NCT01595438, NCT01599806, NCT01644643 and NCT01808092) were originally sponsored by AstraZeneca and are now sponsored by Pfizer. The population PK analyses and the global (excluding the US) INFORM surveillance program were funded by AstraZeneca. AstraZeneca’s rights to ceftazidime-avibactam were acquired by Pfizer in December 2016. All authors had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

POTENTIAL CONFLICTS OF INTEREST

W.W.N. is a former employee of AstraZeneca and current shareholder in AstraZeneca. G.G.S. is a former employee of and shareholder in AstraZeneca, and current employee of Pfizer. P.N., H.B., A.W. and S.D. are former employees of and current shareholders in AstraZeneca. K.Y. is a former contractor for AstraZeneca. M.M. is a former employee of Wright Dose Ltd, Altrincham, UK, which received funding from AstraZeneca for support and assistance with the population PK analyses; she is also a shareholder in
AstraZeneca. T.R. is an employee of and shareholder in Allergan. I.C. is a former employee of and current shareholder in Allergan.


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Table 1. Patients with favorable per-pathogen microbiological response† at test of cure pooled across one Phase II and five Phase III prospective clinical trials, analyzed by ceftazidime-avibactam MIC

<table>
<thead>
<tr>
<th>MIC, mg/L</th>
<th>Citrobacter freundii</th>
<th>Enterobacter cloacae</th>
<th>Escherichia coli</th>
<th>Klebsiella pneumoniae</th>
<th>Pseudomonas aeruginosa</th>
</tr>
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<tbody>
<tr>
<td>≤0.03</td>
<td>1/1 (100.0)</td>
<td>1/1 (100.0)</td>
<td>66/73 (90.4)</td>
<td>6/6 (100.0)</td>
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<tr>
<td>0.06</td>
<td>8/8 (100.0)</td>
<td>2/2 (100.0)</td>
<td>234/257 (91.1)</td>
<td>28/32 (87.5)</td>
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<tr>
<td>0.12</td>
<td>8/8 (100.0)</td>
<td>10/12 (83.3)</td>
<td>163/191 (85.3)</td>
<td>50/58 (86.2)</td>
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<tr>
<td>0.25</td>
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<td>17/19 (89.5)</td>
<td>53/59 (89.8)</td>
<td>19/22 (86.4)</td>
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<tr>
<td>0.5</td>
<td>5/6 (83.3)</td>
<td>3/5 (60.0)</td>
<td>16/17 (94.1)</td>
<td>28/35 (80.0)</td>
<td>2/2 (100.0)</td>
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<td>1</td>
<td>1/1 (100.0)</td>
<td>7/7 (100.0)</td>
<td>3/4 (75.0)</td>
<td>27/29 (93.1)</td>
<td>10/15 (66.7)</td>
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<tr>
<td>2</td>
<td>-</td>
<td>1/1 (100.0)</td>
<td>8/9 (88.9)</td>
<td>6/6 (100.0)</td>
<td>34/51 (66.7)</td>
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<td>4</td>
<td>-</td>
<td>1/3 (33.3)</td>
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<td>0/2 (0)</td>
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</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>4/4 (100.0)</td>
<td>-</td>
<td>10/15 (66.7)</td>
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<tr>
<td>&gt;32</td>
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<td>0/1 (0)</td>
<td>-</td>
<td>0/1 (0)</td>
<td>6/9 (66.7)</td>
</tr>
</tbody>
</table>

† Patients could have >1 pathogen. Microbiological outcomes were categorized as eradication or presumed eradication of the baseline pathogen (i.e. favorable response); persistence or persistence with increasing MIC (i.e. unfavorable response); or indeterminate.

Data pooled from the ceftazidime-avibactam arms of the microbiologically evaluable (ME) population of the Phase II trial in patients with cIAI (NCT00752219) (39) and the extended ME (eME) populations of the Phase III trials in patients with cIAI (RECLAIM 1&2; NCT01499290, NCT01500239, and RECLAIM 3; NCT01726023) (40, 43), cUTI (RECAPTURE 1&2; NCT01595438, NCT01599806) (41), cIAI or cUTI caused by ceftazidime non-susceptible pathogens (REPRISE; NCT01644643) (42) and NP including VAP (REPROVE; NCT01808092) (44). Intra-abdominal cultures require an invasive procedure, and were obtained only if clinically indicated; therefore, microbiological
responses for patients with cIAI were presumed based on clinical outcomes. n: number of favorable responses; N: total number of patients for whom MIC data were available. The dashed line shows the approved ceftazidime-avibactam susceptible clinical breakpoint of MIC ≤8 mg/L applied to both Enterobacteriaceae and P. aeruginosa (8, 9).
Table 2. Patients with favorable per-pathogen microbiological response† at test of cure for ceftazidime non-susceptible pathogens pooled across one Phase II and five Phase III prospective clinical trials, analyzed by ceftazidime-avibactam MIC

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<tr>
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<td>-</td>
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<td>-</td>
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<td>12/12 (100.0)</td>
<td>25/30 (83.3)</td>
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<td>7/7 (100.0)</td>
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<tr>
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<td>8</td>
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<td>-</td>
<td>3/3 (100.0)</td>
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<td>&gt;32</td>
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<td>-</td>
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FIGURE LEGENDS

Figure 1. Joint PTA† for patients with cIAI and normal renal function receiving ceftazidime-avibactam 2000-500 mg q8h plotted as a function of ceftazidime-avibactam MIC (A) overlaid with the ceftazidime-avibactam MIC distributions against Enterobacteriaceae (n=34,062) from the INFORM global surveillance program, 2012–2014; (B) overlaid with the ceftazidime-avibactam MIC distributions against Pseudomonas aeruginosa (n=7,062) from the INFORM global surveillance program, 2012–2014; (C) sensitivity analysis of PTA at different joint PK-PD targets

† Defined as simultaneous attainment of 50% $f_{T>MIC}$ of ceftazidime-avibactam for ceftazidime and 50% $f_{T>C_{T}}$ of 1 mg/L for avibactam, with both targets having to be achieved for a simulated patient to be categorized as achieving the joint target. Ceftazidime-avibactam MICs were evaluated with avibactam tested at a fixed concentration of 4 mg/L. PTA was evaluated for ceftazidime-avibactam MIC values of 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, and 128 mg/L. The values above the bars are the numbers of isolates tested at each MIC. The arrows show the position of the approved ceftazidime-avibactam susceptible clinical breakpoint of MIC ≤8 mg/L (8, 9). This set of isolates of Enterobacteriaceae was also the source of analyses of phenotypically- and genotypically-defined resistant sub-populations (3, 4, 6) as discussed in the text. The isolates of P. aeruginosa have been presented and analyzed in detail elsewhere (5).
Figure 2. Distributions of ceftazidime-avibactam MICs† against (A) *Enterobacteriaceae* (n=2615) and (B) *Pseudomonas aeruginosa* (n=276) across one Phase II and five Phase III prospective clinical trials

† The ranges of MICs tested were up to 32 mg/L in the Phase II trial, and up to 256 mg/L in the Phase III trials. The upper limit plotted here was >128 mg/L, for comparability with Figure 1. Three isolates of *Enterobacteriaceae* and one isolate of *P. aeruginosa* from the Phase II trial tested with ceftazidime-avibactam MIC >32 mg/L and are excluded from these frequency distributions.

Data pooled from the microbiological modified intent-to-treat (mMITT) populations of the following trials: Phase II cIAI (NCT00752219) (39), Phase III cIAI (RECLAIM 1&2; NCT01499290, NCT01500239, and RECLAIM 3; NCT01726023) (40, 43), Phase III cUTI (RECAPTURE 1&2; NCT01595438, NCT01599806) (41), Phase III cIAI and cUTI caused by ceftazidime non-susceptible pathogens (REPRISE; NCT01644643) (42) and NP including VAP (REPROVE; NCT01808092) (44). Ceftazidime-avibactam MICs were evaluated with avibactam tested at a fixed concentration of 4 mg/L. The values above the bars are the numbers of isolates tested at each MIC. The arrows show the position of the approved ceftazidime-avibactam susceptible clinical breakpoint of MIC ≤8 mg/L (8, 9).