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Evidence at time of regulatory approval and cost of new antibiotics in 2016-19: cohort study of FDA approved drugs

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ABSTRACT

OBJECTIVE To review the clinical evidence, regulatory background, and cost of antibiotics approved by the US Food and Drug Administration (FDA), 2016-19.

DESIGN Cohort study of FDA approved drugs.

DATA SOURCES FDA databases, ClinicalTrials.gov, and drug labelling. Launch prices were extracted from IBM Micromedex Red Book.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Antibiotics approved by the FDA from October 2016 to December 2019 were identified, and key features of their clinical development were extracted from publicly available FDA databases, ClinicalTrials.gov, and drug labelling. Launch prices were extracted from IBM Micromedex Red Book to evaluate the cost of treatment against comparators.

RESULTS 15 new antibiotics received at least one special regulatory designation and were supported by a median of two pivotal trials. More than half of the pivotal trials used an active control non-inferiority design. All drugs were approved based on surrogate outcome measures. 52 postmarketing requirements and commitments were included across the cohort (median 3 for each drug). From January 2021, 27 postmarketing requirements and commitments were listed as pending, seven as ongoing, three as delayed, one as submitted, eight as released, and four as fulfilled. The most expensive new antibiotic was pretomanid at $36 399 (£29 618; €34 582) for a course of treatment, and the least expensive was rifamycin ($176). Cost ratios between study drugs and comparators ranged from 0.48 to 134.

CONCLUSIONS New antibiotics have been approved by the FDA in recent years mostly based on fewer, smaller, and non-inferiority pivotal trials that often used surrogate outcome measures but were commonly more costly. Efforts to incentivise the development of antibiotics should balance growing the antibiotic development pipeline with ensuring that clinical trials provide clinically relevant evidence of effectiveness in showing added benefits for the patient.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antibiotic resistance, associated with more than 35 000 deaths annually, is a public health problem, particularly for infections caused by Gram negative bacteria.

⇒ A vibrant development pipeline of new antibiotics to treat antibiotic resistant infections and improve patient outcomes is needed.

WHAT THIS STUDY ADDS

⇒ Most antibiotics introduced in the US in 2016-19 were approved by the Food and Drug Administration based on trials with a non-inferiority design that evaluated changes in surrogate outcome measures.

⇒ Postmarketing commitments and requirements were common.

⇒ These new antibiotics were often found to be non-inferior and more costly than the older effective comparator drugs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ These trends should be taken into account by policymakers considering new incentives for the development of antibiotics.

⇒ Incentives for the development of new antibiotics should balance the need for a strong antibiotic development pipeline with ensuring that new drugs show added value for patients by, for example, improving patient outcomes in patient with antimicrobial resistant infections.

Introduction

Since the discovery of antibiotics almost a century ago, bacteria have acquired antibiotic resistance by various means.[1] According to the Centers for Disease Control and Prevention (CDC), every year at least 2.8 million people in the US are infected with bacteria resistant to at least one antibiotic.[1] Antibiotic resistance, associated with more than 35 000 deaths annually, is a public health problem, particularly for infections caused by Gram negative bacteria. A vibrant development pipeline of new interventions to treat infections and improve patient outcomes is needed.

In recent years, however, antibiotic development has slowed.[2] Between 1990 and 2000, the US Food and Drug Administration approved 21 new antibiotics compared with six in 2000-10.[3] Some have criticised the substantial testing required of new antibiotics to justify regulatory approval by the FDA.[4] Large pharmaceutical manufacturers have left antibiotic development, citing the high cost of development and the limited returns on drugs, at least compared with other disciplines, such as cancer treatments.[5] Also, when new antibiotics are approved, low uptake has been reported.

Legislators in the US have enacted multiple approaches to enhance the antibiotic development pipeline. The Generating Antibiotic Incentives Now (GAIN) Act of 2012 provided a five-year extension on guaranteed protection from entry of generic drugs for new antibiotics that treat multidrug resistant bacterial infections.[6] The act also made antibacterial and antifungal drugs with in vitro activity against resistant or other qualifying pathogens but without requiring added patient benefits automatically eligible for special FDA pathways intended to

streamline development and regulatory review. The 21st Century Cures Act of 2016 authorised a new expedited regulatory pathway, the limited population antimicrobial drug pathway, for studies conducted in populations with limited or no options.[7] Other policies are being developed, including a plan to provide more payments for new antibiotics used in hospitals. Other initiatives, like the Pioneering Antimicrobial Subscriptions To End Upsurging Resistance (PASTEUR) Act, which allows Congress to authorise large upfront payments for new antibiotics potentially again without requiring added patient benefits, are under discussion.[8]

To evaluate the recent output from the antibiotic development pipeline and explore the potential effect of new proposals, we reviewed a cohort of antibiotics approved from 2016 to 2019. Our goal was to understand the regulatory history of the new antibiotics, the evidence on which they were approved, and their cost.

Methods

From Drugs@FDA, we identified antibiotics that received their first FDA approval between October 2016 and December 2019. Drugs approved based solely on animal testing were not included in our cohort.

Data sources and extraction

Regulatory information

We used regulatory review documents from Drugs@FDA to extract the clinical characteristics of each drug: approved indications, target enrolled populations, method of administration, susceptible pathogens, and in vitro activity against ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp) pathogens.[9 10] We also identified the in vitro activity of each drug against bacteria included in the CDC's urgent threat pathogens list: carbapenem resistant *Acinetobacter*, *Clostridiodes difficile*, carbapenem resistant *Enterobacteriaceae*, and drug resistant *Neisseria gonorrhoeae*.[1]

We then extracted characteristics relevant to each drug's regulatory review process: date of investigational new drug filing, indicating the start of human clinical trials; date of new drug application filing, indicating the start of the FDA review; date of FDA approval; manufacturer; and any special regulatory designations that were assigned to the antibiotic during its development or FDA review periods.[11] We used this information to determine each drug's development time, defined as the time between investigational new drug filing and new drug application filing. Special regulatory designations included fast track, breakthrough treatment, accelerated approval, Orphan Drug Act, and priority review. We also tracked limited population antibacterial drug status and qualified infectious disease product status, the special designation created by the GAIN Act for antibacterials and antifungals with in vitro activity against a list of pathogens. Press releases from drug sponsors and other public sources provided confirmatory information on each drug's FDA designations.

Pivotal trials

The FDA often designates some clinical trials as pivotal trials when a drug is approved. These trials provide the main body of clinical evidence in support of the drug's efficacy and form the basis for FDA approval. For each pivotal trial, we extracted the indication or indications studied, study population, comparator regimen, primary end points, trial size and arms, and statistical hypothesis and analysis plan. These details were confirmed in ClinicalTrials.gov.[12] FDA law and regulations define a direct outcome used as a primary endpoint as a measure of how patients feel, function, or survive.[13] Direct endpoints, also referred to as true or clinically significant endpoints, look at outcomes directly relevant to patients, clinicians, and payers. These include survival and patient reported symptoms or function in their daily lives.[14] Indirect endpoints do not directly measure how a patient feels, functions, or survives, but are believed to reflect changes in a direct patient outcome and thus serve as surrogate measures of that effect. Clinician reported outcomes of signs of disease or clinician decisions (eg, prescribing more drug treatments), observer reported outcomes, and biomarkers (ie, objective measures of biological processes) are indirect endpoints.[15] We classified the primary endpoints as direct versus indirect endpoints. Indirect endpoints were further categorised into survival, patient reported outcomes of signs of disease, clinician reported outcomes, observer reported outcomes, and biomarkers.

Postmarketing requirements and commitments

We extracted postmarketing commitments or postmarketing requirements for each of our study drugs. Postmarketing requirements are studies and trials that manufacturers are required to complete under statutes and regulations, such as the Animal Efficacy Rule, Pediatric Research Equity Act, or the Food and Drug Administration Amendments Act (FDAAA). Postmarketing commitments are studies and trials that the manufacturer agrees to conduct, but which are not mandated by statute or regulation.[16] We recorded postmarketing commitments reportable under section 506B of the federal Food, Drug, and Cosmetic Act, but excluded non-reportable postmarketing commitments listed in the original approval letters. These details were identified in the drug's original approval letter listed in the Drugs@FDA database, and their statuses were identified from

the FDA's online database of postmarketing requirements and postmarketing commitments.

The FDA database categorises postmarketing requirements and postmarketing commitments into several different open or closed status categories. Open status includes pending, ongoing, delayed, terminated, and submitted postmarketing requirements or commitments. Pending studies have not yet started, but also do not meet the criteria to be listed as delayed. Ongoing studies are proceeding according to or ahead of schedule. Delayed studies are behind schedule. Terminated studies were ended by the manufacturer before completion and the FDA has not yet received a report. Submitted studies have been completed and a final report submitted to the FDA, but the FDA has not yet notified the applicant that the postmarketing commitment has been satisfied.[17] Closed status includes fulfilled and released postmarketing commitments and postmarketing requirements. Fulfilled studies have been completed; the FDA has received the final report and notified the applicant that the postmarketing commitment has been satisfied. The FDA lists some postmarketing commitments as released when they determine that the study is no longer feasible or would not provide meaningful information.

Cost of treatment

We extracted the dose, method of administration, and course of treatment of each drug from its FDA labelling. We then used the 2020 wholesale acquisition unit cost listed in IBM Micromedex Red Book to calculate the cost of treatment.[18] If a study drug was indicated for use in combination with other drugs, we included their cost in our calculation of the total cost of treatment. For all study drugs other than pretomanid for tuberculosis and secnidazole for bacterial vaginosis, we used the comparator regimen in their pivotal trials as the comparison point for our analysis. Where a pivotal trial did not use an active comparator, we relied on input from providers, professional guidelines, and recommendations from authorities, such as the CDC, to identify the most appropriate comparator treatment. For pretomanid, we used the World Health Organization's guidelines to select the comparator regimen.[19] Metronidazole was recommended as the best comparator for secnidazole. Our cost calculations did not account for optional step-downs to oral drug treatment if included as an option in pivotal trials.

We similarly used IBM Micromedex Red Book to extract the wholesale acquisition cost price of the comparator drugs, but we calculated the cost of treatment for comparator regimens mainly based on the dose and method of administration used in pivotal trials, rather than their labels. We used discretion in selecting the particular National Drug Code used to calculate the cost of a comparator regimen. Factors considered included the method of administration, dose, wholesale acquisition unit cost, and the last date when the wholesale acquisition cost price was updated. We matched the method of administration used in pivotal trials, and selected the least costly National Drug Code (in terms of unit wholesale acquisition cost) that came in a dose that most aligned with the course of treatment. If necessary, we chose a more expensive National Drug Code to reflect a more current price or a more appropriate dose option. Online supplemental appendix 1 shows the full calculations and methodology (cost analysis).

Patient and public involvement

Neither patients nor the public were involved in the design, or conduct, or reporting, or dissemination plans of this research, because the study involved a review of publicly available data from regulatory and other sources relating to antibiotic drugs. The work will be disseminated to policymakers and patient groups focusing on antibiotic innovation.

Results

Our cohort had 15 new antibiotics: pretomanid, imipenem-cilastatin-relebactam, lefamulin, rifamycin, omadacycline, eravacycline, plazomicin, delafloxacin, secnidazole, meropenem-vaborbactam, ozenoxacin, bezlotoxumab, amikacin liposome inhalation suspension, cefiderocol, and omeprazole magnesium-amoxicillin-rifabutin (table 1). Online supplemental appendix 2 has a full list of data sources for each drug.

Approved indications and other regulatory characteristics

Four drugs were approved for complicated urinary tract infections, two for complicated intra-abdominal infections, two for community acquired bacterial pneumonia, and two for acute bacterial skin and skin structure infections. One drug each was approved for multidrug resistant tuberculosis, traveller's diarrhoea, bacterial vaginosis, impetigo, prevention of *Clostridodiodes difficile* recurrence, *Mycobacterium avium* complex lung disease, and *Helicobacter pylori* infection. Two drugs were simultaneously approved for two indications each, omadacycline for acute bacterial skin and skin structure infections and community acquired bacterial pneumonia, and imipenem-cilastatin-relebactam for complicated urinary tract infections and complicated intra-abdominal infections. Nine drugs showed in vitro activity against ESKAPE pathogens. Omadacycline and delafloxacin had an FDA approved indication for disease due to methicillin resistant *Staphylococcus aureus*. Bezlotoxumab, a human monoclonal antibody, was the only drug to target a CDC urgent threat pathogen (*C difficile*), and the only drug with a new mechanism of action (binding to *C difficile* toxin B).

Table 1 | Clinical characteristics of antibiotics approved by US Food and Drug Administration, 2016-19

Drug	Indications*	FDA approved target population	Susceptible pathogens†	Method of administration	New mechanism of action	In vitro activity *v* ESKAPE‡ pathogens
Bezlotoxumab	Prevention of recurrence of *Clostridodiodes difficile* infection	Adults with *C difficile* infection on treatment and high risk for recurrence	*C difficile*	Intravenous	Yes	No
Delafloxacin	ABSSSI	Adults with ABSSSI from susceptible bacteria	*Staphylococcus aureus (MSSA/MRSA), Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae, Streptococcus anginosus, Staphylococcus intermedius, Streptococcus constellatus, Streptococcus pyogenes, Enterococcus faecalis, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa*	Oral, intravenous	No	Yes
Meropenem-vaborbactam	Complicated urinary tract infections	Adults with complicated urinary tract infections from susceptible bacteria	*E coli, K pneumoniae, E cloacae* spp complex	Intravenous	No	Yes
Secnidazole	Bacterial vaginosis	Adult women with bacterial vaginosis	Most isolates of *Bacteroides, Gardnerella vaginalis, Prevotella, Mobiluncus, Megasphaera* like type I/II	Oral	No	No
Ozenoxacin	Impetigo	Adults and children (aged ≥2 months) with impetigo caused by *S aureus* or *S pyogenes*	*S aureus, S pyogenes*	Topical	No	Yes
Plazomicin	Complicated urinary tract infections	Adults with complicated urinary tract infection from susceptible organisms with limited alternatives, including pyelonephritis	*E coli, K pneumoniae, Proteus mirabilis, E cloacae*	Intravenous	No	Yes
Eravacycline	Complicated intra-abdominal infections	Adults with complicated intra-abdominal infections	*E coli, K pneumoniae, Citrobacter freundii, E cloacae, Klebsiella oxytoca, E faecalis, Enterococcus faecium, S aureus, S anginosus, S intermedius, S constellatus, Clostridium perfringens, Bacteroides* sp, *Parabacteroides distasonis*	Intravenous	No	Yes
Amikacin liposome inhalation suspension	*Mycobacterium avium* complex lung disease	Adults with *M avium* complex who do not achieve negative sputum after at least 6 months of treatment, and limited alternative options (in combination with antibacterial drug)	*M avium*	Inhaled	No	No
Omadacycline	ABSSSI, CABP	Adult patients with CABP or ABSSSI caused by susceptible microorganisms	CABP: *Streptococcus pneumoniae, S aureus* (MSSA), *Haemophilus influenzae, Haemophilus parainfluenzae, K pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, Chlamydia pneumoniae* ABSSSI: *S aureus* (MRSA/MSSA), *S lugdunensis, S pyogenes, S anginosus, S intermedius, S constellatus, E faecalis, E cloacae, K pneumoniae*	Oral, intravenous	No	Yes

Continued

Table 1 Continued

Drug	Indications*	FDA approved target population	Susceptible pathogens†	Method of administration	New mechanism of action	In vitro activity *v* ESKAPE‡ pathogens
Rifamycin	Traveller's diarrhoea	Adults with traveller's diarrhoea caused by non-invasive strains of *E coli*	*E coli*	Oral	No	No
Imipenem-cilastatin-relebactam	Complicated urinary tract infections, complicated intra-abdominal infections	Adults with limited or no alternative treatment options for complicated urinary tract infections and complicated intra-abdominal infections	(All Gram negative bacteria) complicated urinary tract infections: *E cloacae*, *E coli*, *Klebsiella aerogenes*, *K pneumoniae*, *P aeruginosa*. Complicated intra-abdominal infections: *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *C freundii*, *E cloacae*, *E coli*, *Fusobacterium nucleatum*, *K aerogenes*, *Klebsiella oxytoca*, *K pneumoniae*, *Parabacteroides distasonis*, *P aeruginosa*	Intravenous	No	Yes
Pretomanid	Tuberculosis	Adults with pulmonary Extensively drug resistant, treatment intolerant, or non-responsive multidrug resistance (combination with bedaquiline and linezolid)	*M tuberculosis*	Oral	No	No
Lefamulin	CABP	Adults with CABP caused by susceptible organisms	*S pneumoniae*, *S aureus* (MSSA), *H influenzae*, *L pneumophila*, *M pneumoniae*, *C pneumoniae*	Oral, intravenous	No	Yes
Omeprazole magnesium-amoxicillin-rifabutin	*H pylori*	Adults with infections	*H pylori*	Oral	No	No
Cefiderocol	Complicated urinary tract infections	Adults with complicated urinary tract infections from susceptible organisms with limited or no alternative treatment options	*E coli*, *K pneumoniae*, *P mirabilis*, *P aeruginosa*, *E cloacae* complex	Intravenous	No	Yes

ABSSSI=acute bacterial skin and skin structure infections; CABP=community acquired bacterial pneumonia; MSSA=methicillin sensitive *Staphylococcus aureus*; MRSA=methicillin resistant *Staphylococcus aureus*.

*All information for indications covered by the first FDA approval.

†As listed in the FDA label.

‡ESKAPE=*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp, determined by identifying susceptible pathogens on the FDA label, and fact checked through FDA press releases.

Four drugs were approved for oral administration, six for intravenous administration, one for topical application, one for inhalation, and three in both oral and intravenous formulations.

Among 14 drugs with available data, the median development time was 8.2 years (interquartile range 5.9-9.1), defined as the time between investigational new drug filing and submission of new drug application. Meropenem-vaborbactam had the shortest total development time of 3.0 years and delafloxacin the longest at 15.3 years. All drugs received at least one special regulatory designation intended to speed up development or regulatory review. Eleven drugs received priority review designation, eight received fast track, two received Orphan Drug Act, two received breakthrough, and one received accelerated approval. Thirteen of the 15 drugs in our cohort received a qualified infectious disease product designation. Two drugs, pretomanid and amikacin liposome inhalation suspension, formally received limited population antibacterial drug approval (table 2) whereas three other drugs (plazomicin, imipenem-cilastatin-relebactam, and cefiderocol) were labelled for populations with limited or no treatment options.

Design and evidence from pivotal trials

The drugs in our cohort were supported by 28 total pivotal trials (median 2, range 1-3). The median number of patients enrolled in a trial was 388 (interquartile range 270.5-690, range 31-1446). The only pivotal trial with no comparison with an active or placebo control was the Nix-TB trial, a single arm multicentre study that compared pretomanid in combination with bedaquiline and linezolid with a putative historical control based on a literature review of surrogate outcomes of sputum culture in patients with a new diagnosis of extensively drug resistant tuberculosis not treated with pretomanid, delamanid, bedaquiline, or linezolid.[20] Of the 27 other trials, 17 compared the drug with an active comparator and 10 with placebo.

Fifteen trials used active-controlled non-inferiority hypotheses. Non-inferiority margins were 10% (in 7/15 trials), 12.5% (2/15), 15% (4/15), and 20% (1/15). One pivotal trial for rifamycin specified a non-inferiority margin in the form of a hazard ratio. To determine if a new treatment is non-inferior, researchers use a non-inferiority margin, defined as the maximum acceptable loss of effectiveness compared with an effective older agent. Ten studies used a superiority approach to show that the new drug was more efficacious than an existing one (one historical control and eight concurrent placebo control groups, and one comparison with a standard of care plus placebo add-on). Two trials had no specified hypothesis and used descriptive statistics to evaluate results. All drugs were approved on the basis of indirect outcome assessments as endpoints.

Most pivotal trials focused on composite primary endpoints that incorporated more than one of the endpoint categories of survival, patient reported outcomes, observer reported outcomes, clinician reported outcomes, and biomarkers. Patient reported outcomes were used in four pivotal trials but evaluated signs of disease rather than patients' symptoms, clinician reported outcomes in 19, and biomarkers in 14. No observer reported outcomes were used in the pivotal trials for our drug cohort. None of the trials used patient reported outcomes to evaluate patients' symptoms or function (online supplemental appendix 3).

All trials with superiority hypotheses showed significantly superior results. Of trials with non-inferiority hypotheses, 11 met that trial's statistical criteria for non-inferiority, one trial did not show non-inferiority (imipenem-relebactam-cilastatin in complicated urinary tract infections) whereas three trials (all in complicated urinary tract infections) showed significantly superior results. The results of the three superiority trials were driven by surrogate outcomes of urine culture without superiority for patient outcomes. The two trials with no hypotheses enrolled patients with resistant pathogens and the results were uninterpretable or showed worse outcomes with the new agent (cefiderocol showed a 16% increase in mortality).

Postmarketing requirements and commitments

We found 52 postmarketing requirements and postmarketing commitments (median 3) (online supplemental appendix 4). Pretomanid and lefamulin had the most at seven each; ozenoxacin and omeprazole magnesium-amoxicillin-rifabutin had none. Nearly half of these (25, 48%) were postmarketing requirements required under FDAAA section 505 (o), 21 (40%) under the Pediatric Research Equity Act, and one (2%) under accelerated approval; we found five postmarketing commitments under section 506B (10%). For nine drugs, the FDA required their sponsors to conduct US surveillance studies over five years after approval to monitor development of bacterial resistance based on in vitro data rather than patient outcomes. For 10 drugs, testing of efficacy and safety in children was required. As of January 2021, 27 postmarketing commitments were listed as pending, six as ongoing, three as delayed, one as submitted, eight as released (one was replaced with another postmarketing requirement), four as fulfilled, and three were no longer listed in the online database. No study drug had submitted or fulfilled all of its postmarketing commitments.

Drug prices and total cost of treatment

Comparative cost information was available for 13 study drugs, and the most expensive was pretomanid at $36 399 (£29 618; €34 582). The least expensive was rifamycin for traveller's diarrhoea ($176). The

Table 2 | Regulatory characteristics of new antibiotics approved by US Food and Drug Administration, 2016-2019

Drug (brand name)	Filed to start clinical trials	New drug application filed	Approval date	Sponsor (current manufacturer, if different)	LPAD designation	QIDP designation	Other FDA special programmes or designations
Bezlotoxumab (Zinplava)	November 2005	November 2015	October 2016	Merck Sharp & Dohme (N/A)	▶ No	▶ No	▶ Fast track ▶ Priority review
Delafloxacin (Baxdela)	June 2001, March 2007	October 2016	June 2017	Melinta Therapeutics (N/A	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Meropenem-vaborbactam (Vabomere)	December 2013	December 2016	August 2017	Rempex Pharmaceuticals (N/A)	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Secnidazole (Solosec)	December 2013	January 2017	September 2017	Symbiomix Therapeutics (Lupin Pharmaceuticals)	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Ozenoxacin (Xepi)	February 2010	June 2016	December 2017	Ferrer Internacional (N/A)	▶ No	▶ No	▶ None
Plazomicin (Zemdri)	December 2008	October 2017	June 2018	Achaogen (Cipla)	▶ No ▶ Labelled for limited population	▶ Yes	▶ Priority review
Eravacycline (Xerava)	August 2009	December 2017	August 2018	Tetraphase Pharmaceuticals (N/A)	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Amikacin liposome inhalation suspension (Arikayce)	February 2011	March 2018	September 2018	Insmed Incorporated (N/A)	▶ Yes	▶ Yes	▶ Accelerated approval ▶ Fast track ▶ Breakthrough treatment ▶ Priority review ▶ Orphan drug
Omadacycline (Nuzyra)	Not found	February 2018	October 2018	Paratek Pharmaceuticals (N/A)	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Rifamycin (Aemcolo)	December 2009	March 2018	November 2018	Cosmo Technologies (Redhill Biopharma)	▶ No	▶ Yes	▶ Priority review ▶ Fast track
Imipenem-cilastatin-relebactam (Recarbrio)	September 2010	November 2018	July 2019	Merck Sharp & Dohme (N/A)	▶ No ▶ Labelled for limited population	▶ Yes	▶ Priority review ▶ Fast track
Pretomanid (Pretomanid)	April 2005	December 2018	August 2019	The Global Alliance for TB Drug Development (Mylan)	▶ Yes	▶ Yes	▶ Priority review ▶ Orphan drug ▶ Fast track
Lefamulin (Xenleta)	October 2009, January 2015	December 2018	August 2019	Nabriva Therapeutics Ireland DAC (N/A)	▶ No	▶ Yes	▶ Priority review ▶ Fast track
Omeprazole magnesium-amoxicillin-rifabutin (Talicia)	October 2013	May 2019	November 2019	Redhill Biopharma (N/A)	▶ No	▶ Yes	▶ Priority review ▶ Fast track
Cefiderocol (Fetroja)	March 2013	December 2018	November 2019	Shionogi (N/A)	▶ No ▶ Labelled for limited population	▶ Yes (for Gram negative infections)	▶ Fast track

LPAD=limited population antibacterial drug; QIDP=qualified infectious disease product; N/A=not available.

QIDP, LPAD, and FDA regulatory designations apply to the indications and formulations listed on the original approval, and exclude indications that failed to gain approval or have subsequently gained approval.

*Drugs not designated as going through LPAD pathway but labelling claim based on approval for population with limited or no options.

cost ratios between study drugs and comparator regimens ranged from 0.48, for ozenoxacin for impetigo compared with topical retapamulin, to 134 for intravenous omadacycline for community acquired bacterial pneumonia compared with oral moxifloxacin. The study drugs that were less expensive than their comparators (giving a cost ratio of <1) were ozenoxacin for impetigo compared with topical retapamulin, and oral delafloxacin compared with intravenous vancomycin and aztreonam, with cost ratios of 0.48 and 0.84, respectively. Table 3 provides a summary of the results of the cost analysis.

Bezlotoxumab and amikacin liposome inhalation suspension required special calculation in the cost analysis. Bezlotoxumab, indicated for the prevention of recurrence of *C difficile*, did not have a comparator treatment on the market. The cost of treatment with weight based bezlotoxumab is $2850 (for a patient weighing 75 kg), but without a comparator, calculating a cost ratio was not possible. Amikacin liposome inhalation suspension, for *Mycobacterium avium* complex lung disease, was the only study drug intended for chronic use, and no comparator regimen exists. A month's supply of amikacin liposome inhalation suspension costs $12 381, with only one supporting pivotal trial in patients treated for 8-16 months. Treatment across this time period would cost $161 394-$215 192, making amikacin liposome inhalation suspension the most expensive drug by course of treatment in our cohort.

Discussion

Principal findings

The number of new antibiotics on the market has grown in line with policy incentives designed to increase the quantity of approved drug treatments. Our previous study examined a cohort of eight antibiotics approved between January 2010 and December 2015. In this study, we examined 15 new antibiotics approved in a shorter timeframe (October 2016-November 2019). This more recent cohort of new antibiotics had similar regulatory and pivotal trial characteristics to the cohort of antibiotics approved in 2009-15. In both cohorts, all drugs received at least one special regulatory designation intended to speed up development or review, but the application of these designations was inconsistent. Most pivotal trials had non-inferiority hypotheses; and reliance on surrogate endpoints was found (none used patient reported outcomes to directly evaluate patient symptoms or function, or both).

The limited number of pivotal trials, small numbers of patients enrolled in the trials, wider non-inferiority margins allowing greater losses of efficacy than the 2009-15 cohort, and limited postmarketing evidence because of incomplete postmarketing requirements and postmarketing commitments make it difficult to determine the real world value of improved patient outcomes with these new drug treatments. More than half of the 28 pivotal trials, and all trials for common infections like urinary tract infections and pneumonia, were non-inferiority trials. Non-inferiority trials are most appropriate when the need for more treatment options with improved adverse effects might justify a trade-off for slightly reduced efficacy, and also do not result in irreparable patient harm. We found non-inferiority trials allowing worse effectiveness of 10-20%, a wider range than in a similar study of antibiotics approved in 2010-15 (10-15%).[21] Non-inferiority hypotheses can be used to prioritise non-efficacy benefits.[22] These same trials are designed to exclude patients who lack current treatment options, however, and thus are less likely to provide evidence that the drug provides meaningful efficacy benefits above existing treatments, especially given their higher costs.[23] One non-inferiority trial failed to show non-inferiority, with the new drug 18.3% less effective than the older agent. The FDA review found that this trial was not adequate or well controlled (as required by law), but still used the trial as the basis for regulatory approval, also relying on in vitro data and animal models. These trial results were not prominently described in the drug's labelling.

Three non-inferiority trials showed significant superiority, mainly from the results of urine culture, a surrogate measure of unclear validity, without superiority for direct patient outcomes. Two trials were designed with no hypotheses and used only descriptive statistics, two design choices not classically associated with the adequate and well controlled investigations described in FDA regulations as being needed for new drugs to be approve. These two studies enrolled patients with resistant pathogens and the results were uninterpretable because of the small numbers of patients or showed increased mortality with the new agent. We found three drugs labelled for patients with limited or no treatment options despite a lack of substantial evidence from studies enrolling these patients.

All of the study drugs in our cohort were approved on the basis of at least one indirect outcome assessment as an endpoint, including many of the trials with superiority hypotheses. Indirect endpoints, also called surrogate endpoints, have become increasingly common in clinical trials since their introduction in the early 1990s to speed up HIV drugs coming to market.[24] Indirect endpoints are appropriate when clinical outcomes take years or longer to emerge, such as in oncology or other chronic conditions where physical changes accumulate over time. Indirect endpoints are also useful when the surrogate strongly reflects patient benefit. Use of indirect endpoints can accelerate clinical trials, decrease development costs, and get drugs to market quicker.[25] We found an average development time of about eight years, similar to results from other reviews of the development of antibiotics.[2]

Table 3 | Dose, duration, and cost of antibiotics recently approved by US Food and Drug Administration (2016-19) and comparator regimens

Recently approved antibiotic			Comparator			
Drug (brand name)	Dose	Cost (WAC, $)	Drug	Dose	Cost range (WAC, $)	Cost factor
Pretomanid (Pretomanid)	200 mg daily for 26 weeks plus linezolid 1200 mg daily orally and bedaquiline 400 mg daily orally for 2 weeks then 200 mg 3 times a week for 24 weeks	36 399	Isoniazid, rifampin, pyrazinamide, ethambutol	Intensive phase: 300 mg isoniazid, 600 mg rifampin, 1500 mg pyrazinamide, and 1200 ethambutol daily for 8 weeks. Continuation phase: 300 mg isoniazid and 600 mg rifampin daily for 18 weeks	1380	26.37
Imipenem-cilastatin-relebactam (Recarbrio)	1.25 g intravenously over 30 min, every 6 hours, for 4-14 days	4280-14 980	Imipenem-cilastatin	500 mg intravenously four times a day for 4-14 days	104-364	41.15
			Imipenem-cilastatin and colistimethate sodium	Cilastatin and colistimethate sodium (300 mg) ×1 followed by 300 mg cilastatin and colistimethate sodium every 12 hours and 500 mg imipenem intravenously four times a day for 4-14 days	536-1756	7.99-8.53
Lefamulin (Xenleta)	150 mg every 12 hours intravenously for 5-7 days or 600 mg tablets every 12 hours for 5 days	Intravenously: 1025-1435. Orally: 1375	Moxifloxacin	(For CABP) 400 mg moxifloxacin orally or intravenously daily for 7-14 days	Intravenously: 315-630. Orally: 21-41	Intravenously: 3.25-2.28 Orally: 66.81-33.41
Rifamycin (Aemcolo)	388 mg every 12 hours for 3 days	176	Ciprofloxacin	(For Traveller's diarrhoea) 500 mg orally every 12 hours for 5-7 days	2-3	92.65-66.18
Omadacycline (Nuzyra)	Loading: 200 mg intravenously over 60 min or 100 mg intravenously over 30 min, twice on day 1, then 100 mg intravenously daily or 300 mg tablets daily. Total 7-14 days	(All Indications, intravenously) 2760-5175	ABSSSI: Linezolid CABP: Moxifloxacin	(ABSSSI, Linezolid) 600 mg intravenously or tablets twice daily for 10-14 days (CABP, Moxifloxacin) 400 mg moxifloxacin orally or intravenously daily for 7-14 days	(ABSSSI, Linezolid) intravenously: 720-1440. Orally: 69-137. (CABP, Moxifloxacin) intravenously: 315-630. Orally: 21-41	ABSSS: Omadacycline intravenously, linezolid intravenously =3.83-3.59. Omadacycline intravenously, linezolid orally =40.23-37.72. CABP: Omadacycline intravenously, moxifloxacin intravenously =8.76-8.21. Omacadycline intravenously, moxifloxacin orally =134.11-125.73
Eravacycline (Xerava)	1 mg/kg intravenously twice daily for 4-14 days	588-2058	Ertapenem	1.0 g intravenously daily for 4-14 days	400-1400	1.47
			Meropenem	1.0 g intravenously three times a day for 4-14 days	85-149	6.89-13.78

Continued

Table 3 Continued

Recently approved antibiotic			Comparator			
Drug (brand name)	Dose	Cost (WAC, $)	Drug	Dose	Cost range (WAC, $)	Cost factor
Plazomicin (Zemdri)	15 mg/kg intravenously daily for 4-7 days	283-496	Meropenem	1 g intravenously three times a day for 4-7 days	85-149	3.32
Delafloxacin (Baxdela)	300 mg intravenously over 60 min twice daily for 5-14 days or 450 mg tablet twice daily for 5-14 days	Intravenously: 1325-3710. Orally: 744-2083	Vancomycin and aztreonam	15 mg/kg intravenously vancomycin and 2 g intravenously aztreonam twice daily for 5-14 days	884-2474	Delafloxacin intravenously 1.50-1.10. Delafloxacin orally 0.84
Secnidazole (Solosec)	2 g of granules once orally	282	Metronidazole	(Bacterial vaginosis) 750 mg orally daily for 7 days	6	48.00
Meropenem-vaborbactam Vabomere)	4 g intravenously three times a day for up to 14 days	29 938	Piperacillin-tazobactam	4 g/0.5 g intravenously three times a day for up to 10 days	754	39.72
Ozenoxacin (Xepi)	Apply thin layer to affected area twice daily for up to 5 days (dose unspecified)	297 (one 30 g tube ozenoxacin)	Retapamulin	Apply thin layer to the affected area twice a day for 5 days (dose unspecified)	623	0.48
Bezlotoxumab (Zinplava)	One time intravenously 10 mg/kg	2850 (for patient weighing 75 kg)	None available	-	-	-
Amikacin lipsosome inhalation suspension (Arikayce)	Daily oral inhalation of one 590 mg/8.4 mL vial, for indefinite use	12 380 (28 day supply) 1 61 394-2 15 192 (8-16 months)	Rifampin, ethambutol, and azithromycin	Azithromycin (500 mg), rifampin (600 mg), and ethambutol (25 mg/kg) three times a week for 8-16 months	111 (28 day supply) 1438-1918 (8-16 months)	(28 day supply) 111.90. (8-16 months) 112.21
Cefiderocol (Fetroja)	2 g intravenously three times a day for 7-14 days	7700-15 400	Imipenem/cilastatin	Imipenem/cilastatin (1 g:1 g) intravenously three times a day for 7-14 days	397-794	19.6-19.4
Omeprazole magnesium-amoxicillin-rifabutin (Talicia)	Four capsules three times a day for 14 days	669	Amoxicillin and omeprazole	1000 mg amoxicillin and 10 mg omeprazole three times a day for 14 days	9	77.21

$1 (£0.81; €0.95).

The use of indirect endpoints is questionable in acute diseases when direct outcomes can be measured rapidly. Also, indirect measures in acute diseases do not always reflect clinical benefit. For example, use of indirect assessment or biomarker of urine culture gives misleading superior results in trials when no added benefit is shown for the patient centred outcomes of survival or symptoms.[26] The expectation is that changes in indirect measures reflect changes in direct endpoints, but this validation is not always performed.[25] The efficacy of drugs approved based on unvalidated indirect measures is unclear. We have seen in this analysis that drugs approved on validated or unvalidated indirect outcomes are often priced as if they have already shown direct benefit to the patient. Our analysis showed that many of these drugs obtain full FDA approval (rather than accelerated approval) despite doubts on whether the indirect outcomes reflect benefit to the patient.

Nearly all of the trials in our cohort of drugs involved comparison with a placebo or active comparator. Pretomanid, however, was approved based on one single-arm study analysing 45 participants that compared pretomanid with a historical control and used a biomarker endpoint. (Inhaled amikacin was similarly based on a single-arm study with a biomarker endpoint.) Guidelines from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use recommend not using historical controls when patient and disease factors can affect outcomes (eg, in tuberculosis).[27] Pretomanid was approved based on limited evidence of questionable rigour, and was also the most expensive drug in our cohort. Furthermore, pretomanid along with inhaled amikacin was granted an Orphan Drug Act designation. Tuberculosis is a rare disease in the US, but is the main cause of mortality from infectious diseases globally, suggesting the need for further discussion of the correct application of special regulatory pathways.[28] These regulatory pathways allow new antibiotics to get regulatory approval with limited clinical data supporting their efficacy. Approval of new antibiotics based on smaller, fewer, and less rigorous pivotal trials that enrol patients who might not have unmet needs, produce new antibiotics with unclear evidence of effectiveness.[29] But these new antibiotics are often more costly: the study drugs were up to 134 times more expensive than the comparator regimen used in pivotal trials. In this context of evidentiary questions, small numbers of prescriptions for some of the new drugs leading to limited revenue for their manufacturers is not surprising. Rationale for use of other special regulatory designations was similarly questionable in certain cases; for example, secnidazole received QIDP status and five additional years of regulatory exclusivity despite bacterial vaginosis not being a serious, life-threatening disease as intended by law to receive this designation.

Limitations

The drugs in our cohort are often indicated for use (although often not tested) in patient populations with multidrug resistant or extensively drug resistant infections. Studies have shown that these patients are often excluded from trials of antibiotics.[30] Because these drugs are often marketed for use in multidrug resistant or extensively drug resistant infections, clinicians might use them for these indications. The new antibiotic might not be a direct substitute for the comparator in the pivotal trials, which we used in our cost analyses. Another limitation is that we did not conduct a systematic analysis of the safety profiles for each of our study drugs compared with other drugs for the same indication, or compared with evidence of benefit. These non-efficacy benefits might include lower toxicity, fewer adverse events, and greater potential for adherence (which might result in greater real world efficacy), and justify approving the drug based on slightly reduced efficacy.[31] Some drugs in our cohort had greater safety concerns than their predecessors. Plazomicin, for example, increased harms of renal insufficiency in patients, as noted in the drug's labeling.

Thirdly, in our cost analysis, we used the comparator in the drug's pivotal trials. The comparator chosen by the drug sponsor might not be the regimen recommended by professional guidelines or the most cost effective option for the indication studied. Some of the comparator regimens were more expensive than generic regimens currently recommended for clinical use. For example, ozenoxacin for impetigo was compared with retapumulin in its pivotal trials and had the lowest cost ratio in our cohort. Retapumulin is a similarly new expensive antibiotic, however, which likely skews the cost ratio towards a more favourable lower number. Generic mupirocin, by contrast, can also treat impetigo, and is available as a low cost over-the-counter treatment. Also, because we used discretion in choosing the comparator National Drug Code, small variations in the cost of treatment with comparator regimens might exist. Fourthly, our cost analysis was also based on wholesale acquisition unit prices that do not account for rebates, which are typically confidential, and so the cost of treatment for each drug does not always reflect the cost to a payer. Finally, all of the postmarketing commitments and postmarketing requirements had not been completed for any of the drugs in our cohort, which limited the scope of our analysis. Hence we could not draw associations between evidence of effectiveness shown in the pivotal trials and any confirmatory evidence provided by a drug's postmarketing requirements and postmarketing commitments.

Conclusions

This study of antibiotic innovation in the past five years showed that new antibiotics meant to fill unmet medical needs for improved efficacy lacked evidence that they do so on real clinical endpoints before approval by the FDA. These trends should be taken into account by policymakers considering new incentives for the development of antibiotics. For example, the PASTEUR bill would provide large government payments based on contracts for new antibiotics considered high priority.[8] Contracts under the PASTEUR Act are intended to determine payment on public health value rather than the quantity of an antibiotic, but the version of the Act introduced in the US Senate in 2021, like the preceding GAIN Act of 2012, did not require added benefits to be shown in patients with unmet needs to qualify for a contract. We have shown in this study that the value of a new antibiotic drug is not always clear based on testing before approval by the FDA. Efforts like the PASTEUR Act deal with the barrier of low sales potential to new antibiotic development but might not account for whether these drugs provide sufficient added benefit to the patient to justify payment. Increasing the number of agents coming to market should balance the robustness of evidence of improved direct patient outcomes compared with current standards of care, therefore meeting the needs of patients.

Contributors MM-M, JHP, and ASK conceptualised the study. MM-M and BLB were responsible for data collection and analysis. MM-M drafted the manuscript. BLB, JHP, and ASK reviewed the manuscript and provided substantial textual edits. MM-M is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

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Appendix 1: Cost Analysis

1. Pretomanid

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Pretomanid [49502-0476-26]**	200 mg daily orally for 26 weeks, *in combination with:* ▪ Linezolid 1,200 mg daily orally for up to 26 weeks ▪ Bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week for 24 weeks for a total of 26 weeks	▪ Pretomanid 19.78/200 mg tablet (Package Size: 26 tablets) ▪ Linezolid 2.43/600 mg tablet (Package Size: 20 tablets) ▪ Bedaquiline: 159.57/100 mg tablet (Package Size: 188 tablets)	▪ Pretomanid: 3,599.96 ▪ Linezolid: 884.52 ▪ Bedaquiline: 31,914.00 **36,398.48**
Comparator	**Isoniazid (INH) [10135-0584-01]** **Rifampin (RIF) [00904-5282-61]** **Pyrazinamide (PZA) [61748-0012-05]** **&** **Ethambutol (EMB) [68850-0012-02]**	Intensive Phase: 300 mg INH, 600 mg RIF, 1500 mg PZA, and 1200 EMB once daily for 8 weeks Continuation Phase: 300 mg INH and 600 mg RIF once daily for 18 weeks	▪ INH 0.16040/300 mg tablet (Package Size: 100 tablets) ▪ RIF 1.10550/300 mg tablet (Package Size: 100 tablets) ▪ PZA: 4.86616/500 mg tablet (Package Size: 500 tablets) ▪ EMB 0.78000/400 mg tablet (Package Size: 100 tablets)	**Intensive** ▪ INH: 8.98 ▪ RIF: 123.82 ▪ PZA: 817.51 ▪ EMB: 131.04 **Continuation** ▪ INH: 20.21 ▪ RIF: 278.59 **1,380.15**
Cost Factor	**26.37**			
Notes	▪ **Total costs are calculated based on unit cost rather than package cost.** ▪ **Additional Reference NDCs** o Linezolid: 72606-0001-07			

	○ Bedaquiline: 59676-0701-01 ○ Isoniazid: 10135-0584-01 ○ Rifampin: 00904-5282-61 ○ Pyrazinamide: 61748-0012-05 ○ Ethambutol: 68850-0012-02 ▪ Costs as of Date ○ Pretomanid: 11.07.2019 ○ Linezolid: 10.08.2019 ○ Bedaquiline: 04.19.2013 ○ Isoniazid: 05.01.2015 ○ Rifampin: 09.12.2016 ○ Pyrazinamide: 02.28.2017 ○ Ethambutol: 11.01.2016

2. Imipenem-Cilastatin-Relebactam

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	Imipenem-Cilastatin-Relebactam [00006-3856-02]	[All Indications] 1.25 g by IV infusion over 30 minutes, every 6 hours, for 4-14 days	267.50/1.25 g vial (Package Size: 25 vials)	4,280 - 14,980
Comparator	Imipenem-Cilastatin (IMI) [63323-0349-93] (Study PN003, PN004)	500 mg IV infusion every 6 hours, for 4 – 14 days	[Imipenem-Cilastatin] 6.50000/unit of 250-250 mg powder for solution (Package Size: 25 units of 250-250 mg)	104.00 – 364.00
	Colistimethate Sodium (CMS) [25021-0159-10] & Imipenem-Cilastatin (IMI) [63323-0349-93] (Study PN013)	Loading dose of colistimethate sodium (300 mg), followed by 300 mg CMS every 12 hours and 500 mg IMI IV infusion every 6 hours, for 4 – 14 days	[Colistimethate Sodium] 24.00000/unit of 150 mg powder for solution (Package Size: 1 unit) [Imipenem-Cilastatin] 6.50000/unit of 250-250 mg powder for solution (Package Size: 25 units of 250-250 mg)	536.00 – 1,756.00
Cost Factor	IMI **41.15** IMI+CMS **7.99, 8.53**			
Notes	▪ Imipenem-Cilastatin-Relebactam is available in a combination of 500 mg imipenem, 500 mg cilastatin, and 250 mg relebactam. ▪ Cost ranges, and cost factor ranges, reflect cost for the shortest and longest course of treatment indicated. ▪ Additional Reference NDCs o Imipenem-cilastatin (250-250 mg): 63323-0349-93 o Colistimethate sodium: 25021-0159-10 ▪ Costs as of Date o Imipenem-Cilastatin-Relebactam: 01.06.2020 o Imipenem-cilastatin (250-250 mg): 06.16.2016 o Colistimethate sodium: 12.15.2014			

3. Lefamulin

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Lefamulin [72000-0110-30, 72000-0120-06]**	150 mg every 12 hours by IV infusion over 60 minutes for 5 – 7 days OR 600 mg tablets every 12 hours for 5 days	6.83/mL (Package Size: 6 vials, 15 mL each, at 10 mg/mL) 137.50/600 mg tablet (Package Size: 30 tablets)	**IV: 1,024.50 - 1,434.50** **Oral: 1,375.00**
Comparator	**Moxifloxacin [67457-0323-25, 65862-0603-30]**	[For CABP] 400 mg moxifloxacin orally OR by IV infusion once daily for 7 – 14 days	0.18/mL (Package Size: 12 units of 250 mL at 400 mg/250 mL) 2.94/400 mg tablet (Package Size: 30 tablets)	**IV: 315.00 – 630.00** **Oral: 20.58 – 41.16**
Cost Factor	**IV: 3.25, 2.28** **Oral: 66.81, 33.41**			
Notes	▪ **Costs as of Date** ○ Lefamulin (IV 72000-0110-30, tablet 72000-0120-06): 09.01.2019 ○ Moxifloxacin (IV, 67457-0323-25): 10.03.2017 ○ Moxifloxacin (tablet, 65862-0603-30): 05.15.2018			

4. Rifamycin

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Rifamycin [71068-0001-10]**	388 mg twice a day for 3 days	14.67/194 mg tablet (Package Size: 12 tablets)	**176.04**
Comparator	**Ciprofloxacin [55111-0127-01]**	[For Traveler's Diarrhea] 500 mg orally twice daily for 5 – 7 days	0.19/500 mg tablet (Package Size: 100 tablets)	**1.9 – 2.66**
Cost Factor	**92.65, 66.18**			
Notes	▪ **Note that in rifamycin's two pivotal trials, the comparator was placebo in one and ciprofloxacin in the other. The course of treatment with ciprofloxacin in the pivotal was 3 days, but here we have used more conservative guidelines of 5 to 7 days for cost calculation here.** ▪ **Costs as of Date** o Rifamycin: 01.01.2021 o Ciprofloxacin: 07.05.2017			

5. Omadacycline

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Omadacycline [71715-0001-01, 71715-0002-21]**	[ABSSSI] Loading - 200 mg by IV infusion over 60 min OR 100 mg by IV infusion over 30 minutes twice on Day 1. Maintenance - 100 mg IV infusion over 30 minutes once daily OR 300 mg tablets once daily. Alternative - 450 mg tablet once on Day 1 and 2, and 300 mg tablet once daily thereafter. Total course of treatment 7 – 14 days. [CABP] Loading - 200 mg by IV infusion over 60 min OR 100 mg by IV infusion over 30 minutes twice on Day 1. Maintenance - 100 mg IV infusion over 30 minutes once daily OR 300 mg tablets once daily. Total course of treatment 7 – 14 days.	345.00/100 mg package (Package Size: 100 mg solution) 216.71/150 mg tablet (Package Size: 6 tablets)	[All Indications, IV Infusion] **2,760 - 5,175**
Comparator	**ABSSSI: Linezolid [25021-0169-87, 72606-0001-08]** **CABP: Moxifloxacin [67457-0323-25, 65862-0603-30]**	[ABSSSI, Linezolid] 600 mg IV infusion OR tablets twice daily for 10 – 14 days [CABP, Moxifloxacin] 400 mg moxifloxacin orally OR by IV infusion once daily for 7 – 14 days	[ABSSSI, Linezolid] 0.12/mL (Package Size: 10 units of 300 mL at 600 mg/300 mL) 3.43/600 mg tablet (Package Size: 30 tablets) --- [CABP, Moxifloxacin] 0.18/mL (Package Size: 12 units of 250 mL at 400 mg/250 mL) 2.94/400 mg tablet (Package Size: 30 tablets)	**IV: 720.00 – 1,440.00** **Oral: 68.60 – 137.20** [ABSSSI, Linezolid] **IV: 315.00 – 630.00** **Oral: 20.58 – 41.16** [CABP, Moxifloxacin]
Cost Factor	**ABSSSI** IV Omadacycline: IV Linezolid = **3.83 – 3.59** IV Omacadycline: Oral Linezolid = **40.23 – 37.72** **CABP** IV Omadacycline: IV Moxifloxacin = **8.76 – 8.21** IV Omacadycline: Oral Moxifloxacin = **134.11 – 125.73**			

Notes	▪ The alternative dosage and administration for the ABSSSI indication was not used in total cost calculation. Only the IV administration in maintenance was used in total cost calculation. That is, the oral route was disregarded to simplify cost calculation. ▪ Note that each study drug may have more than one NDC, not all of which are noted in these tables. The NDC chosen to calculate total cost of a course of treatment is based on the NDC(s) with the lowest unit cost at the time of writing OR NDCs for which cost information was available in the IBM Micromedex Red Book. ▪ Costs as of Date o Omadacycline (IV, 71715-0001-01): 12.10.2018 o Omadacycline (tablet, 71715-0002-21): 01.01.2021 o Linezolid (IV, 25021-0169-87): 08.01.2019 o Linezolid (tablet, 72606-0001-08): 06.05.2020 o Moxifloxacin (IV, 67457-0323-25): 10.03.2017 o Moxifloxacin (tablet, 65862-0603-30): 05.15.2018

6. Eravacycline

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Eravacycline [71773-0050-05]**	1 mg/kg IV infusion over 60 minutes every 12 hours for total of 4 – 14 days	49.00/50 mg powder for solution (Package Size: 50 mg)	[75 kg patient] **588.00 – 2,058.00**
Comparator	**Ertapenem [55150-0282-09] (Study TP-434-008)**	1.0 g IV infusion once daily for 4 to 14 days	100.0000/1 g powder (Package Size: 10 units at 1 g each)	**400.00 – 1,400.00**
	Meropenem [72572-0415-10] (Study TP-434-025)	1.0 g IV infusion three times daily for 4 to 14 days	7.11000/1 g powder (Package Size: 10 units at 1 g each)	**85.32 – 149.31**
Cost Factor	Ertapenem: **1.47** Meropenem: **6.89, 13.78**			
Notes	▪ **Note that each study drug may have more than one NDC, not all of which are noted in these tables. The NDC chosen to calculate total cost of a course of treatment is based on the NDC(s) with the lowest unit cost at the time of writing OR NDCs for which cost information was available in the IBM Micromedex Red Book.** ▪ **Costs were calculated based for a 75 kg male patient.** ▪ **Additional Reference NDCs** o Ertapenem: 55150-0282-09 o Meropenem: 72572-0415-10 ▪ **Costs as of Date** o Eravacycline: 05.30.2019 o Ertapenem: 05.03.2019 o Meropenem: 08.27.2020			

7. Plazomicin

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	Plazomicin [71045-0010-02]	15 mg/kg IV infusion over 30 minutes once daily for 4 -7 days	31.5000/10 ml vial (Package Size: 10 vials of 10 mL at 50 mg/ml)	[75 kg patient] **283.50 - 496.13**
Comparator	**Meropenem [72572-0415-10]**	1 g IV infusion three times daily for 4 - 7 days	7.11000/1 g powder (Package Size: 10 units at 1 g each)	**85.32 – 149.31**
Cost Factor	**3.32**			
Notes	▪ **Additional Reference NDCs** o Meropenem: 72572-0415-10 ▪ **Costs as of Date** o Plazomicin: 07.17.2018 o Meropenem: 08.27.2020			

8. Delafloxacin

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Delafloxacin [70842-0102-03, 70842-0101-01]**	300 mg IV infusion over 60 minutes every 12 hours for 5 – 14 days OR 450 mg tablet twice daily for 5 – 14 days	132.5000/300 mg powder (Package Size: 10 300 mg units) 74.42/450 mg tablet (Package Size: 20 tablets)	**IV: 1,325 - 3,710** **Oral: 744.19 - 2,083.76**
Comparator	**Vancomycin [70594-0042-03]** **&** **Aztreonam [63323-0401-26]**	15 mg/kg IV vancomycin & 2 g IV aztreonam, twice daily for 5 – 14 days	[Vancomycin] 0.15/1 mL solution (Package Size: 12 units of 200 mL solution at 1 g/200 mL) [Aztreonam] 27.31000/1 g powder (Package Size: 10 units of 1 g powder each)	[75 kg patient] Vancomycin: 337.50 – 945.00 Aztreonam: 546.20 – 1,529.36 **883.70 – 2,474.36**
Cost Factor	IV Delafloxacin: **1.50, 1.10** Oral Delafloxacin: **0.84**			
Notes	▪ **Additional Reference NDCs** ○ Vancomycin: 70594-0042-03 ○ Aztreonam: 63323-0401-26 ▪ **Costs as of Date** ○ Delafloxacin IV: 10.20.2017 ○ Delafloxacin tablets: 04.01.2019 ○ Vancomycin: 04.01.2019 ○ Aztreonam: 09.04.2015			

9. Secnidazole

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Secnidazole [27437-0051-01]**	2 grams of granules once orally	282.25/2 g granules (Package Size: 2 g granules)	**282.25**
Comparator	**Metronidazole [62332-0016-31]**	[Bacterial vaginosis] 750 mg orally once daily for 7 days	0.28/250 mg tablet (Package Size: 100 tablets)	**5.88**
Cost Factor	**48.00**			
Notes	▪ **Costs as of Date** o Secnidazole: 12.01.2019 o Metronidazole: 12.02.2016			

10. Meropenem-vaborbactam

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	Meropenem-vaborbactam [70842-0120-06]	2 g/2 g IV infusion over 3 hours, every 8 hours, for up to 14 days	178.200/1 g powder for solution (Package Size: 6 1 g units)	**29,937.60**
Comparator	**Piperacillin-tazobactam [00206-8862-02]**	4 g/0.5 g IV infusion, every 8 hours, for up to 10 days	0.25125/mL premix solution (Package Size: 12 units of 100 mL solution at 4 g/0.5 g)	**753.75**
Cost Factor	**39.72**			
Notes	▪ Note that the length of treatment in the pivotal trials with meropenem-vaborbactam was up to 10 days. The FDA label indicates a course of treatment up to 14 days, which we have opted to use to calculate cost of treatment here. ▪ Optional stepdowns to oral treatment (typically levofloxacin) not included in cost calculation. ▪ **Additional Reference NDCs** o Piperacillin-tazobactam: 00206-8862-02 ▪ **Costs as of Date** o Meropenem-vaborbactam: 04.01.2019 o Piperacillin-tazobactam: 01.01.2021			

11. Ozenoxacin

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	Ozenoxacin [70363-0011-30]	Apply thin layer to affected area twice daily for up to 5 days (Dosage unspecified.)	9.90/g 1% cream (Package Size: 30 g tube)	**297.00** **[One 30 g tube ozenoxacin]**
Comparator	**Retapamulin [16110-0518-30]**	Apply thin layer to the affected area twice a day for 5 days (Dosage unspecified.)	20.76033/g 1% cream (Package Size: 30 g tube)	**622.81** **[One 30 g tube retapamulin]**
Cost Factor	**0.48**			
Notes	▪ **Additional Reference NDCs** o Retapamulin: 16110-0518-30 ▪ **Costs as of Date** o Ozenoxacin: 10.26.2018 o Retapamulin: 01.02.2021			

12. Bezlotoxumab

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Bezlotoxumab [00006-3025-00]**	One-time IV infusion of 10 mg/kg over 60 minutes	95.00/mL (Package Size: 40 mL at 25 mg/mL)	**2,850.00** [75 kg patient]
Comparator	**None available.**	-	-	-
Cost Factor	No calculation possible.			
Notes	▪ **Costs as of Date** o Bezlotoxumab: 12.08.2016			

13. Amikacin liposome inhalation suspension

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Amikacin liposome inhalation suspension [71558-0590-28]**	Once daily oral inhalation of one 590 mg/8.4 mL vial, for 8 – 16 months	52.64/mL (Package Size: 28 vials of 8.4 mL at 590 mg/8.4 ml)	**12,380.93** [28-day supply] **161,394.24 – 215,191.78** [8 – 16 months]
Comparator	**Rifampin [00904-5282-61]** **Ethambutol [62991-3060-01]** **&** **Azithromycin [00069-3070-30]**	Azithromycin (500 mg), rifampin (600 mg), and ethambutol (25 mg/kg) three times a week, for 8 – 16 months.	[Rifampin] 1.10550/300 mg capsule (Package Size: 100 capsules) [Ethambutol] 2.16750/g powder (Package Size: 25,000 grams) [Azithromycin] 2.94800/500 mg tablet (Package Size: 30 tablets)	[For a 75 kg patient] Rifampin: 2.21/dose Ethambutol: 4.06/dose Azithromycin: 2.95/dose **110.64** [28-day supply] **1,438.32 – 1,917.76** [8 – 16 months]
Cost Factor	[28-day supply] **111.90** [8 -16 months] **112.21 (across the range)**			
Notes	▪ Pivotal trials for amikacin sulfate used a background regiment of at least two ATS/IDSA recommended drugs as the comparator. More than half of the comparison group in the pivotal trial were on a rifamycin, ethambutol, and a macrolide. Here we've used azithromycin as the representative macrolide based on IDS guidelines, and rifampin as the representative rifamycin. ▪ **Additional Reference NDCs** o Rifampin: 00904-5282-61 o Ethambutol: 62991-3060-01 o Azithromycin: 00069-3070-30 ▪ **Costs as of Date** o Amikacin sulfate: 01.01.2021 o Rifampin: 01.01.2021 o Ethambutol: 01.01.2013			

	○ Azithromycin: 01.01.2021

14. Cefiderocol

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	**Cefiderocol [59630-0266-10]**	2 g IV infusion over 3 hours, every 8 hours, for 7 to 14 days	183.33/g powder for solution (Package Size: 10 units of 1 g each)	**7,699.86 – 15,399.72**
Comparator	**Imipenem/Cilastatin [00409-3507-10]**	Imipenem/cilastatin (1 g: 1 g) IV infusion every 8 hours for 7 – 14 days	9.45/500 mg-500 mg powder for solution (Package Size: 25 units)	**396.90 – 793.80**
Cost Factor	**19.6, 19.4**			
Notes	▪ **Additional Reference NDCs** o Imipenem/Cilastatin: 00409-3507-10 ▪ **Costs as of Date** o Cefiderocol: 02.24.2020 o Imipenem/Cilastatin: 07.01.2013			

15. Omeprazole magnesium-amoxicillin-rifabutin

	Drug [NDC]	Dosage & Administration	Unit Cost (WAC, $)	Total Cost (WAC, $)
Study Antibiotic	Omeprazole magnesium-amoxicillin-rifabutin [57841-1150-02]	4 capsules every 8 hours for 14 days	3.98/capsule (Package Size: 168 capsules)	668.64
Comparator	Amoxicillin [65862-0016-05] & Omeprazole [62175-0114-37]	1000 mg amoxicillin & 10 mg omeprazole every 8 hours for 14 days	[Amoxicillin] 0.047/250 mg tablet (Package Size: 500 capsules) [Omeprazole] 0.018/10 mg capsule (Package Size: 100 capsules)	Amoxicillin: 7.90 Omeprazole: 0.76 8.66
Cost Factor	77.21			
Notes	▪ Talicia is available in a combination of 250 mg amoxicillin, 10 mg omeprazole magnesium, and 12.5 mg rifabutin capsules. ▪ Additional Reference NDCs o Amoxicillin: 65862-0016-05 o Omeprazole: 62175-0114-37 ▪ Costs as of Date o Omeprazole magnesium-amoxicillin-rifabutin: 01.01.2021 o Amoxicillin: 09.12.2006 o Omeprazole: 10.18.2019			

Appendix 2. Drug-Specific Citations

Databases

Drugs@FDA: US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. FDA. Accessed January 7, 2021. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
PMC: FDA/Center for Drug Evaluation and Research, Office of New Drugs. Postmarket Requirements and Commitments. FDA. Updated October 29, 2020. Accesdsed January 7, 2021. https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

Bezlotoxumab (Zinplava)

Label: Zinplava. Prescribing information. Merck Sharp & Dohme Corp.; 2016. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761046s000lbl.pdf
Summary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Division Director Summary Review; BLA 761046, Bezloxtumab for injection. CDER; 2016. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761046Orig1s000SumR.pdf
Risk Assessment and Risk Mitigation Review(s): US Food and Drug Administration, Center for Drug Evaluation and Research. Vision of Risk Management Review, Evaluation to determine if a REMS is necessary. CDER; 2016. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761046Orig1s000RiskR.pdf
Medical Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Clinical Review; BLA 761046, Bezlotoxumab. CDER; 2016. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761046Orig1s000MedR.pdf
AdisInsight: Bezlotoxumab – Merck & Co. AdisInsight Drugs. Updated July 12, 2020. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800044552

Delafloxacin (Baxdela)

Label: Baxdela. Prescribing information. Melinta Therapeutics, Inc.; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208610s000,208611s000lbl.pdf
Summary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Division Director Summary Review; NDAs 208610 and 208611, Baxdela (delafloxacin). CDER; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208610Orig1s000,208611Orig1s000SumR.pdf
Clinical Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Clinical Review; NDA 208610 and NDA 208611, BAXDELA (delafloxacin meglumine). CDER; 2016. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208610Orig1s000,208611Orig1s000MedR.pdf
AdisInsight: Delafloxacin – Melinta Therapeutics/Wakunaga Pharmaceutical. AdisInsight Drugs. Updated November 20, 2020. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800009417

Meropenem-vaborbactam (Vabomere)

Label: Vabomere. Prescribing information. The Medicines Company; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf

Summary Review. US Food and Drug Administration, Center for Drug Evaluation and Research. Combined Cross-Discipline Team Leader, Division Director, and Office Director Summary Review; NDA 209776 Vabomere (meropenem-vaborbactam). CDER; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209776Orig1s000SumR.pdf
Clinical Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Clinical Review; NDA 209776 (Meropenem-vaborbactam). CDER; 2017. Accessed January 7, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209776Orig1s000MedR.pdf
AdisInsight: Meropenem/vaborbactam – Melinta Therapeutics. AdisInsight Drugs. Updated July 8, 2020. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800039513

Secnidazole (Solosec)

Label: Solosec. Prescribing information. Symbiomix Therapeutics LLC; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209363s000lbl.pdf
Summary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA 209363l; Combined Cross-Discipline Team Leader, Division Director, and Deputy Office Director Summary Review. CDER; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209363Orig1s000SumR.pdf
Clinical Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Clinical Review; NDA 209363, SYM 1219 (secnidazole). CDER; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209363Orig1s000MedR.pdf
AdisInsight: Secnidazole – Lupin. AdisInsight Drugs. Updated November 19, 2020. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800040719

Ozenoxacin (Xepi)

Label: Xepi. Prescribing information. Medimetriks Pharmaceuticals, Inc.; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208945lbl.pdf
Summary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA 208945: Cross-Discipline Team Leader, Division Director and Deputy Office Director Summary Review for Regulatory Action. CDER; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208945Orig1s000SumR.pdf
Risk Assessment and Risk Mitigation Review(s): US Food and Drug Administration, Center for Drug Evaluation and Research. Division of Risk Management Review, Addendum to DRISK Review to determine if a REMS is necessary, dated February 23, 2017. CDER; 2017. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208945Orig1s000RiskR.pdf
Clinical Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Clinical Review; NDA 208945, Ozenoxacin cream 1%. CDER; 2017. Accessed January 7, 2021.
AdisInsight: Ozenoxacin – Ferrer/Maruho. AdisInsight Drugs. Updated April 16, 2019. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800016781

Plazomicin (Zemdri)

Label: Zemdri. Prescribing information. Achaogen, Inc.; 2018. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210303Orig1s000lbl.pdf

Summary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA 210303, Plazomicin for injection; Cross-Discipline Team Leader, Division Director and Office Director Summary Review for Regulatory Action. CDER; 2018.
Risk Assessment and Risk Mitigation Review(s): US Food and Drug Administration, Center for Drug Evaluation and Research. Division of Risk Management Review, Evaluation of Need for a REMS. CDER; 2018. Accessed January 7, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210303Orig1s000RiskR.pdf
AdisInsight: Plazomicin – Cipla. AdisInsight Drugs. Updated July 7, 2020. Accessed January 7, 2021.
https://adisinsight.springer.com/drugs/800029572

Eravacycline (Xerava)

Label: Xerava. Prescribing information. Tetraphase Pharmaceuticals, Inc.; 2018. Accessed January 7, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211109lbl.pdf
Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA Multi-Disciplinary Review and Evaluation – NDA 211109: XERAVA (eravacycline) for injection. CDER; 2018. Accessed January 7, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211109Orig1s000MultidisciplineR.pdf
AdisInsight: Eravacycline – Tetraphase Pharmaceuticals. AdisInsight Drugs. Updated August 31, 2020. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800032231

Amikacin sulfate (Arikayce)

Label: Arikayce. Prescribing information. Insmed Incorporated; 2018. Accessed January 7, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207356s000lbl.pdf
Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA Multi-Disciplinary Review and Evaluation – NDA 207356. CDER; 2018. Accessed January 7, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207356Orig1s000MultidisciplineR.pdf
AdisInsight: Amikacin liposomal inhaled – Insmed. AdisInsight Drugs. Updated January 5, 2021. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800021086

Omadacycline (Nuzyra)

Label: Nuzyra. Prescribing information. Paratek Pharmaceuticals, Inc.; 2018. Accessed January 7, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209816_209817lbl.pdf
Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA Multi-Disciplinary Review and Evaluation – NDAs 209816 and 209817. CDER; 2018. Accessed January 7, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209816Orig1s000,209817Orig1s000MultidisciplineR.pdf
AdisInsight: Omadacycline – Paratek Pharmaceuticals. AdisInsight Drugs. Updated December 11, 2020. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800017923

Rifamycin (Aemcolo)

Label: Aemcolo. Prescribing information. Cosmo Technologies, Ltd.; 2018. Accessed January 7, 2021.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210910s000lbl.pdf

Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA Multi-disciplinary Review and Evaluation – NDA 210910. CDER; 2018. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210910Orig1s000MultidisciplineR.pdf
AdisInsight: Rifamycin controlled-release – Cosmo/Dr Falk Pharma/Salix. AdisInsight Drugs. Updated December 12, 2020. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800026559

Imipenem-cilastatin-relebactam (Recarbrio)

Label: Recarbrio. Prescribing information. Merck Sharp and Dohme Corp.; 2019. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212819s000lbl.pdf
Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA Multi-disciplinary Review and Evaluation (NDA 212819): RECARBRIO (imipenem/cilastatin/relebactam for injection). CDER; 2018. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212819Orig1s000MultidisciplineR.pdf
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Pretomanid (Pretomanid)

Label: Pretomanid. Prescribing information. Mylan Laboratories, Ltd.; 2019. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf
Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA Multi-disciplinary Review and Evaluation – NDA 212862. CDER; 2016. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000MultidisciplineR.pdf
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Lefamulin (Xenleta)

Label: Xenleta. Prescribing information. Nabriva Therapeutics, Inc.; 2019. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211672s000,211673s000lbl.pdf
Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. NDA/BLA Multi-disciplinary Review and Evaluation NDA 211672 and NDA 21167: XENLETA (Lefamulin injection and tablets). CDER; 2018. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211672Orig1s000,%20211673Orig1s000MultidisciplineR.pdf
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Omeprazole magnesium-amoxicillin-rifabutin (Talicia)

Label: Talicia. Prescribing information. RedHill Biopharma Inc; 2019. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213004lbl.pdf
Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Multi-Disciplinary Review and Evaluation NDA 213004: TALICIA (rifabutin, amoxicillin, omeprazole). CDER; 2019. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213004Orig1s000MultidisciplineR.pdf

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Cefiderocol (Fetroja)

Label: Fetroja. Prescribing information. Shionogi Inc.; 2019. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209445s000lbl.pdf
Multi-Disciplinary Review: US Food and Drug Administration, Center for Drug Evaluation and Research. Multi-Disciplinary Review and Evaluation NDA 209445: FETROJA (cefiderocol) for Injection. CDER; 2019. Accessed January 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209445Orig1s000MultidisciplineR.pdf
AdisInsight: Cefiderocol – Shinogi. AdisInsight Drugs. Updated January 6, 2021. Accessed January 7, 2021. https://adisinsight.springer.com/drugs/800036159

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%).

Appendix 4: Post-Market Commitments and Requirements

See https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm. All PMCs are copied verbatim from the FDA source.

Drug	Commitments and Requirements	Reportable Under*	Current Status (as of Q 1 2021)
Pretomanid	1. Conduct a study to evaluate the effect of Pretomanid Tablets on human semen.	FDAAA Section 505 (o)(3)	Pending
	2. Conduct a global surveillance study for a five-year period after the introduction of Pretomanid Tablets to the market to monitor changes in M. tuberculosis susceptibility to pretomanid.	FDAAA Section 505 (o)(3)	Pending
	3. Conduct a study to evaluate pharmacokinetics and safety of Pretomanid Tablets in subjects with renal impairment.	FDAAA Section 505 (o)(3)	Pending
	4. Conduct a study to evaluate pharmacokinetics and safety of Pretomanid Tablets in subjects with mild, moderate, and severe hepatic impairment.	FDAAA Section 505 (o)(3)	Pending
	5. Conduct a two-year rat carcinogenicity study with pretomanid.	FDAAA Section 505 (o)(3)	Pending
	6. Conduct the ZeNix trial to evaluate various doses and treatment durations of linezolid plus bedaquiline and Pretomanid Tablets for treatment of extensively drug-resistant pulmonary tuberculosis.	FDAAA Section 505 (o)(3)	Pending
	7. Conduct the SimpliciTB trial to evaluate Pretomanid Tablets, bedaquiline, moxifloxacin, and pyrazinamide for treatment of drugresistant pulmonary tuberculosis.	FDAAA Section 505 (o)(3)	Pending
Imipenem-cilastatim-relebactam	1. Conduct an open label, single-dose study to evaluate the pharmacokinetics, safety and tolerability of imipenem, cilastatin and relebactam in children from birth to less than 18 years of age with proven or suspected Gram-negative infections.	Pediatric Research Equity Act	Pending
	2. Conduct a randomized, open-label, active controlled trial to evaluate the safety and tolerability of imipenem, cilastatin and relebactam in children from birth to less than 18 years of age with complicated urinary tract infections and complicated intra-abdominal infections.	Pediatric Research Equity Act	Released [As of 06/04/2020]
	3. Conduct a United States surveillance study for 5 years from the date of marketing to determine if resistance to imipenem, cilastatin, and relebactam had developed in those organisms specific to the indication in the label.	FDAAA Section 505(o)(3)	Pending
Lefamulin	1. Conduct a single-dose study to evaluate the pharmacokinetics and safety of intravenous XENLETA (lefamulin) in children from birth to less than 18 years of age with suspected or confirmed bacterial infections receiving standard of care.	Pediatric Research Equity Act	Pending

	2. Conduct a single-dose study to evaluate the pharmacokinetics and safety of oral XENLETA (lefamulin) in children from birth to less than 18 years of age with suspected or confirmed bacterial infections receiving standard of care.	Pediatric Research Equity Act	Pending
	3. Conduct a randomized active-controlled study to assess the safety and pharmacokinetics of XENLETA (lefamulin) in children from 2 months to less than 18 years of age with CABP.	Pediatric Research Equity Act	Pending
	4. Conduct a United States surveillance study for 5 years from the date of marketing to determine if resistance to XENLETA (lefamulin) has developed in those organisms specific to the CABP indication in the label.	FDAAA Section 505 (o)(3)	Pending
	5. Conduct a pregnancy surveillance program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to XENLETA (lefamulin) during pregnancy.	FDAAA Section 505 (o)(3)	Pending
	6. Conduct an in vitro Mouse Lymphoma Assay (MLA) that evaluates higher doses of lefamulin reaching 10-20% Relative Total Growth (RTG) and in accordance with the Organisation for Economic Co-operation and Development (OECD) Guidelines for the Testing of Chemicals #476.	FDAAA Section 505 (o)(3)	Pending
	7. Conduct an in vitro Mouse Lymphoma Assay (MLA) that evaluates higher doses of the lefamulin metabolite BC-8041 reaching 10-20% Relative Total Growth (RTG) and in accordance with the OECD Guideline for the Testing of Chemicals #476.	FDAAA Section 505 (o)(3)	Pending
Rifamycin	1. Conduct a randomized, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AEMCOLO (rifamycin) for the treatment of travelers' diarrhea in children from 6 to 11 years of age.	Pediatric Research Equity Act	Delayed [Final protocol due 12/2019; submitted 01/2020.]
	2. Conduct a randomized, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AEMCOLO (rifamycin) for the treatment of travelers' diarrhea in children from 12 to 17 years of age.	Pediatric Research Equity Act	Pending
	3. Conduct human factors validation study for AEMCOLO (rifamycin) packaging.	Section 506B	Fulfilled
Omadacycline	1. Conduct a single dose pharmacokinetic and safety study in children ages 8 to 17 years who are receiving antibacterial drug therapy for an infectious disease.	Pediatric Research Equity Act	Delayed [Final protocol submitted 02/2020, after original milestone]
	2. Conduct an active-controlled safety study in children 8-17 years who have acute bacterial skin and skin structure infections.	Pediatric Research Equity Act	Pending
	3. Conduct an active-controlled safety study in children 8-17 years who have community-acquired bacterial pneumonia.	Pediatric Research Equity Act	Pending

	4. Conduct an active-controlled safety and efficacy study in adults with community-acquired bacterial pneumonia.	FDAAA Section 505 (o)(3)	Pending
	5. Conduct a United States surveillance study for 5 years from the date of marketing to determine if resistance to NUZYRA (omadacycline) has developed in those organisms specific to the indications in the label.	FDAAA Section 505 (o)(3)	Pending
Eravacycline	1. Conduct a study to evaluate the pharmacokinetics, safety, and tolerability of a single dose of intravenous XERAVA (eravacycline) in pediatric patients from 8 years to less than 18 years of age with suspected or confirmed bacterial infection.	Pediatric Research Equity Act	Released [As of 01/02/2020]
	2. Conduct a randomized, multicenter, active-controlled trial to evaluate the safety and tolerability of intravenous XERAVA (eravacycline) in pediatric patients from 8 years to less than 18 years of age with complicated intra-abdominal infections. The dose for this study will be determined upon review of the data from the single-dose, non-comparative study assessing the pharmacokinetics of XERAVA (eravacycline) in pediatric patients from 8 years to less than 18 years of age.	Pediatric Research Equity Act	Released [As of 01/02/2020]
	3. A United States surveillance study for 5 years from the date of marketing to determine if resistance to XERAVA (eravacycline) has developed in those organisms specific to the indication in the label.	FDAAA Section 505(o)(3);	Ongoing
Plazomicin	1. Conduct an open-label multiple dose pharmacokinetic and safety study of plazomicin in hospitalized children ages birth to 18 years with infections and receiving standard-of-care antibacterial drugs.	Pediatric Research Equity Act	Released [As of 03/13/2020]
	2. Conduct a randomized active-controlled pharmacokinetic and safety trial of plazomicin in children ages birth to 18 years with cUTI including acute pyelonephritis.	Pediatric Research Equity Act	Released [As of 03/13/2020]
	3. Conduct US surveillance studies for five years from the date of marketing plazomicin to determine if resistance to plazomicin has developed in those organisms specific to the indication in the label.	FDAAA Section 505(o)(3)	Pending
	4. Conduct a clinical study in subjects with end stage renal disease (ESRD) receiving hemodialysis to evaluate the pharmacokinetics of plazomicin.	Section 506B	Pending

	5. Establish an FDA cleared or approved in vitro diagnostic device for therapeutic drug monitoring of plazomicin that is recommended for patients with baseline creatinine clearance <90 mL/min in patients with complicated urinary tract infections (cUTI).	Section 506B	No longer listed
Delafloxacin	1. Conduct US surveillance studies for five years from the date of marketing Baxdela to determine if resistance to delafloxacin has developed in those organisms specific to the ABSSSI indication in the label.	FDAAA Section 505(o)(3)	Released
	2. Conduct a tissue distribution study in pregnant rats treated during the period of organogenesis with the oral formulation and with the intravenous formulation of Baxdela with the excipient sulfobutylether beta-cyclodextrin (SBECD) to assess the distribution of the drug substance to the reproductive tract and developing fetus.	FDAAA Section 505(o)(3)	No longer listed
	3. If the results of the tissue distribution studies from PMR 3220-2 demonstrate greater exposure of the fetus / maternal reproductive tract to delafloxacin with the intravenous formulation, conduct an embryo-fetal developmental toxicology study in pregnant rats treated during the period of organogenesis with the intravenous formulation of Baxdela to identify possible effects of delafloxacin with the excipient sulfobutylether betacyclodextrin (SBECD) on fetal development during the period of organogenesis.	FDAAA Section 505(o)(3)	No longer listed
Secnidazole	1. Conduct an open label, multicenter, safety study of Solosec (secnidazole) oral granules in healthy postmenarchal adolescent females ages 12 years to less than 18 years of age with bacterial vaginosis.	Pediatric Research Equity Act	Ongoing
Meropenem-vaborbactam	1. Conduct an open-label, sequential study to assess the pharmacokinetics (PK), safety, and tolerability of VABOMERE and the PK of meropenem and vaborbactam in children from birth to < 18 years of age with selected serious bacterial infections.	Pediatric Research Equity Act	Ongoing
	2. Conduct a randomized, single-blind, active comparator study to evaluate the safety, tolerability, and PK of VABOMERE versus piperacillin-tazobactam for the treatment of pediatric subjects from 3 months to <18 years of age with complicated Urinary Tract Infections (cUTI) including acute pyelonephritis.	Pediatric Research Equity Act	Pending

	3. Conduct an open-label, active comparator study to evaluate the PK, safety, and tolerability of multiple doses of VABOMERE vs. comparator in neonates (less than or equal to 90 days of age) with late onset sepsis.	Pediatric Research Equity Act	Pending
	4. Conduct a US surveillance study for five years from the date of marketing to determine if resistance to VABOMERE has developed in those organisms specific to the indications in the label.	FDAAA Section 505(o)(3)	Ongoing
	5. Conduct a "Thorough QT/QTc Study" to evaluate whether VABOMERE has a threshold pharmacologic effect on cardiac repolarization.	FDAAA Section 505(o)(3)	Fulfilled
Ozenoxacin	**None listed**		
Bezlotoxumab	1. Conduct a randomized, double-blind, placebo-controlled trial of safety, efficacy, and pharmacokinetics of Zinplava (bezlotoxumab) in pediatric patients from 1 to less than 18 years of age receiving antibacterial therapy for C. difficile infection.	Pediatric Research Equity Act	Ongoing
Amikacin liposome inhalation suspension (Arikayce)	1. Conduct a randomized, double-blind, placebo-controlled clinical trial to assess and describe the clinical benefit of ARIKAYCE in patients with nontuberculous mycobacterial (NTM) lung disease caused by MAC. The trial will evaluate the effect of ARIKAYCE on a clinically meaningful endpoint, as compared to an appropriate control in the intended patient population of patients with MAC infection.	Accelerated Approval	Delayed
	2. Provide and implement an email, standard mail, and facsimile communication plan to include a Dear Healthcare Provider letter as well as targeted educational materials to clinicians and professional societies.	Section 506B	Submitted
	3. Provide results of a drug utilization assessment including ICD-10 code or other information on the indication and patient demographic/clinical characteristics of users of ARIKAYCE through pharmacies that will be distributing ARIKAYCE, and the results of chart reviews of a random subset of patients who are prescribed ARIKAYCE.	Section 506B	Ongoing
Cefiderocol	1. Conduct an open-label, randomized, multicenter, active-controlled trial to evaluate the pharmacokinetics, safety and tolerability of FETROJA (cefiderocol) in children from 3 months to less than 18 years of age with cUTI. The dose for this study for children 3 months to less than 12 years of age will	Pediatric Research Equity Act	Released [As of 09/25/2020]

	be determined by the data from a single-dose, non-comparative study assessing the pharmacokinetics of FETROJA (cefiderocol) in pediatric patients from 3 months to less than 12 years of age with suspected or confirmed Gram-negative infections.		
	2. Conduct an open-label, single arm non-comparative study to evaluate the pharmacokinetics, safety and tolerability of multiple doses of FETROJA (cefiderocol) in children from birth to less than 3 months of age with suspected or confirmed cUTI. The dose for this study will be determined by the data from a single-dose, noncomparative study assessing the pharmacokinetics of FETROJA (cefiderocol) in pediatric patients from birth to less than 3 months of age with suspected or confirmed Gram-negative infections.	Pediatric Research Equity Act	Released [As of 09/25/2020]
	3. Conduct US surveillance studies for five years from the date of marketing FETROJA to determine if resistance to cefiderocol has developed in those organisms specific to the cUTI indication in the label.	FDAAA Section 505 (o)(3)	Pending
	4. Conduct a study to define the mechanism(s) of resistance to FETROJA (cefiderocol) for isolates identified as being resistant to cefiderocol in the surveillance study (five years from the date of marketing).	FDAAA Section 505 (o)(3)	Pending
	5. Submit the final study report for the completed CREDIBLE-CR trial (1424R2131), "A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens".	FDAAA Section 505 (o)(3)	Fulfilled
	6. Submit the final study report for the completed APEKS-NP trial, "Clinical Study of S-649266 for the Treatment of Nosocomial Pneumonia Caused by Gram-negative Pathogens".	FDAAA Section 505 (o)(3)	Fulfilled
Omeprazole magnesium-amoxicillin-rifabutin (Talicia)	**None listed**		

* PMRs reportable under: FDAAA Section 505(o)(3); Pediatric Research Equity Act; Accelerated Approval
PMCs reportable under: Section 506B
Only PMRs and PMCs that are reportable and included in original approval letter have been included, unless otherwise noted.

** This PMR was not originally listed in the approval letter, but according to the FDA, it replaces PMR 1 and PMR 2. As such, it has been included here.