

Supplementary Material

Microbiological, Clinical, and Pharmacokinetic/Pharmacodynamic Data to Support EUCAST Aztreonam-Avibactam Minimum Inhibitory Concentration Susceptibility Breakpoints Against Enterobacterales

**Susan R. Raber, Rujia Xie, Halley Rogers, Elena Soto, Francis F. Arhin,
Gregory G. Stone, Heidi Leister-Tebbe, Joseph W. Chow**

S. R. Raber (ORCID ID 0009-0000-2554-9719), Pfizer Inc., La Jolla, CA, USA

R. Xie, Pfizer Inc., Singapore, Singapore

H. Rogers, Pfizer Inc., New York, NY, USA

E. Soto, Pfizer R&D UK Limited., Sandwich, Kent, UK

F. F. Arhin (ORCID 0009-0004-2118-685X), Pfizer Inc., Kirkland, Quebec, Canada

G. G. Stone, Pfizer Inc., Groton, CT, USA

H. Leister-Tebbe, Pfizer Inc., Collegeville, PA, USA

J. W. Chow (ORCID 0000-0002-5934-5877), Pfizer Inc., Collegeville, PA, USA

Correspondence to: S. R. Raber, Pfizer Inc., 10777 Science Center Drive, San Diego, CA 92121, USA; e-mail: susanraber@gmail.com

Table S1 Summary of phase 3 aztreonam-avibactam clinical trial designs and efficacy and safety outcomes

Study	Design	Patients	Treatments and duration ^a	Key efficacy outcomes	Safety outcomes
REVISIT NCT03329092 [1]	Phase 3, prospective, randomized, open-label, central assessor-blinded parallel group, comparative study	422 hospitalized adults with cIAI or HAP/VAP with a confirmed or suspected infection caused by a Gram-negative pathogen	Randomized 2:1 to: Aztreonam-avibactam (+ metronidazole for cIAI) or Meropenem ± colistin at investigator discretion 5–14 days for cIAI 7–14 days for HAP/VAP	Primary endpoint Adjudicated clinical cure rates at the TOC visit (overall ITT analysis set) were: 68% (193/282 [95% CI 62.8, 73.7]) for aztreonam-avibactam and 66% (92/140 [95% CI 57.6, 73.2]) for meropenem ± colistin. Treatment difference was 2.7% (95% CI –6.6, 12.4) Secondary endpoints Per patient favorable microbiological response at the TOC visit: 76% (128/169) of patients in the aztreonam-avibactam group and 74% (68/92) in the meropenem group (micro-ITT analysis set) Per-pathogen favorable microbiological response rates at TOC for Enterobacterales (micro-ITT analysis sets) were 130/174 (74.7%) in the aztreonam-avibactam group and 71/98 (72.4%) in the meropenem ± colistin group 28-day all-cause mortality rates (ITT analysis set) were (4% [12/282] for aztreonam-avibactam and 7% [10/140] for meropenem	64% (177/275) of patients in the aztreonam-avibactam group and 64% (87/137) in the meropenem ± colistin group experienced a treatment-emergent AE (safety analysis set) Serious AEs were experienced by 19% (53/275) of patients treated with aztreonam-avibactam and 18% (25/137) of patients treated with meropenem There were no treatment-related serious AEs in the aztreonam-avibactam group and one in the meropenem ± colistin (moderate abnormal hepatic function)
ASSEMBLE NCT03580044 [2]	Phase 3, prospective, randomized, open-label,	15 hospitalized adults with cIAI, HAP/VAP, cUTI, or BSI caused by	Randomized 2:1 to:	Primary endpoint Clinical cure rates at the TOC visit (micro-ITT	Treatment-emergent AEs were reported in 11/12 (92%) of patients in the aztreonam-avibactam group and in 2/2

parallel-group, comparative study	confirmed MBL-producing Gram-negative pathogens)	Aztreonam-avibactam (+ metronidazole for cIAI) or BAT (based on standard of care at each study site)	analysis set) were 42% (5/12) for aztreonam-avibactam and 0% (0/3) for BAT	(100%) patients in the BAT group (safety analysis set). Serious AEs were reported in 5/12 (42%) and 2/2 patients in the aztreonam-avibactam and BAT groups, respectively. There were no treatment-related serious AEs in the aztreonam-avibactam group and one in the BAT group (acute kidney injury)
		5–14 days for cIAI/cUTI/BSI 7–14 days for HAP/VAP	Secondary endpoints 60% (6/10) of patients in the aztreonam-avibactam group and 0% (0/1) of patients in the BAT group had favorable per-patient microbiological response at TOC (micro-ITT analysis set). Per-pathogen favorable microbiological response rates at TOC for Enterobacterales (micro-ITT analysis sets) were 50% (6/12) in the aztreonam-avibactam group and 0/3 in the BAT group 28-day all-cause mortality rates were 8% (1/12) for aztreonam-avibactam and 33% (1/3) for BAT (ITT analysis set), both deaths occurred in patients with HAP/VAP	

AE adverse event, *BAT* best available therapy, *BSI* bloodstream infection, *CI* confidence interval, *cIAI* complicated intra-abdominal infection, *cUTI* complicated urinary tract infection, *HAP* hospital-acquired pneumonia, *ITT* intent-to-treat, *MBL* metallo- β -lactamase, *micro-ITT* microbiological ITT, *TOC* test-of-cure, *VAP* ventilator-acquired pneumonia

^aThe aztreonam-avibactam dosing regimen in both the ASSEMBLE and REVISIT trials included two loading doses (an initial loading dose of 500 mg aztreonam + 167 mg avibactam, followed by an extended loading dose of 1500 mg aztreonam + 500 mg avibactam [adjusted for renal function]) followed by maintenance doses (1500 mg aztreonam + 500 mg avibactam [adjusted for renal function]) every 6 h; the approved European doses include a simplified dosing regimen with a single loading dose [3].

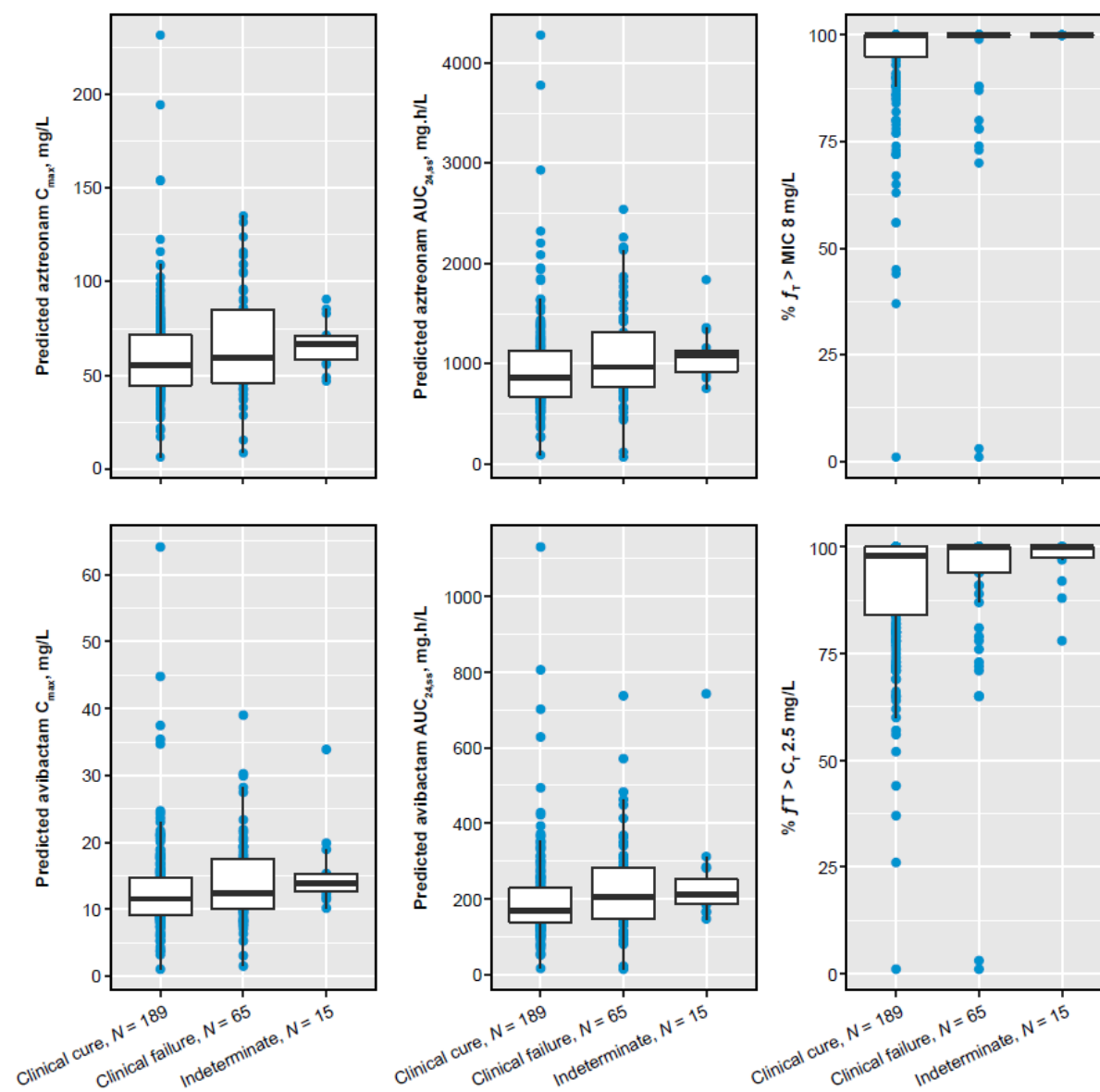
Table S2 Microbiological responses at the TOC visit for patients with Enterobacterales and predicted steady-state aztreonam and avibactam exposures in the REVISIT and ASSEMBLE phase 3 trials (micro-ITT analysis set)

Microbiological response	Aztreonam				Avibactam		
	N	C _{max,ss} (mg/L)	AUC _{24,ss} (mg·h/L)	% fT > MIC _{ATM} of 8 mg/L	C _{max,ss} (mg/L)	AUC _{24,ss} (mg·h/L)	% fT > C _T of 2.5 mg/L
Favorable	138	56.35 (38.32)	889.7 (43.7)	93.81 (15.94)	11.73 (42.32)	178.9 (47.38)	89.89 (20.0)
Unfavorable	49	57.14 (53.01)	908.4 (70.3)	81.42 (97.33)	12.49 (60.23)	193.4 (78.59)	79.35 (97.1)
Indeterminate	7	66.43 (23.32)	1091.3 (25.0)	100 (0)	15.95 (37.59)	254.2 (52.46)	99.57 (1.15)

Data are geometric mean (% coefficient of variation) unless stated otherwise

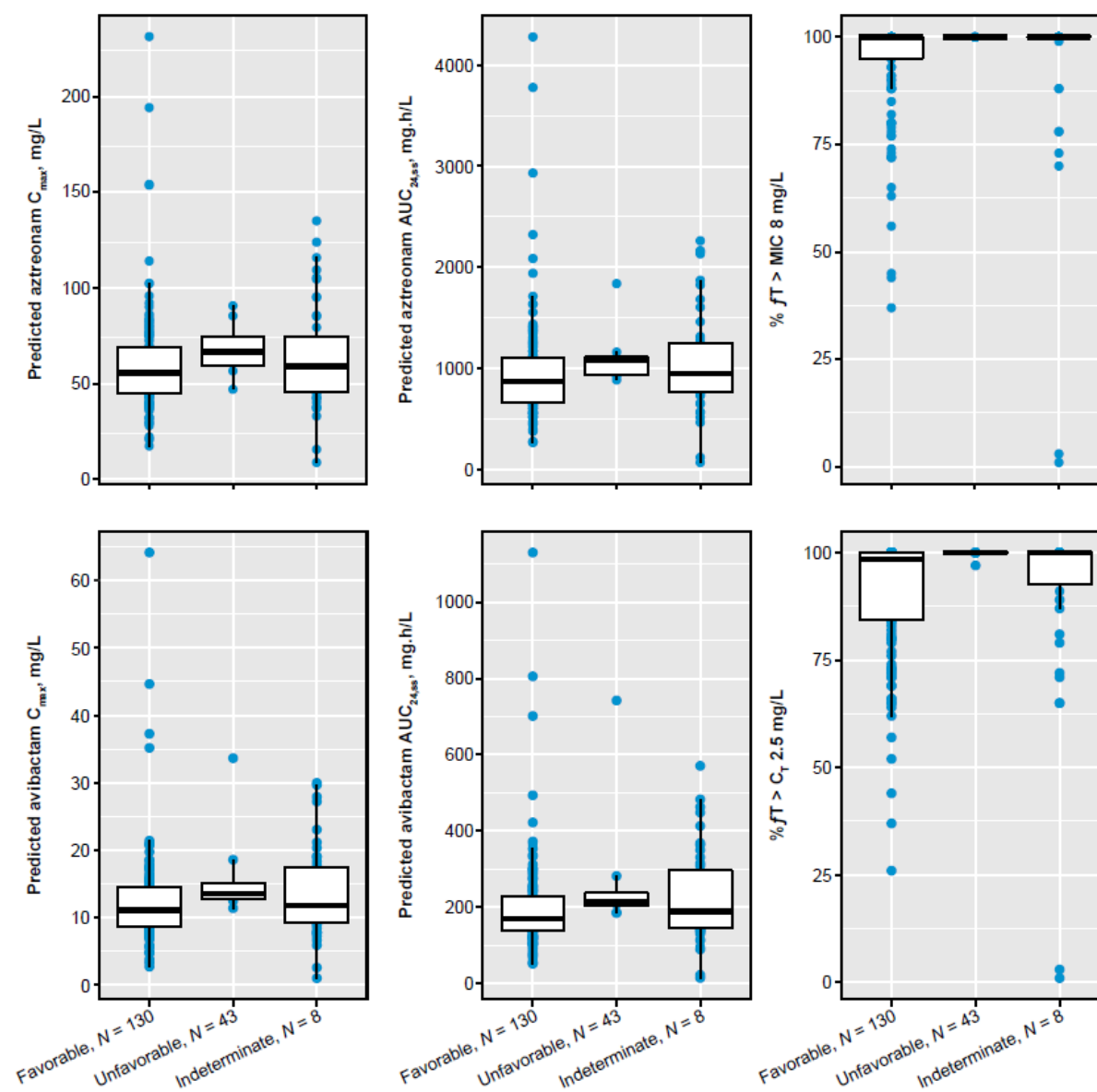
% fT > C_T percent of time that free plasma concentrations are above the threshold concentration over a dosing interval, % fT > MIC_{ATM} percent of time that free plasma concentrations are above the minimum inhibitory concentration over a dosing interval, ATM aztreonam, AUC_{24,ss} area under the plasma concentration–time curve during 24 h at steady state, C_{max,ss} maximum plasma concentration for a dosing interval at steady state, micro-ITT microbiological intent-to-treat, TOC test-of-cure

Fig. S1 Clinical response at the TOC visit in the REVISIT and ASSEMBLE studies versus aztreonam and avibactam exposure and PK/PD targets for aztreonam-avibactam and avibactam (ITT analysis set with paired exposure/efficacy)



% f_T percent of time that free plasma concentrations, $AUC_{24,ss}$ area under the plasma concentration–time curve during 24 h at steady-state, C_{max} maximum plasma concentration, ITT intent-to-treat, MIC minimum inhibitory concentration, PK/PD pharmacokinetic/pharmacodynamic, TOC test-of-cure

Fig. S2 Per-participant microbiological response at the TOC visit in the REVISIT and ASSEMBLE studies versus aztreonam and avibactam exposure and PK/PD targets for aztreonam-avibactam and avibactam (micro-ITT analysis set).



% fT percent of time that free plasma concentrations, $AUC_{24,ss}$ area under the plasma concentration–time curve during 24 h at steady-state, C_{max} maximum plasma concentration, *micro-ITT* microbiological intent-to-treat, *PK/PD* pharmacokinetic/pharmacodynamic, *TOC* test-of-cure

References

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3. Pfizer Inc. Summary of product characteristics: Emblaveo 1.5 g/0.5 g powder for concentrate for solution for infusion; 2024 [cited 8 January 2025]. Available from: https://www.ema.europa.eu/en/documents/product-information/emblaveo-epar-product-information_en.pdf.