Appendix 3. Characteristics of Pivotal Trials Supporting FDA Approval of Antibiotics, 2016-2019

Drug	Trial ID*	Indication	Comparator	Primary End Point	Endpoint Type	Hypothesis	Treatment Group, n	Comparator Group, n	Absolute Risk Reduction (95% CI)
Pretomanid	NCT02333799	TB	Matched historical control cohort and results reported in the literature	Favorable outcome, defined as absence of bacteriologic failure, relapse, or clinical failure 6 months after the end of treatment	Biomarker [Indirect]	Superiority	104	-	Favorable Outcome: 91% (84-96)
Imipenem-Cilastatin-Relebactam	NCT01505634	cUTI	Imipenem-cilastatin and placebo combination (IV or IV+oral)	Microbiological and clinical response, coded as favorable in the case of eradication or unfavorable in the case of persistence or persistence with acquisition of resistance	Biomarker & ClinRo [Indirect]	Non-Inf.* (Margin: 15%)	74	81	Favorable Response: IMI/REL 250 mg: 85.1% IMI/Placebo: 92.6% Difference: -7.5 (-18.3, 2.6)
	NCT01506271	cIAI	Imipenem-cilastatin and placebo combination (IV)	Microbiological and clinical response, coded as favorable in the case of eradication or unfavorable in the case of persistence or persistence with acquisition of resistance	Biomarker & ClinRo [Indirect]	Non-Inf.* (Margin: 15%)	89	92	Favorable Response: IMI/REL 250 mg: 89.9% IML/Placebo: 90.2% Difference: 1.7(-8.8, 12.3)
	NCT 02452047	Imipenem non-susceptible bacterial infections, including HABP/VABP, and cIAI, cUTI	Colistimethate sodium (CMS) and imipenem cilastatin (IV)	Favorable overall response, based on survival at day 28 (HABP/VABP), composite clinical and microbiological response (cUTI) and clinical response only (cIAI).	Biomarker & ClinRo [Indirect]	No prespecified hypothesis/descriptive statistics**	21	10	Favorable Response: IMI/REL: 71.4% (49.8, 86.4) CMS + IMI: 70.0% (39.2, 89.7)
Lefamulin	NCT02559310	CABP	Moxifloxacin (IV)	Percentage of patients responding to study drug at 96 ± 24 hours after first dose	ClinRo [Indirect]	Non-Inf. (Margin: 12.5%)	276	275	Favorable Response Lefamulin: 87.3% Moxifloxacin: 90.2% Difference: 2.9 (-8.5, 2.8), p = 0.0003
	NCT 02813694	CABP	Moxifloxacin (oral)	Percentage of patients responding to study drug at 96 ± 24 hours after first dose	ClinRo [Indirect]	Non-Inf. (Margin: 10%)	370	368	Favorable Response Lefamulin: 90.8% Moxifloxacin: 90.8% Difference: 0.0 (-4.4, 4.5), p < 0.0001
Rifamycin	NCT01142089	TD	Placebo	Time to last unformed stool	PRO on disease signs [Indirect]	Superiority	199	65	Time to Last Unformed Stool (Median, Hours) Rifamycin: 46.0 Placebo: 68.0

									Hazard Ratio: 1.825, (1.276, 2.611), p=0.0008
	NCT01208922	TD	Ciprofloxacin (oral)	Time to last unformed stool	PRO on disease signs [Indirect]	Non-Inf. (Hazard Ratio > 0.764)	420	415	Time to Last Unformed Stool (Median, Hours) Rifamycin: 44.3 Ciprofloxacin: 40.3 Hazard Ratio: 0.962 (0.826, 1.119)
Omadacycline	NCT02531438	CABP	Moxifloxacin (IV)	Successful response to therapy 72 to 120 hours after first dose of study drug, based on cough, sputum production, pleuritic chest pain, and dyspnea	ClinRo [Indirect]	Non-Inf. (Margin: 10%)	386	388	Successful Response: Omadacycline: 81.1% Moxifloxacin: 82.7% Difference:-1.6 (-7.1, 3.8)
	NCT02378480	ABSSSI	Linezolid (IV)	Clinical success 48 to 72 after first dose, based on lesion size reduction of at least 20%	ClinRo [Indirect]	Non-Inf. (Margin: 10%)	316	311	Successful Response: Omadacycline: 84.8% Linezolid: 85.5% Difference: -0.7 (-6.3, 4.9)
	NCT02877927	ABSSSI	Linezolid (oral)	Clinical success 48 to 72 after first dose, based on lesion size reduction of at least 20%	ClinRo [Indirect]	Non-Inf. (Margin: 10%)	360	360	Successful Response: Omadacycline: 87.5% Linezolid: 82.5% Difference: 5.0 (-0.2, 10.3)
Eravacycline	NCT01844856	cIAI	Ertapenem (IV)	Clinical response at test-of-cure visit	ClinRo [Indirect]	Non-Inf. (Margin: 10%)	220	226	Clinical Cure Rate (%) Eravacycline: 86.8% Ertapenem: 87.6% Difference: -0.8 (-7.1, 5.5)
	NCT02784704	cIAI	Meropenem (IV)	Clinical response at test-of-cure visit	ClinRo [Indirect]	Non-Inf. (Margin: 12.5%)	195	205	Clinical Cure Rate (%) Eravacycline: 90.8% Meropenem: 91.2% -0.5 (-6.3, 5.3)
Plazomicin	NCT02486627	cUTI, including acute pyelonephritis	Meropenem (IV)	Composite microbiological eradication and programmatically derived clinical cure rate at Day 5 and test of cure visit	Biomarker & ClinRo [Indirect]	Non-Inf. (Margin: 15%)	191	197	Composite Cure (Day 5) Plazomicin: 88.0% Meropenem 91.4% Difference: -3.4 (-10.0, 3.1) Composite Cure (Test of Cure) Plazomicin: 81.7% Meropenem 70.1% Difference: 11.6 (2.7, 20.3)
Delafloxacin	NCT01811732	ABSSSI	Vancomycin and aztreonam (IV)	Objective clinical response, defined as a reduction of at least 20% in lesion spread	ClinRo [Indirect	Non-Inf. (Margin: 10%)	331	329	Clinical Response (%) Delafloxacin: 78.2% Vancomycin/Aztreonam: 80.9% Difference: -2.6 (-8.8, 3.6)

	NCT01984684	ABSSSI	Vancomycin and aztreonam (IV)	Objective clinical response, defined as a reduction of at least 20% in lesion spread	ClinRo [Indirect	Non-Inf. (Margin: 10%)	423	427	Clinical Response (%) Delafloxacin: 83.7% Vancomycin/Aztreonam: 80.6% Difference: -3.1 (-2.0, 8.3)
Secnidazole	NCT02147899	Bacterial vaginosis (BV)	Placebo	Clinical outcome at TOC, based on vaginal discharge, whiff test, and proportion of clue cells on vaginal wet mount	Biomarker & ClinRo [Indirect]	Superiority	62	62	Clinical Response Rate (%) Secnidazole: 67.7% Placebo: 17.7% Difference: 50.0 (33.4, 66.7), p<0.0001 Cochran-Mantel-Haenzel tests: X2= 32.4769, df = 1, p<0.0001
	NCT02418845	Bacterial vaginosis (BV)	Placebo	Clinical outcome at TOC, based on vaginal discharge, whiff test, and proportion of clue cells on vaginal wet mount	Biomarker & ClinRo [Indirect]	Superiority	107	57	Clinical Response Rate (%) Secnidazole: 53.3% Placebo: 19.3% Difference: 34.0 (18.7, 49.3) p<0.001 Cochran-Mantel-Haenzel tests: X2= 17.5851, df = 1, p<0.0001
Meropenem-Vaborbactam	NCT02166476	cUTI (including acute pyelonephritis)	Piperacillin-tazobactam saline (IV)	Proportion of patients achieving overall success, based on clinical cure or improvement and microbiological eradication, at end of treatment	Biomarker & ClinRo [Indirect]	Non-Inf. (Margin: 15%)	192	182	Clinical Success Rate (%)* Meropenem-Vaborbactam: 98.4% Pipercillin-tazobactam: 94.0% Difference: 4.5 (0.7, 9.1)
Ozenoxacin	NCT01397461	Impetigo	Placebo	Clinical response at end of therapy, based on improvement in Skin Infection Rating Scale (SIRS) and physician evaluation	ClinRo [Indirect	Superiority	155	156	Clinical Success Rate (%) Ozenoxacin: 34.8% Placebo: 19.2% Difference: 0.155 (0.056, 0.255), p = 0.003
	NCT02090764	Impetigo	Placebo	Clinical response at end of therapy, based on improvement in Skin Infection Rating Scale (SIRS) and physician evaluation	ClinRo [Indirect]	Superiority	203**	199	Clinical Success Rate (%) Ozenoxacin: 55.2% Placebo: 39.2% Difference: 0.160 (0.063, 0.256), p = 0.001

Bezlotoxumab	NCT01241552	Prevention of CDI recurrence	Placebo***	CDI recurrence through week 12 following clinical cure of initial episode	PRO for disease signs + Biomarker [Indirect]	Superiority	386	395	CDI Recurrence Rate (%) Bezlotoxumab: 17.4% Placebo: 27.6% Difference: -10.1 (-15.9, -4.3), p=0.0006
	NCT01513239	Prevention of CDI recurrence	Placebo***	CDI recurrence through week 12 following clinical cure of initial episode	PRO for disease signs + Biomarker [Indirect]	Superiority	395	378	CDI Recurrence Rate (%) Bezlotoxumab: 15.7% Placebo: 25.7% Difference: -9.9 (-15.5, -4.2), p=0.0006
Amikacin liposome inhalation suspension (ALIS)	NCT02344004	Mycobacterium avium complex (MAC) lung disease	Multi-drug background regimen of at least 2 antibacterials based on ATS/IDSA guidelines	Sputum culture conversion by 6 months	Biomarker [Indirect]	Superiority	224	112	Sputum Conversion Rate (%) ALIS + Background Regimen: 29.0% Background Regimen: 8.9% Difference: 20.5 (12.2, 28.7), p < 0.0001 Odds Ratio: 4.22 (2.08, 8.57), p <0.0001
Cefiderocol	NCT02321800	cUTI (including pyelonephritis)	Imipenem-Cilastatim (IV)	Composite of microbiological eradication and clinical response at test of cure visit	Biomarker & ClinRo [Indirect]	Non-Inf.**** (Margin: 20%)	252	119	Clinical Response Rate (%) Cefiderocol: 72.6% Imipenem-Cilastatin: 54.6% Difference: 18.6 (8.2, 28.9), p = 0.0004
	NCT02714595	HABP/VABP /cUTI/BSI/sepsis	Best available therapy (BAT)	Clinical response at test of cure visit for HABP/VABP/BSI/sepsis and microbiological response for cUTI	Biomarker & ClinRo [Indirect]	No prespecified hypothesis/descriptive statistics	101	51	Mortality Cefiderocol 34/101 (34%) BAT 9/51 (18%) Difference: 16% (0.83 to 28.6)!
Omeprazole Magnesum-Amoxicillin-Rifabutin	NCT03198507	H. pylori infection	Placebo	Eradication of H. pylori as confirmed via 13C Urea Breath Test testing 23-35 days after treatment completion	Biomarker [Indirect]	Superiority†	66	37	Response Rate (%) Omeprazole magnesium-amoxicillin rifabutin: 89.4% Placebo: 2.7% Difference: 86.7% (74.3, 93.9), p < 0.001
	NCT01980095	H. pylori infection	Amoxicillin and omeprazole (oral)	Eradication of H. pylori as confirmed via 13C Urea Breath Test testing or fecal antigen test 43-71 days after treatment initiation	Biomarker [Indirect]	Superiority	228	227	Response Rate (%) Omeprazole magnesium-amoxicillin rifabutin: 83.8% Amoxicillin and omeprazole: 57.7% Difference: 26.1 (18.0, 34.1), p<0.0001

Legend:
HABP: Hospital-acquired bacterial pneumonia

VABP: Ventilator-associated bacterial pneumonia
cIAI: Complicated intra-abdominal infection
cUTI: Complicated urinary tract infection
CABP: Community-acquired bacterial pneumonia
ABSSI: Acute bacterial skin and skin-structure infection
TD: Traveler's diarrhea
ITTC: Intent to treat clinical

*With additional testing for superiority to control if non-inferiority was established
**Primary goal was to gain clinical experience at different infection sites
*** Included another monocloncal antibody for comparison. Efficacy based on comparison to placebo.
**** If met, additional testing for 15% non-inferiority margin.
†Required eradication rate of omeprazole magnesium-amoxicillin-rifabutin was set at 70%.
! Data from Bassetti et al Lancet ID 2021 Feb;21(2):226-240. PMID 33058795

ClinRo: Clinician reported outcome – data capture from observers with expertise or training
PRO: Patient reported outcome – data captured directly from patients on either signs or symptoms
ObsRO: Observer-Reported Outcomes – data captured from observers without need for clinical expertise or training

Direct measure – measurement of patient survival, symptoms or patients function in their daily lives
Indirect measure – measurement of laboratory test, signs of disease, or clinician actions e.g decisions to admit to hospital or prescribe another drug, used as substitute for direct measure of patent outcomes.
* The studies of imipenem/cilastatin/relebactam were two dose-ranging studies. The cUTI study did not meet the definition for non-inferiority posed by the sponsor in the FDA's analysis (lower bound of 95% confidence interval -18.9% for the primary endpoint). For cIAI, the study had 80% power and a non-inferiority margin of -15% (the FDA analysis showed a lower bound of the 95% CI of -8.8%).