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ANTIMICROBIAL DRUGS MARKET RETURNS ANALYSIS

FINAL

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DISCLAIMER

LIST OF ACRONYMS

AACT	Access to Aggregate Content of ClinicalTrials.gov
AB	Actual benefit
ABSSSI	Acute bacterial skin and skin structure infection
ACB	Actual clinical benefit
AM	Antimicrobial
ASPR	Office of the Assistant Secretary for Preparedness and Response
AST	Antimicrobial susceptibility test
BARDA	HHS Biomedical Advanced Research and Development Authority
BL-BLI	Beta-lactam/beta-lactamase inhibitor
BLA	Biologics license application
CABP	Community-acquired bacterial pneumonia
CAPM	Capital asset pricing model
CAV	Clinical added value
CBER	FDA's Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	FDA's Center for Drug Evaluation and Research
CDI	*Clostridioides difficile* (aka *C. difficile*) infection
CIAI	Complicated intra-abdominal infection
CMC	Chemistry, manufacturing, and controls
COPD	Chronic obstructive pulmonary disease
CPP	Cost per patient
CRE	Carbapenem-resistant *Enterobacterales*
CRO	Contract research organization
CTTI	Clinical Trials Transformation Initiative
CUTI	Complicated urinary tract infection
DRG	Diagnosis-related group
ERG	Eastern Research Group, Inc.
ESKAPE	*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species
FDA	U.S. Food and Drug Administration
FPDS-NG	Federal Procurement Data System (FPDS) – Next Generation
GAIN	*Generating Antibiotic Incentives Now* Act of 2012
HABP/VABP	Hospital-acquired bacterial pneumonia / ventilator-associated bacterial pneumonia
HAS	Haute Autorité de Santé
HTA	Health technology assessment
ICER	Institute for Clinical and Economic Review
IDSA	Infectious Diseases Society of America
INAHTA	International Network of Agencies for Health Technology Assessment
IND	Investigational new drug
IQWiG	Institute for Quality and Efficiency in Health Care
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Intravenous
MCDA	Multicriteria decision analysis
MDR	Multidrug resistant
NCE	New chemical entity
NDA	New drug application
NIAID	National Institute of Allergy and Infectious Disease
NICE	U.K. National Institute for Health and Care Excellence

NIH	National Institutes of Health
NME	New molecular entity
OCOC	Opportunity cost of capital
PAG	Project advisory group
P&T	Pharmacy & Therapeutics
PHS	U.S. Public Health Service
PIDD	Primary immune deficiency disease
PDP	Product development partnership
R&D	Research and development
RE	Relative effectiveness
QIDP	Qualified infectious disease product
USPTO	United States Patent and Trademark Office
WHO	World Health Organization

EXECUTIVE SUMMARY

In 2017, at least 2.8 million people in the U.S. acquired serious infections with bacteria that are resistant to one or more antimicrobial drugs and 35,000 have died as a result. Resistance to antimicrobials is viewed as a global threat with antimicrobial drug use in human and animal health driving resistance. Compounding the problem is an insufficiently robust global antimicrobial drug pipeline which currently includes a total of 43 antimicrobial compounds in different stages of development with only 15 showing promise against pathogens showing resistance to most of the antimicrobials available. There are over 100 antimicrobial drugs that are used to treat a variety of bacterial diseases at present (Powers, 2004; Stephens, 2021). However, without the development of new drugs, expansion of resistance will continue to reduce the effectiveness of currently available antimicrobial drugs and leave many patients with few, if any, treatment options. Stakeholders have proposed that pharmaceutical companies are avoiding antimicrobial drug development because they anticipate poor market performance (i.e., low sales revenues) for these drugs.

This study examines how recently approved antimicrobial drugs are performing relative to their added clinical benefit and the contributing factors to this performance compared to other types of drugs. Using public and proprietary data sources coupled with expert interviews, we estimate the development cost and comparative added clinical benefit of a total of 32 drugs (Table E - 1) of which 12 are antimicrobials (AM cohort), 14 are oncology drugs (oncology cohort), and the remaining 6 are other types of drugs that are similar to antimicrobials with respect to certain characteristics such as treatment duration and DRG-style[1] reimbursement (non-AM comparator cohort). We then compare the comparative added clinical benefit of each drug to its market performance within each drug cohort.

Table E - 1. Drugs Selected for Analysis

AM Cohort Drugs	Non-AM Comparator Cohort Drugs	Oncology Cohort Drugs
Avycaz	Bridion	Erivedge
Baxdela	Giapreza	Ibrance
Dalvance	Lokelma	Portrazza
Nuzyra	Surfaxin	Braftovi
Orbactiv	Veltassa	Darzalex
Sivextro	Vistogard	Vitrakvi
Teflaro		Rubraca
Vabomere		Jevtana
Vibativ		Yondelis
Xerava		Cometriq
Zemdri		Zelboraf
Zerbaxa [a]		Stivarga
		Cyramza

We find that the drugs in the AM cohort have average to high development and approval costs when compared to the non-AM comparator and oncology cohort drugs. However, once cost of failures and opportunity cost of capital are accounted for, drugs in the AM cohort have the lowest expected capitalized development and approval costs of $1,508 million on average, which is less

[1] A diagnosis-related group (DRG) is a patient classification system that Medicare uses to classify costs associated with a given inpatient hospital stay and determines how much to reimburse for those hospital stays. Under this system, Medicare pays a predetermined amount based on the patient's DRG instead of "pay[ing] the hospital for each specific service it provides" (Centers for Medicare and Medicaid Services, 2019).

than that estimated for drugs in the non-AM comparator ($3,198 million) and oncology ($6,293 million) cohorts. In other words, compared to those drugs in the non-AM comparator and oncology cohorts, AM cohort drugs are the least costly to develop and obtain regulatory approval for.

Using a series of evaluation metrics garnered from different information sources, such as European health technology assessments (HTAs), Trinity Drug Index, and others (Table E - 2), we rank each drug compared to the others in the same cohort using an iterative process with a weighting routine. We then calculate the overall comparative added clinical benefit score for each drug within each cohort which provides more of a qualitative ranking. Drugs with high comparative added clinical benefit include Zerbaxa, Avycaz, Vabomere, and Sivextro in the AM cohort, Veltassa and Lokelma in the non-AM comparator cohort, and Rubraca, Zelbograf, Ibrance, and Erivedge in the oncology cohort.

Table E - 2. List of Evaluation Metrics Used in Assessing Comparative Added Clinical Benefit

Evaluation Metric	AM Cohort Drugs	Non-AM Comparator Cohort Drugs	Oncology Cohort Drugs
New Molecular Entity	✓	✓	✓
New Chemical Entity	✓	✓	✓
Route of Administration	✓	✓	✓
Annual Number of U.S. Cases		✓	✓
Estimated Market Size	✓		
Number of Drugs for Indication	✓	✓	✓
Activity against ESKAPE Pathogens	✓		
Activity against CDC urgent WHO critical pathogens	✓		
Trinity Drug Index Therapeutic Score	✓	✓	✓
Trinity Drug Index Commercial Score	✓	✓	✓
Trinity Drug Index R&D Score	✓	✓	✓
HAS Actual Clinical Benefit (ACB)	✓	✓	✓
HAS Clinical Added Value (CAV)	✓	✓	✓
NICE	✓	✓	✓
IQWiG	✓	✓	✓
Automated AST Device Incorporation	✓		
QDIP Designation	✓		
BARDA Funding	✓		
P&T Community Decision	✓	✓	✓
IDSA Guideline Inclusion	✓	✓	
ICER Assessment			✓
Medicaid Coverage in Top Ten Largest Medicaid Markets [a]	✓	✓	✓

HAS = Haute Autorité de Santé
NICE = National Institute for Health and Care Excellence
IQWIG = Institute for Quality and Efficiency in Health Care
AST = Antimicrobial Susceptibility Test
QDIP = Qualified Infectious Disease Product
BARDA = Biomedical Advanced Research and Development Authority
P&T = Pharmacy & Therapeutics
IDSA = Infectious Diseases Society of America
ICER = Institute for Clinical and Economic Review
[a] The top ten Medicaid markets include California, New York, Texas, Pennsylvania, Florida, Ohio, Illinois, Massachusetts, Michigan, and New Jersey.

We then evaluate the market performance for all drugs selected using quarterly sales data from IQVIA MIDAS and compare this performance against the comparative added clinical benefit

estimated for each drug. Our analysis indicates that there is a direct relationship between market performance defined as nine quarters of cumulative global sales since market launch and comparative added clinical benefit within each cohort. In other words, drugs with higher overall comparative added clinical benefit scores tend to have higher early market sales compared to other drugs in the same cohort on average, although there are a few exceptions. While this relationship holds across all three drug cohorts examined here, the magnitude of sales is exponentially higher for the oncology cohort drugs than those in the AM and non-AM comparator cohorts. The average cumulative 9 quarter sales for the highest-ranking AM and non-AM comparator drugs are $42 million and $62 million, respectively, and $1,041 million for the oncology drugs.

Overall, this analysis shows that markets do in fact reward comparative added clinical benefit within each therapy area (i.e., bacterial infections, cancer, etc.). However, there are large discrepancies in commercial market performance (i.e., magnitude of sales revenue) among different therapy areas that reflect inherent differences in patient populations, treatment durations, the setting in which these drugs are used (outpatient versus inpatient), and DRG-based reimbursement that incentivizes cost containment in hospitals.

1 INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), at least 2.8 million people in the U.S. acquire serious infections each year with bacteria that are resistant to one or more of the antimicrobial (AM) drugs designed to treat those infections. Of these, approximately 35,000 die because of drug-resistant infections (Centers for Disease Control and Prevention, 2019a). Meanwhile, the current global AM drug pipeline, comprised of 252 and 43 AM compounds in different stages of preclinical and clinical development, respectively, is not sufficiently robust to meet current and future patient demand according to some experts (The Pew Charitable Trusts, 2021a; World Health Organization, 2019). While there is no agreement on what a healthy AM pipeline looks like, many find the relatively small number of pipeline AM compounds (15 out of 43) with some potential activity for serious and life-threatening infections caused by pathogens of concern worrisome given the attrition rates in clinical trials (National Academies of Sciences, Engineering, and Medicine, 2022). Without the continued development of pipeline AM compounds and new AM compounds, expansion of resistance will continue to reduce the effectiveness of currently available AM drugs and leave many patients with few, if any, treatment options.

Despite the potential of new products to reduce the social burden associated with resistant infections, the expected returns of an AM drug on the market remain low. In the 1980s, commercializing new AM drugs was a relatively straightforward process. There were few barriers to adding new AM drugs to formularies and given the widespread use and efficacy of broad-spectrum AM drugs, developers could often rely on some degree of robust market uptake. In the 2000s, as resistance patterns emerged, some AM drugs began losing efficacy and stewardship (i.e., efforts by healthcare providers to ensure that AM drugs are used only when necessary and appropriate) increased, resulting in fewer and less frequent AM drug prescriptions (Centers for Disease Control and Prevention, 2021; Eastern Research Group, Inc., 2018).[2] As a result, the commercial prospects for AM drugs shrank.

Antimicrobial stewardship in recent decades has been pivotal in shifting several newly-approved non-generic AM drugs to the last line of defense. Standardizing the appropriate use of drugs in healthcare facilities can reduce resistance, slow the spread of multidrug-resistant (MDR) infections, and ultimately improve patient outcomes, but also inherently causes new AM drugs to have slower market uptake than most other drugs. While reducing antimicrobial resistance (AMR), decreasing the spread of MDR infections, and improving patient outcomes are the desirable goals from a societal perspective, such measures, if successful, are further expected to reduce the number of MDR infections which will naturally contribute to slower market uptake and lower utilization of future AM drugs. There are additional factors that compound the problem of slow market uptake including the fact that AM drugs often have short treatment durations and that many new AM drugs target infections affecting small patient populations.

Based on responses in a series of interviews ERG conducted with stakeholders including infectious disease, intensive care unit, and emergency room doctors that are likely to routinely prescribe AM drugs in a hospital setting, doctors tend to be cautious and do not prescribe new AM drugs if there are older, often generic, AM drugs available as first-line treatments (Eastern Research Group, Inc., 2018). Recommended prescribing practices have also started to be implemented in the electronic health records based on how hospital administrators set their stewardship goals. These hospital administrators, including the pharmacy and therapeutics committees, must approve new

[2] According to data from the CDC, outpatient antibiotic prescriptions in the U.S. decreased by 10 percent from 2011 to 2018. They further decreased by 25 percent from 2019 to 2020 due to the COVID-19 pandemic, which exceeded the 15 percent reduction goal in the 2015 – 2020 Combating Antibiotic Resistant Bacteria (CARB) National Action Plan (Centers for Disease Control and Prevention, 2021).

medications before doctors can prescribe them, taking into consideration the clinical value of the drug, cost of the drug, and whether there are effective alternatives on the formulary. This has led to older, cheaper, broad-spectrum AM drugs being the preferred first line options. Exceptions are new AM drugs that have a shorter course of treatment or drugs that offer oral formulations, as opposed to intravenous administration, which allow the patient to be discharged more quickly.

According to some observers, the AM pipeline has also been affected by decreased investor interest and the subsequent exit of large pharmaceutical companies from the development space. A World Health Organization (WHO) study in Europe found that since 1990, the number of large pharmaceutical companies that were actively developing AM drugs has dropped from 18 to 4 and smaller companies have started to fill that space (Renwick, et al., 2016). The estimated average price tag for developing a new AM drug is between $1.3 billion (in 2018 dollars) (Wouters, et al., 2020)[3] and $1.9 billion (in 2018 dollars) (Towse, et al., 2017)[4] accounting for failures and cost of capital. The average yearly revenue for an AM drug, on the other hand, is $46 million according to industry analysts (Plackett, 2020). One study estimated the net present value (i.e., the sum of all development investment costs and expected present value of future revenues) for an AM drug at around $44.5 million (in $ 2018 converted from Euros) compared to $752.6 million to $1.2 billion for neurological or musculoskeletal drugs (Sciarretta, et al., 2016).[5] Under these circumstances, the business case for investing in AM drug development is weak. However, none of these estimates account for the hundreds of millions of dollars in federal government investment in the development of these AM drugs in recent years that were intended to offset a large portion of R&D expenditures incurred by the developers. According to public records,[6] the U.S. federal government investment alone was nearly half a billion dollars for five of the AM drugs approved during the 2014-2018 period exclusive of the value of several additional benefits, such as tax incentives and additional years of exclusivity protections.

Despite the diminished interest in developing AM drugs from investors and large pharmaceutical companies, implementation of a series of market incentives, such as grants for clinical research, product development partnerships (PDPs), tax credits, and additional years of exclusivity protections availed by the *Generating Antibiotic Incentives Now* (GAIN) Act of 2012, has helped to keep the AM pipeline viable, even resulting in modest gains. As can be observed from Figure 1, there has been a noticeable increase in the average number of novel AM drugs approved by FDA per year after the passage of the GAIN Act from 0.8 approvals per year during the 2002-2012 period to 1.4 approvals per year during the 2012-2021 period (GlobalData, 2018; Cunha, et al., 2019; Dheman, et al., 2021). Moreover, even though the AM drug pipeline is still viewed to be lackluster by some, the total number of AM drug candidates in the pipeline has increased by 10.5 percent from 38 to 43 (Figure 2) from 2014 to 2020 (Cunha, et al., 2019; The Pew Charitable Trusts, 2021b).

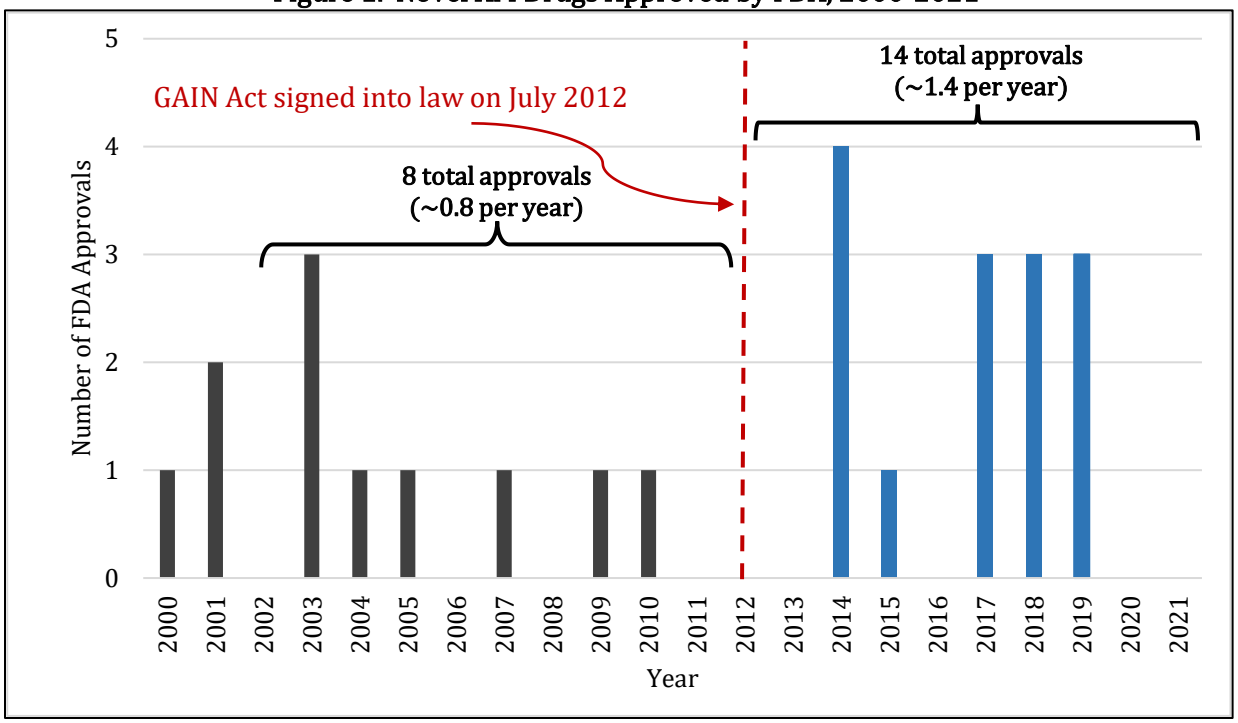
[3] The reported estimate is based on a sample size of five anti-infectives for systemic use approved during 2009-2018 period. The reported 95 percent confidence bounds around the mean estimate are $672.5 million to $1.9 billion (Wouters, et al., 2020).

[4] The reported estimate in Towse et al (2017) is $1.581 in 2011 dollars. We used U.S. Medical Care Price Index to calculate the corresponding estimate in 2018 dollars (U.S. Bureau of Labor Statistics, 2021).

[5] The corresponding reported estimates in Sciarretta et al. (2016) are $42.61 million, 720 million, and $1.15 billion in 2016 dollars. We used U.S. Medical Care Price Index to calculate the corresponding estimate in 2018 dollars (U.S. Bureau of Labor Statistics, 2021).

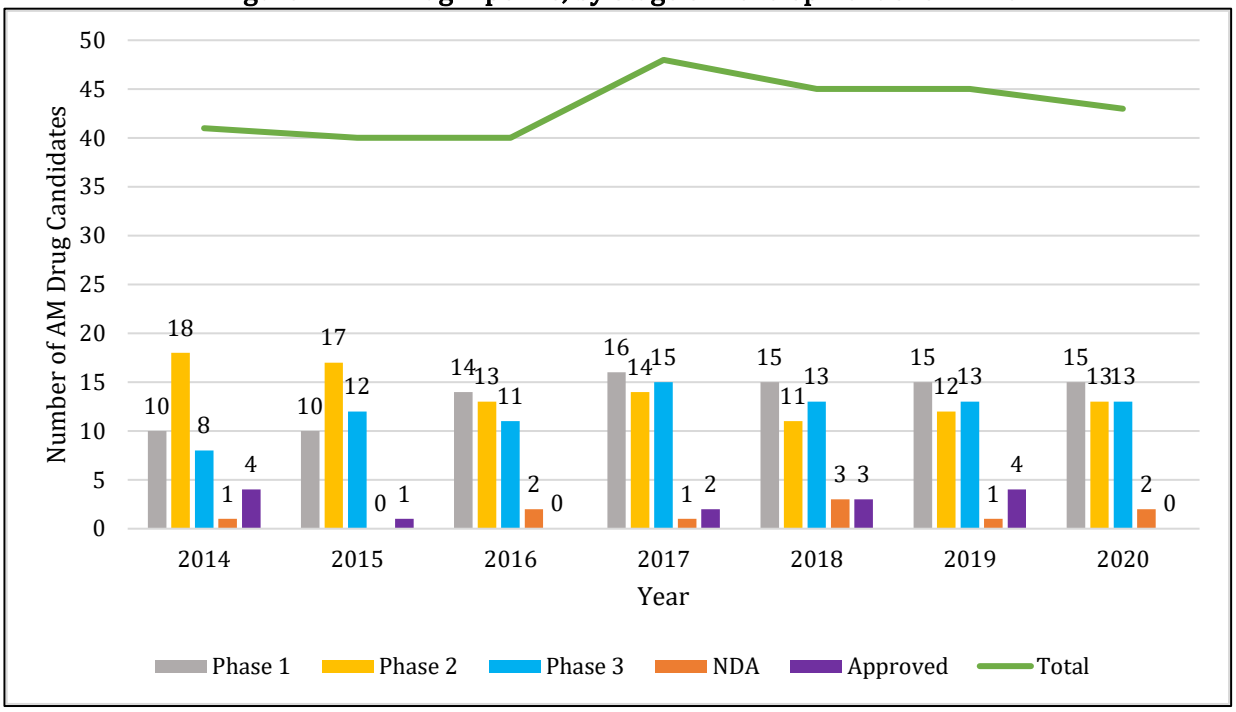
[6] The figure is based on a query of the Federal Procurement Data System (FPDS) – Next Generation (NG)which is a central repository of information on Federal contracting. FPDS contains detailed information on contract actions over $3,000 (FY2004 and later data).

Figure 1. Novel AM Drugs Approved by FDA, 2000-2021



Source: Adapted from GlobalData (2018) and updated with data from Dheman, et al. (2021) and Cunha et al. (2019).

Figure 2. AM Drug Pipeline, by Stage of Development over Time



Source: Adapted from Cunha et al. (2019)
NDA = New Drug Application phase; Approved = Received marketing approval; Total = Sum of Phase 1, Phase 2, Phase 3, NDA, and Approved drug candidates.

During the same 2014-2020 period, FDA approved a total of 23 AM drugs, of which 20 (87 percent) had expected activity against ESKAPE pathogens, pathogens designated as urgent threats by the CDC, and/or the WHO threat pathogens.[7] Of these 20 antimicrobial drugs, 15 received qualified infectious disease product (QIDP) designations from the FDA, which made them eligible for priority review, and were granted extended exclusivity protections.[8] Even though the GAIN Act appears to have vitalized the AM pipeline during the 2010s, other factors likely have contributed to the increase in new AM drug approvals as well. These included changes in FDA guidance designed to streamline AM development programs and clinical trial designs followed by the establishment of the Limited Population Antibacterial Product (LPAD) pathway in 2016 (Section 3042 of Pub. L. 114-255) for certain drugs that are intended to treat serious or life-threatening infections in a limited population of patients with unmet needs (U.S. Food and Drug Administration, 2018). There also are additional incentives included in two bills under consideration in Congress, the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act and the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act, that could further alter the AM development landscape and help bring novel AM drugs that address unmet needs to market. The DISARM Act would allow CMS to reimburse qualified AM drugs outside of the diagnosis-related group (DRG) payment system. Supporters of the bill argue that it would improve 1) patient outcomes by providing hospitals more freedom to select appropriate AM drugs and 2) financial viability of companies marketing these AM drugs. The PASTEUR Act would create a subscription payment model for new qualified AM drugs that delinks payment from sales volume. Under this model, AM drugs that meet certain criteria would earn annual U.S. government contracts valued $750 million to $3 billion. Supporters of the bill anticipate that this would reduce marketing risk, thereby incentivizing more companies to enter the AM drug development space (Presidential Advisory Council on Combating Antibiotic-resistant Bacteria, 2021).

Even though the total number of compounds in the AM pipeline may appear less than dire, according to a 2019 report from the World Health Organization (WHO), the majority of these compounds are not substantially different from existing AM drugs and do not have in vivo activity against those most worrisome MDR gram-negative bacteria as expected, based on in vitro studies conducted during development (World Health Organization, 2019).[9] WHO (2019) further notes that the newly approved AM drugs' "…lack of differentiation against existing treatments, …non-inclusion in clinical guidelines and …higher prices in comparison to existing generic treatments make it difficult to predict their place in the treatment landscape." This sentiment is echoed by others who point out that some of the recently approved AM drugs appear to have no or only minor added clinical value over existing treatments (Nambiar, 2019; Schulz, et al., 2019).

2 STUDY OBJECTIVES

Given the ongoing concern about poor returns on investment for AM drugs, the primary objective of this study is to compare the development costs, comparative added clinical benefit, and market performance of novel AM drugs to other types of drugs approved for the U.S. market during

[7] ESKAPE pathogens include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species (Mulani, et al., 2019). CDC urgent threat pathogens are: *Clostridioides difficile*, carbapenem-resistant *Acinetobacter*, carbapenem-resistant *Enterobacterales* (CRE), *Candida auris*, and drug-resistant *Neisseria gonorrhoeae*. WHO critical threat pathogens are: carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant ESBL-producing *Enterobacteriaceae* (World Health Organization, 2017).

[8] For accepted new drug applications that are designated as Priority Review, FDA aims to take action within 6 months compared to 10 months under standard review (U.S. Food and Drug Administration, 2018).

[9] Demonstrated in vitro activity against a pathogen during development does not always translate to similar activity in vivo for AM drugs.

the 2010 – 2018 period. The comparative study will allow us to answer several questions that are of interest to policymakers, such as:

- What is the average development cost for a novel AM drug? How does this development cost compare to other types of drugs?
- What is the comparative added clinical benefit of novel AM drugs?
- What has been the observed market performance of novel AM drugs versus other types of drugs?
- How have AM drugs performed commercially relative to their comparative added clinical benefit? Is the relationship between market performance and comparative added clinical benefit for AM drugs comparable to that for other types of drugs?

3 DRUGS SELECTED FOR ANALYSIS

To answer the research questions above, we selected three drug cohorts for analysis: AM drugs, comparator non-AM drugs, and oncology drugs. The AM drug cohort comprised of 12 AM drugs approved by FDA during the 2010 – 2018 period. The comparator non-AM drug cohort included 6 drugs commonly used in an inpatient setting for short durations and the oncology drug cohort had 14 oncology drugs of which 4 were large and 10 were small molecule drugs. All drugs in the comparator non-AM and oncology cohorts were approved during the 2010 – 2018 period as were the AM drugs. The sections below describe the selection criteria we used for each cohort in detail. The data compiled on each drug are provided in Appendix A.

3.1 AM DRUG COHORT

We expect that different segments of the AM market (e.g., oral versus intravenous AM drugs) perform differently. Thus, the AM drug cohort needed to have a balanced mix of different types of AM drugs to be representative. Table 1 presents the list of AM drugs approved by FDA for the U.S. market during the 2010 – 2018 period (20 total) along with their characteristics. Only 2 (10 percent) out of the 20 drugs are narrow spectrum; 10 (50 percent) are intravenous, 4 (20 percent) have oral and intravenous formulations, 3 (15 percent) are topical, and 3 (15 percent) are oral.

Based on discussions with the Project Advisory Group (PAG) formed for this study and other experts, we grouped the AM drugs, excluding the antifungal drug Cresemba (isavuconazonium sulfate),[10] and the nitroimidazole drug Solosec (secnidazole) for bacterial vaginosis,[11] depicted in Table 1 into the following five different market segments:

- *Segment 1 – Non-systemic oral/topical AM drugs*. From Table 1, there are four AM drugs that fall into this segment, including Xtoro (finafloxacin otic suspension 0.3%), Zymaxid (gatifloxacin ophthalmic solution), Aemcolo (rifamycin), and Xepi (ozenoxacin).

[10] Anti-fungal drugs were deemed out of scope for this analysis.

[11] Secnidazole was excluded from consideration because its activity against the types of pathogens associated with bacterial vaginosis is similar to metronidazole or tinidazole, the standard therapy (Petrina, et al., 2017).

Table 1. AM Drugs Approved for the U.S. Market and Selected AM Drug Cohort (Denoted with [a] Next to Proprietary Name), 2010-2018

Market Segment	Trade Name	Established Name	Class	Spectrum	Gram-positive, Gram-negative or Both?	Route of Administration	Approved For
NA	Cresemba	isavuconazonium sulfate	Triazole antifungal	NA	NA	Oral & IV	Invasive aspergillosis, invasive mucormycosis
	Solosec	secnidazole	Nitroimidazole	Broad	Both	Oral	Bacterial vaginosis
1	Xtoro	finafloxacin otic suspension 0.3%	Fluoroquinolone	Broad	Both	Topical	Acute otitis externa
	Zymaxid	gatifloxacin ophthalmic solution	Fluoroquinolone	Broad	Both	Topical	Bacterial conjunctivitis
	Aemcolo	rifamycin	Rifamycin	Broad	Both	Oral	Traveler's diarrhea
	Xepi	ozenoxacin	Fluoroquinolone	Broad	Gram-positive	Topical	Impetigo
2	Zemdri [a]	plazomicin	Aminoglycoside	Broad	Gram-negative	IV	CUTI
	Avycaz [a]	ceftazidime + avibactam	Cephalosporin/beta-lactamase inhibitor	Broad	Both	IV	CIAI, CUTI
	Vabomere [a]	meropenem + vaborbactam	Carbapenem/beta-lactamase inhibitor	Broad	Both	IV	CUTI
	Zerbaxa [a]	ceftolozane + tazobactam	Cephalosporin/beta-lactamase inhibitor	Broad	Both	IV	CIAI, CUTI
	Xerava [a]	eravacycline	Tetracycline	Broad	Both	IV	CIAI
3	Dalvance [a]	dalbavancin	Glycopeptide	Broad	Gram-positive	IV	ABSSSI
	Orbactiv [a]	oritavancin	Glycopeptide	Broad	Gram-positive	IV	ABSSSI
	Vibativ [a]	telavancin	Glycopeptide	Broad	Gram-positive	IV	HABP/VABP, ABSSSI
4	Teflaro [a]	ceftaroline fosamil	Cephalosporin	Broad	Both	IV	ABSSSI, CABP
	Baxdela [a]	delafloxacin	Fluoroquinolone	Broad	Both	Oral & IV	ABSSSI
	Sivextro [a]	tedizolid phosphate	Oxazolidinone	Broad	Gram-positive	Oral & IV	ABSSSI
	Nuzyra [a]	omadacycline	Tetracycline	Broad	Both	Oral & IV	CABP, ABSSSI
5	Zinplava	bezlotoxumab	Monoclonal antibody	Narrow	Gram-positive	IV	Recurrent *C. difficile* infection
	Dificid	fidaxomicin	Macrolide	Narrow	Gram-positive	Oral	*C. difficile* associated diarrhea

NA = Not applicable
IV = Intravenous
CUTI = Complicated urinary tract infection
CIAI = Complicated intra-abdominal infection
ABSSSI = Acute bacterial skin and skin structure infection
HABP/VABP = Hospital-acquired bacterial pneumonia / ventilator-associated bacterial pneumonia
CABP = Community-acquired bacterial pneumonia
[a] Indicates that the drug is included in the study AM drug cohort.

- *Segment 2 – Systemic IV AM drugs with broad-spectrum activity against most gram-negative bacteria responsible for serious hospitalization-requiring infections.* Relative to their generic, in-class predecessors (beta-lactam-beta-lactamase inhibitor [BL-BLI] combinations, aminoglycosides, tetracyclines), drugs in this segment have variable additional activity against a subset of bacteria expressing resistance to these older drugs (class A-D beta-lactamases, AG resistance, TCN resistance, efflux and porin mutants). This segment includes the following five AM drugs from Table 1: Zemdri (plazomicin), Avycaz (ceftazidime + avibactam), Vabomere (meropenem + vaborbactam), Zerbaxa (ceftolozane + tazobactam), and Xerava (eravacycline).
- *Segment 3 – Systemic IV AM drugs with broad-spectrum activity against gram-positive bacteria.* Drugs in this segment are long-acting glycopeptides with a similar spectrum of gram-positive activity as vancomycin. This segment includes Dalvance (dalbavancin), Orbactiv (oritavancin), and Vibativ (telavancin).
- *Segment 4 – Systemic AM drugs often with both IV and oral formulations.* Relative to their generic, in-class predecessors (tetracyclines, oxazolidinones, fluoroquinolones, beta-lactams), drugs in this segment are distinguished by their activity against MRSA, and as such, they are indicated for ABSSSI, and in some cases, CABP. While infections treated with drugs in this segment can require hospitalization, they are not of long duration. This segment includes Nuzyra (omadacycline), Sivextro (tedizolid phosphate), Baxdela (delafloxacin), and Teflaro (ceftaroline fosamil).[12]
- *Segment 5 – AM drugs for treating Clostridioides difficile* (aka *C. difficile*) *infections.* These include Dificid (fidaxomicin) and Zinplava (bezlotoxumab),[13] a monoclonal antibody.

We judged that the drugs in market segments 1 and 5 are not within scope of the current project. Drugs in segment 1 include oral and topical formulations that are available by prescription and self-administered by the patient. Segment 5 drugs are narrow-spectrum and are approved for treating *C. difficile* infections (CDIs). Even though CDI is related to antibiotic drug use, most *C. difficile* isolates remain susceptible to metronidazole and vancomycin, first-line treatments for CDI (Banawas, 2018; Peng, et al., 2017). After eliminating the drugs in market segments 1 and 5, the AM drug cohort included all drugs in market segments 2, 3, and 4 depicted in Table 1, i.e., Zemdri (plazomicin), Avycaz (ceftazidime + avibactam), Vabomere (meropenem + vaborbactam), Zerbaxa (ceftolozane + tazobactam), Xerava (eravacycline), Dalvance (dalbavancin), Orbactiv (oritavancin), Vibativ (telavancin), Teflaro (ceftaroline fosamil), Baxdela (delafloxacin), Sivextro (tedizolid phosphate) and Nuzyra (omadacycline).

3.2 NON-AM COMPARATOR DRUG COHORT

To assess if reported poor commercial market performance of AM drugs is unique, we selected a sample of non-AM drugs that are comparable to AM drugs with respect to several characteristics, which are hypothesized to be relevant for determining market success. This type of analysis is analogous to a case-control study where the AM drugs (cases) are compared to non-AM drugs (controls) that are similar in various attributes to AM drugs with respect to commercial

[12] Unlike the other drugs in this segment, Teflaro (ceftaroline fosamil) is only available in IV form.

[13] Zinplava (bezlotoxumab) is a monoclonal antibody indicated to reduce recurrence of Clostridium difficile infection (CDI). It is not an antimicrobial drug but is used in conjunction with an antimicrobial drug for the treatment of CDI.

market performance (outcome). Table 2 below outlines the attributes that characterize the AM drug cohort that we aimed to match in the non-AM comparator cohort.

Table 2. Attributes of AM Drug Case Cohort for Matching to Non-AM Comparator (Control) Cohort

Attribute	Value
Market entry time period	2010 – 2018
Type of drug	Small molecule
Type of disease	Non-chronic
Type of FDA Submission Classification	Type 1 – New Molecular Entity
Healthcare setting	Primarily inpatient
Reimbursement	Primarily Part A DRG-based
Market competition	High

To select the non-AM comparator cohort, we looked at all new drugs approved by FDA during the 2010-2018 period (CenterWatch, 2019; U.S. Food and Drug Administration, 2018). Based on our analysis of that data, there were a total of 515 new drugs (NDAs and BLAs) approved during that period. Of these, 388 (75 percent) were small molecule drugs and the remaining 127 (25 percent) were large molecule drugs.

We then reviewed the therapeutic areas and the indications for the approved 388 small molecule drugs to identify those that are primarily used for non-chronic diseases. According to the CDC, a chronic disease is defined as a condition "that last[s] one year or more and require[s] ongoing medical attention or limits activities of daily living or both" (Centers for Disease Control and Prevention, 2019b). Chronic diseases include Alzheimer's disease, arthritis, cancer, diabetes, epilepsy, heart disease, autoimmune diseases such as lupus and primary immune deficiency disease (PIDD), and obesity. Of the 388 drugs approved, 297 (77 percent) were for treating chronic diseases including cancer (75 out of 294 drugs, 26 percent), heart disease (27 out of 294 drugs, 9 percent), diabetes (19 out of 294, 6 percent), and HIV infection (15 out of 294 drugs, 5 percent) followed by mental illness and chronic obstructive pulmonary disease (COPD) (both 11 out of 294 drugs, 4 percent).

The remaining 91 drugs (23 percent) were typically for non-chronic conditions of varying duration. Of these drugs, however, more than half (52 out of 91, 57 percent) were for infectious diseases, with 24 (46 percent) out of the 52 anti-infective drugs being antibacterial drugs. Eliminating the 52 drugs for infectious diseases, this left a total of 39 drugs for selection into the non-AM comparator cohort (i.e., control cohort). All dermatology drugs and emergency contraception drugs that were among the remaining 39 were oral formulations for outpatient use and hence were not appropriate for inclusion in the control group, leaving a total of 15 drugs. Since all of the AM drugs selected for analysis were new molecular entities (NMEs) (i.e., the FDA submission classification was Type 1 – New Molecular Entity), we selected the drugs that were NMEs out of the remaining set, leaving us with a total of six drugs in the non-AM comparator cohort; Lokelma (sodium zirconium cyclosilicate), Valtessa (patiromer), Bridion (sugammadex), Giapreza (angiotensin II), Surfaxin (lucinactant), and Vistogard (uridine triacetate) (Table 3).

Table 3. Non-AM Comparator Cohort Candidates and Selected Non-AM Comparator Drug Cohort (Denoted with [a] Next to Proprietary Name)

Trade Name	Established Name	Route of Administration	Healthcare Setting	Approved For
Kidney Disease				
Lokelma [a]	sodium zirconium cyclosilicate	Oral	Inpatient & Outpatient	For treatment of hyperkalemia
Veltassa [a]	patiromer	Oral	Inpatient & Outpatient	For treatment of hyperkalemia
Other Disease				
Bridion [a]	sugammadex	IV	Inpatient	For neuromuscular blockade due to rocuronium and vecuronium during surgery
Giapreza [a]	angiotensin II	IV	Inpatient	For treatment of septic shock
Omidria	phenylephrine + ketorolac	Intraocular	Inpatient	For use in eye surgery to prevent intraoperative miosis and reduce post-operative pain
Surfaxin [a]	lucinactant	Intratracheal	Inpatient	For treatment of respiratory distress syndrome in premature infants
Vistogard [a]	uridine triacetate	Oral	Inpatient & Outpatient	For emergency treatment of patients with a fluorouracil or capecitabine overdose
Pain				
Dsuvia	Sufentanil	Oral	Inpatient	For management of acute pain
Dyloject	diclofenac sodium	IV	Inpatient	For management of mild, moderate, or severe pain
Exparel	bupivacaine liposome	IV	Inpatient	For postsurgical analgesia
Oxaydo (Oxecta)	oxycodone HCl	Oral	Inpatient & Outpatient	For management of acute and chronic moderate to severe pain
Targiniq	oxycodone hydrochloride + naloxone hydrochloride	Oral	Inpatient & Outpatient	For management of severe chronic pain
Troxyca	oxycodone hydrochloride + naloxone hydrochloride	Oral	Inpatient & Outpatient	For management of severe pain
Xartemis	oxycodone hydrochloride + acetaminophen	Oral	Inpatient & Outpatient	For management of acute pain
Zohydro	hydrocodone bitartrate	Oral	Inpatient & Outpatient	For management of severe pain

[a] Indicates that the drug is in the study non-AM comparator cohort and the FDA submission classification is Type 1 – New Molecular Entity.

3.3 ONCOLOGY DRUG COHORT

Oncology drugs are often noted as having robust market performance. Thus, we included a cohort of oncology drugs in addition to the non-AM comparator drug cohort (Section 3.2) for analysis. Similar to the non-AM comparator cohort, we selected the oncology cohort from among those oncology drugs that were approved during the 2010 – 2018 period and were NMEs according to the FDA submission classification.

Out of the 297 small molecule new drug approvals in the U.S. during the 2010 – 2018 period, 74 (25 percent) were for cancer. Of these 74 oncology drug approvals, the majority (56 drugs, or 76 percent) were NMEs according to the type of FDA submission classification information at Drugs@FDA (U.S. Food and Drug Administration, 2019). The types of cancers these 56 drugs are indicated for include non-small cell lung cancer, metastatic breast cancer, leukemia, and lymphoma (see Table 4). Similarly, out of the 128 large molecule new drug approvals during that same time period, 34 (27 percent) were for cancer, and 30 out of 34 were original approvals.

Table 4. Breakdown of Oncology Drugs Approved in the U.S., by Cancer and Drug (Small versus Large Molecule) Type, 2010-2018

Type of Cancer	Large Molecule		Small Molecule		Total	
	Count	Percent	Count	Percent	Count	Percent
Basal Cell Carcinoma	0	0.0%	2	3.8%	2	2.6%
Breast Cancer	2	8.8%	6	10.0%	8	9.6%
Leukemia	5	21.7%	9	14.7%	14	16.8%
Lung Cancer	1	3.9%	8	17.3%	9	13.1%
Lymphoma	3	8.6%	3	5.1%	6	6.2%
Melanoma	1	5.4%	3	6.0%	4	5.8%
Myeloma	2	2.7%	4	8.0%	6	6.3%
Other	4	18.6%	4	5.7%	8	9.7%
Ovarian Cancer	0	0.0%	3	3.6%	3	2.5%
Prostate Cancer	1	2.7%	5	9.8%	6	7.6%
Soft Tissue Sarcoma	1	3.5%	1	3.0%	2	3.1%
Thyroid Cancer	0	0.0%	2	4.3%	2	3.0%
2 Types of Cancer	5	13.9%	4	6.3%	9	8.7%
3 Types of Cancer	3	3.4%	2	2.4%	5	2.7%
More than 3 Types of Cancer	2	6.8%		0.0%	2	2.1%
Grand Total	**30**	**100.0%**	**56**	**100.0%**	**86**	**100.0%**

From these 86 NMEs, we wanted to select a sample 15 oncology drugs that approximately reflected the distribution of types of cancer drugs and the divide between small versus large molecule drugs represented in Table 4. To ensure that our sample was representative and adequately covered different types of cancer drugs, we randomly selected one drug per type of cancer category from all the drugs (small and large molecule) for that category. For example, out of the 9 drugs that treated lung cancer, we randomly selected only one. Although we did not discriminate between small and large molecule selections, a random sampling would tend to approximately follow the 1:2 distribution between large and small molecule drugs. This random sampling method is based on the assumption that the type of cancer is likely more influential for market performance than type of drug (small versus large molecule) and the fact that the comparison of interest is between oncology drugs as a whole and AM drugs, not between large molecule oncology drugs and AM drugs and small molecule oncology drugs and AM drugs.

The oncology drug cohort comprises the 15 drugs depicted in Table 5 and included 5 large molecule drugs, and 10 small molecule drugs, which approximately reflects the distribution of all

eligible NME cancer drugs approved between 2010 and 2018. During analysis, however, we discovered that sales data were unavailable for Asparlas. Therefore, we replaced Asparlas with another drug used for the treatment of acute lymphoblastic leukemia, Erwinaze (asparaginase Erwinia chrysanthemi). However, after further analysis, we found that Erwinaze largely used previous clinical trials that were submitted as part of a biologics license application (BLA) application for ELSPAR (asparaginase). The investigational new drug (IND) request for Erwinia asparaginase was submitted in 1968 and ELSPAR later received approval in 2002, meaning the trials supporting Erwinaze's new drug application (NDA) were much older than those of others in the oncology cohort. These factors caused Erwinaze to be a significant outlier in our development cost, clinical value, and market performance analyses. Thus, we removed Erwinaze from the analysis cohort altogether, leaving the other 14 listed drugs in Table 5 for comparison with the AM cohort.

Table 5. Oncology Drug Cohort

Cancer Category	Trade Name	Established Name	Type of Drug	Route of Administration	Approved For
Basal Cell Carcinoma	Erivedge	Vismodegib ROCHE	Small Molecule	Oral	Metastatic locally advanced basal cell carcinoma
Breast Cancer	Ibrance	Palbociclib PFIZER	Small Molecule	Oral	Metastatic breast cancer
Lung Cancer	Portrazza	Necitumumab LILLY	Large Molecule	Intra-articular, intramuscular, intravitreal	Metastatic squamous non-small cell lung cancer
Lymphoma	Yescarta	axicabtagene ciloleucel GILEAD	Large Molecule	IV	Large B-cell lymphoma
Leukemia	Asparlas [a]	calaspargase pegol-mknl SERVIER	Large Molecule	IV	Acute lymphoblastic leukemia
	Erwinaze [a]	asparaginase Erwinia chrysanthemi JAZZ	Large Molecule	IV	Acute lymphoblastic leukemia in patients that have developed hypersensitivity to E. coli-derived asparaginase
Melanoma	Braftovi	encorafenib + Mektovi (binimetinib) PFIZER	Small Molecule	Oral	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
Myeloma	Darzalex	Daratumumab J&J	Large Molecule	IV	Multiple myeloma
Other	Vitrakvi	Larotrectinib BAYER	Small Molecule	Oral	Solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion and are metastatic
Ovarian Cancer	Rubraca	Rucaparib CLOVIS	Small Molecule	Oral	Ovarian, fallopian tube, or primary peritoneal cancer
Prostate Cancer	Jevtana	Cabazitaxel SANOFI	Small Molecule	IV	Metastatic castration-resistant prostate cancer
Soft Tissue Sarcoma	Yondelis	Trabectedin J&J/PHARMAMAR	Small Molecule	IV	Unresectable or metastatic liposarcoma or leiomyosarcoma
Thyroid Cancer	Cometriq	Cabozantinib EXELIXIS	Small Molecule	Oral	Progressive, metastatic medullary thyroid cancer
2 Types of Cancer	Zelboraf	Vemurafenib ROCHE	Small Molecule	Oral	Unresectable or metastatic melanoma with BRAF V600E mutation or Erdheim Chester Disease with BRAF V600 mutation
3 Types of Cancer	Stivarga	Regorafenib BAYER	Small Molecule	Oral	Metastatic colorectal cancer or unresectable or metastatic gastrointestinal stromal tumor or Hepatocellular carcinoma
More than 3 Types of Cancer	Cyramza	Ramucirumab LILLY	Large Molecule	IV	Gastric or gastro-esophageal junction adenocarcinoma, metastatic non-small cell lung cancer, metastatic colorectal cancer, hepatocellular carcinoma

IV = Intravenous

[a] Excluded from the oncology drug cohort after further analysis of clinical trial information and/or due to unavailable sales information.

4 DEVELOPMENT AND APPROVAL COST ANALYSIS

Development of AM drugs is often cited as expensive and difficult (Rex, et al., 2014; White, A.R. on behalf of the BSAC Working Party on The Urgent Need: Regenerating, 2011; Piddocck, 2012). Towse, et al. (2017) estimated the expected capitalized cost of developing an AM drug targeted against MDR pathogens that would be used exclusively within an acute care setting at $1.9 billion[14] which accounts for the cost of failures and cost of capital. This figure is comparable to the cost of drug development across all therapeutic areas at $1.8 billion but less than half the cost of developing oncology drugs (i.e., antineoplastic and immunomodulating agents) at $4.5 billion reported in Wouters, et al. (2020). Towse, et al. (2017) also found that the development costs would be offset by nearly 60 percent (from $1.9 billion down to $0.8 billion) with matched funding as part of a public-private partnership for R&D combined with the implementation of Tier B framework for registration (Rex, et al., 2014) which would rely on a single Phase 3 study supplemented with small comparative/descriptive studies. The study reported Phase 1, 2, and 3 out-of pocket costs of $19.4 million, $71.5 million, and $237.4 million, respectively along with $48.4 million in post-launch study costs, which appear to be based solely on expert judgment.[15] In a more recent study, Wouters, et al. (2020) estimated the cash outlay needed to develop an anti-infective agent for systemic use at $0.4 billion (95% CI: $0.3 – 0.5 billion) and the expected capitalized development and approval costs that account for failures and cost of capital at $1.3 billion (95% CI: $0.7 - $1.9 billion). These costs were based on a sample of five AM drugs approved during 2009-2018 and included Xerava (eravacycline), Orbactiv (oritavancin), Dificid (fidaxomicin), Nuzyra (omadacycline), and Zerbaxa (ceftolozane + tazobactam), of which four are also in the AM drug cohort. Table 6 presents the costs Wouters, et al. (2020) reported for these drugs by phase.

Table 6. Development and Approval Cost [a] Estimates for Select AM Drugs from Wouters, et al. (2020)

Trade Name	Preclinical	Phase 1	Phase 2	Phase 3	Total	Quality of Estimate
Dificid	$26.3	$4.2	$6.9	$128.7	$166.1	Medium
Nuzyra	NA	$205.9	NA	$255.9	$461.8	Medium [b]
Orbactiv	NA	NA	NA	$155.9	$155.9	Medium
Xerava	NA	$31.0	$31.6	$325.3	$387.9	High [c]
Zerbaxa	NA	NA	$279.3	$628.4	$907.7	Low
Average	**$26.3**	**$80.4**	**$105.9**	**$298.8**	**$415.9**	

Source: Wouters, et al. (2020)
NA = Not available (The authors noted that they were unable to disaggregate expenditures among phases for some drugs and hence did not record costs in those cases.)
[a] Represents the cash outlay unadjusted for failures or cost capital.
[b] Authors reported using the accumulated deficit of $197.9 million as of December 2014 as a proxy for early development since the company appeared to focus solely on Nuzyra.
[c] The figures counted funding extended by the U.S. government from HHS Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Disease (NIAID) at the Natiional Institutes of Health (NIH).

In two independent surveys of pharmaceutical companies involved in AM development, 80 and 84 percent of survey respondents indicated that economic barriers, high costs, and low return on investment, were the main reasons for suspending AM clinical trial development (The Review on

[14] The reported estimate in Towse et al (2017) is $1.581 in 2011 dollars. We used U.S. Medical Care Price Index to calculate the corresponding estimate in 2018 dollars (U.S. Bureau of Labor Statistics, 2021).
[15] The reported corresponding estimates in Towse et al. (2017) are $16.0 million, $59.0 million, $196.0 million, and $40.0 million in 2011 dollars, respectively. We used U.S. Medical Care Price Index to calculate the corresponding estimate in 2018 dollars (U.S. Bureau of Labor Statistics, 2021).

Antimicrobial Resistance, 2015; Bettiol & Harbarth, 2015). Complexity, scientific risk and "unreasonably long recruitment period" were also cited as further development barriers (Bettiol & Harbarth, 2015). Enrollment for clinical trials can also be difficult for AM drugs that target resistant infections, which have short treatment courses requiring immediate treatment, and have small patient populations (Duke Margolis Center for Health Policy, 2019). In particular, studies noted that Phase 3 trials are often so complex and costly that smaller companies and start-ups in the development space are unable to develop new agents (Piddocck, 2012).

In a series of interviews ERG (2018) conducted with AM drug venture capital investors and early-stage drug developers, one expert broke down the cost of developing a novel AM drug into preclinical research ($2 million); staff, researcher and CRO funding ($125 million); facilities, and equipment funding ($125 million); and the three phases of the clinical development (Phase 1 at $12 million, Phase 2 at $7.5 million, and Phase 3 at $35 to $40 million). The expert estimated that these activities combined could cost over $300 million. Other drug developer interviewees in this group agreed that these novel AM drugs rarely have revenues greater than $50 million per year, which makes it difficult to achieve profitability on a timeline acceptable to private investors and before market protections expire.

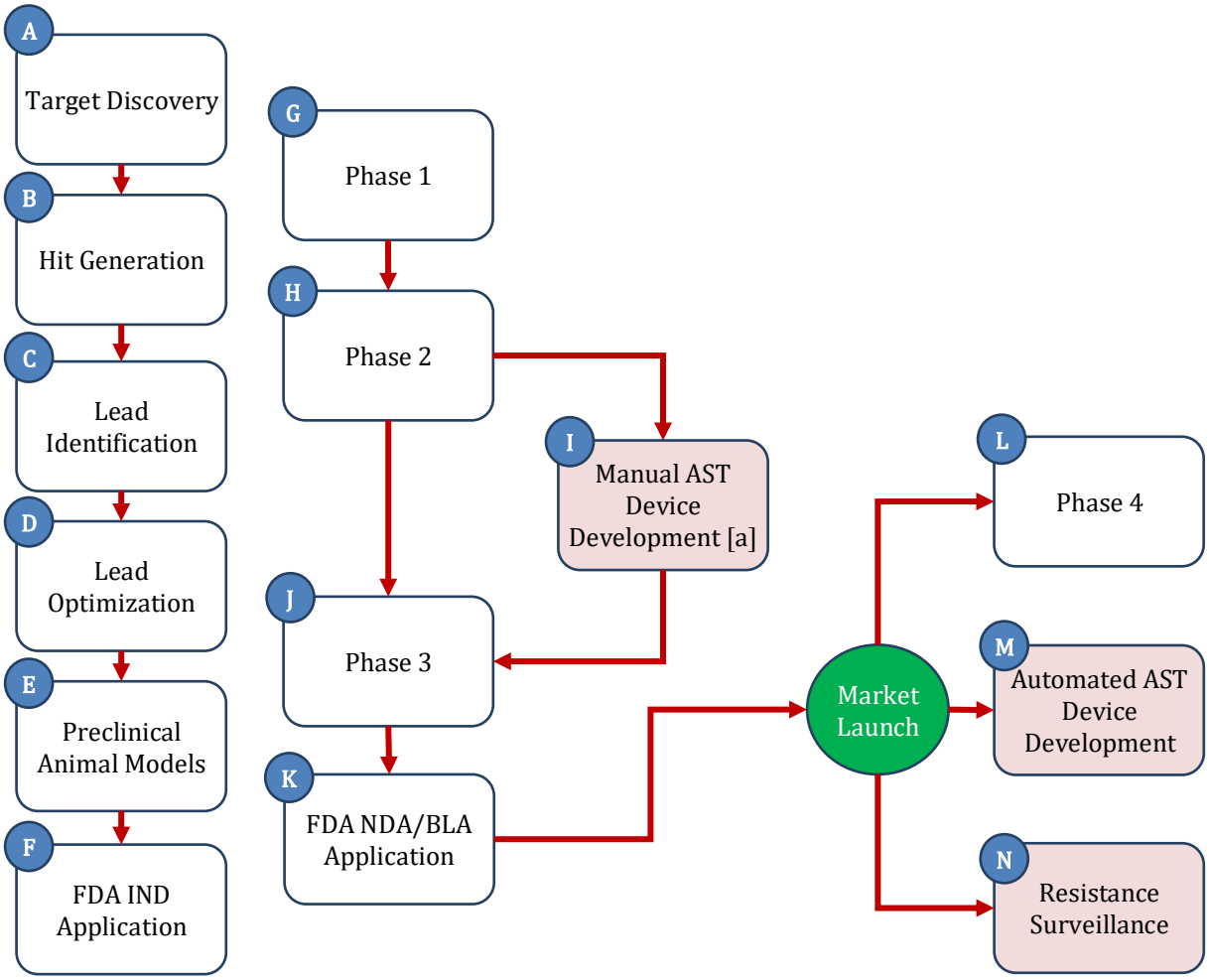
Given the wide range of published development cost estimates and the judgement-based nature of the underlying development stage-specific cost figures that appear to have been used in generating those estimates, we wanted to use a transparent bottom-up model to estimate development costs for each of the drugs in our cohorts. Figure 3 below depicts a stylized model of the drug development process from conception through post marketing activities that we used as the basis of our development cost analysis (Eastern Research Group, Inc., 2020).

From Figure 3, the initial phase of development begins with the exploratory stage which includes identification and validation of a "druggable" target for a specific disease (A—Target Discovery).[16] Once a target candidate is identified and validated, the developer uses screening approaches to identify a "hit" compound (i.e., a compound that interacts with the target of interest) using such strategies as high-throughput screening, phenotypic screening, virtual screening, fragment-based screening and structure-based design (B—Hit Generation) (Lansdowne, 2020). Next, the developer works on refining these "hits" to optimize their pharmacokinetic properties while also investigating their "off-target" interactions to get a sense of potential adverse effects (C—Lead Identification). After optimizing the lead compound (D—Lead Optimization), preclinical in-vitro and in-vivo testing (E—Preclinical Animal Models) is conducted to begin accumulating evidence of the compound's biological affect (U.S. Food and Drug Administration, 2018). The developer then uses animal models to answer such questions as "What does the drug do to the body?," "What does the body do to the drug?," and "It is potent, but is it safe?" (Lansdowne, 2020).

Upon completion of early discovery and preclinical testing (Stages A through E in Figure 3), the developer must submit an investigational new drug (IND) application to the FDA before clinical testing on human subjects may begin (F—FDA IND Submission). The IND application includes "…animal study data and toxicity (side effects that cause great harm) data; manufacturing information; clinical protocols (study plans) for studies to be conducted; data from any prior human research; and information about the investigator." (U.S. Food and Drug Administration, 2018). If the FDA reviews the IND and its proposed clinical study design and the IND becomes in effect, the sponsor may begin testing on humans under the specified IND number.

[16] A target is deemed "druggable" if its activity can be altered by a therapeutic agent (Lansdowne, 2020).

Figure 3. Stylized Model of Drug Development



Note: Pink boxes indicate steps relevant to the development of AM drugs but not to other types of drugs.
[a] Even though the manual AST device development occurs in this timeframe, the devices are not FDA cleared until after the drug has received FDA approval.

Once the IND is in effect, the sponsor may then begin the next phase in development, the clinical stage (Stages G, H, and J in Figure 3), which usually consists of three clinical phases. Most Phase 1 clinical studies test for safety and dosing among a small group (20 to 100) of closely monitored subjects who are either healthy or have the disease or condition.[17] Phase 2 studies enroll several hundred subjects and provide additional information on safety and dosing as well as early evidence of efficacy and adverse events. Most Phase 3 studies enroll 300 to 3,000 or more subjects with the disease or condition and provide a thorough assessment of safety and efficacy of the drug (U.S. Food and Drug Administration, 2018). As expected, patient enrollment by clinical phase for the drugs across our three cohorts are broadly in line with these reported ranges (Table 7).

To support approval, drug efficacy is usually demonstrated through well-controlled randomized and double-blind trials. These trials can be designed to show superiority or noninferiority to a comparator. The goal of a superiority trial is to demonstrate that a new drug is

[17] For AM drugs, Phase 1 subjects are typically health volunteers.

better than an active comparator or placebo whereas a noninferiority trial aims to demonstrate that a new drug is not clinically inferior to an active comparator or placebo. (Christensen, 2007; Head, et al., 2012; U.S. Food and Drug Administration, 2016). Typically, patient enrollment needs for superiority trials tend to be larger than those for noninferiority and equivalence trials given the need to demonstrate a statistically significant improvement over an active comparator or placebo. If a new drug is the same general type as a drug already on the market, the sponsor must conduct a noninferiority study at a minimum (U.S. Food and Drug Administration, 2016). All drugs in the AM cohort have done noninferiority Phase 3 trials whereas most of the drugs in the non-AM comparator and oncology cohorts have done superiority trials. There are several factors that make superiority Phase 3 trials—which often require higher number of patients than those for noninferiority trials—for AM drugs infeasible. It is difficult to recruit patients with a specific pathogen infection quickly especially without appropriate rapid diagnostics. Further, serious infections can progress rapidly before an informed consent can be obtained from the patient and before the patient's culture results are available (National Academies of Sciences, Engineering, and Medicine, 2022).

Table 7. Average Number of Patients Enrolled, by Phase and Drug Cohort

Phase	AM Cohort Drugs	Non-AM Comparator Cohort Drugs	Oncology Cohort Drugs
Clinical			
Phase 1	270 (156 – 507)	155 (27 – 367)	145 (8 – 454)
Phase 2	237 (88 – 430)	244 (2 – 770)	396 (97 – 1,613)
Phase 3	1,948 (627 – 3,532)	1,031 (243 – 1,886)	2,257 (330 – 5,054)
Clinical Total	*2,413* *(889 – 4,046)*	*1,430* *(562 – 2,416)*	*2,314* *(119 – 6,763)*
Post-approval			
Phase 4	1,293 (12 – 7,923)	2,193 (20 – 8,615)	462 (65 – 1,623)
Overall Total	**3,706** **(1,399 – 10,916)**	**3,623** **(622 – 11,031)**	**2,777** **(581 – 7,225)**

Note: The numbers in parentheses represent the minimum and maximum.

Phases 2 and 3 are also when AM drug manufacturers begin working with one or more device manufacturers to facilitate the development of manual Antimicrobial Susceptibility Tests (AST) using the dosage and efficacy data generated (I—Manual AST Device Development). These tests allow users to test a sample of a microorganism against a selection of AM drugs and identify whether that sample is susceptible (S), intermediate (I), or resistant (R) to the AM drugs at the given dosage. Clearance these testing devices by the FDA for marketing are also critical for appropriate drug prescribing in hospital settings and therefore market uptake. Additional manual AST devices are also developed after market approval of the AM drug. However, those device manufacturers that are able to use the clinical data generated during the AM drug's Phase 2 and 3 clinical trials to support their 510(k) application to FDA for their manual AST devices often receive clearance either at, or soon after, drug approval.

Upon completion of clinical trials to support approval, the developer then submits to the FDA a New Drug Application (NDA) if the drug is a pharmaceutical or a Biologics License

Application (BLA)) if the drug is a biologic.[18] The application must demonstrate safety and efficacy, as well as an acceptable manufacturing process, which is confirmed through a manufacturing facility inspection. Once the appropriate center conducts a scientific review, the applicable FDA product advisory committee may be asked to opine on the benefit-to-risk ratio of the drug. The center considers the advisory committee comments (if applicable) before approval, which allows the developer to bring the drug to the market. Once on the market, the drug enters the post-marketing stage, which may include conducting Phase 4 studies to investigate rare cases or special populations and to monitor adverse events; studying the safety and efficacy of the drug on pediatric populations; and submitting batch manufacturing samples to FDA for potency, safety, and purity tests. For AM drugs, post-approval commitments often include these Phase 4 studies, but may also require additional Phase 3 efficacy studies, such as neonatal sepsis studies for gram-positive drugs[19] or additional pneumonia studies. Additionally, automated AST device development commences at this stage as well (M—Automated AST Device Development). Most laboratories often elect to use automated AST devices, which require less labor and test more AM drugs at a time than their manual counterparts. These automated devices run tests in anywhere from 5 to 24 hours depending on the machine and the replication time of the pathogen. Thus, getting on an automated AST device is important for gaining widespread use for AM drug manufacturers but may take several years to accomplish after approval or may not happen at all. The AM drug manufacturers have little or no control over getting their drugs incorporated into these devices or its timing (see Section 5.1.1.7 for further discussion). Even when a drug is approved and its AST method has received a 510(k) clearance from FDA for incorporation into an automated AST device, it may still take significant time for the automated AST device manufacturer to incorporate the drug into its device and make it available for laboratory use.[20] AM drug manufacturers also must complete 5 years of compulsory surveillance of resistance trends (N—Automated Surveillance) (Krause, 2019).

Apart from the development stages depicted in Figure 3, there are additional activities for which the developer expends resources for, such as chemistry, manufacturing, and controls (CMC) and manufacturing plant design/build. However, cost data on these activities are scarce. Because the magnitude of resources spent on these activities are not expected to vary significantly from one type of drug to the next, we did not account for these in our stylized model.

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[18] Only the oncology cohort included 4 large molecule drugs (i.e., biologics) with BLAs; Portrazza (necitumumab), Yescarta (axicabtagene ciloleucel), Darzalex (daratumumab), and Cyramza (ramucirumab). The remaining drugs in the oncology cohort as well as those in the AM and non-AM comparator cohorts were small molecule drugs with NDAs.

[19] Neonatal sepsis studies have been part of the pediatric post-approval commitments and can be requested for gram-negative compounds.

[20] Upon receipt of 510(k) clearance from FDA, the drug's information, including approved breakpoints, must be updated in all automated AST devices that are in operation throughout laboratories across the globe. Automated AST device manufacturers carefully plan for new drug incorporations on a 3- to 4-year cycle based on recent drug approvals and FDA 510(k) application review times. Thus, if an AM drug manufacturer misses getting onto the AST device manufacturers' multi-year plans, they may have to wait several years before being considered again. Some automated AST devices are networked and can be updated remotely, but many are not networked. Devices that are not networked can be updated by inviting a representative from the AST device manufacturer to update the devices, or the device manufacturer may provide specific instructions to laboratory staff on how to update the devices themselves. At present, there is no protocol or timeline for when device manufacturers need to incorporate a drug following 510(k) approval, but after they incorporate a drug onto a panel, they often roll out the new panels while updating the device software. Automated AST device companies often perform these updates a few times a year and choose to bundle several newly approved drugs within each update to save costs as it is a labor-intensive and time-consuming process to visit so many laboratories.

Based on Figure 3, we estimated the cost of developing a drug by considering the cost, duration, the probability of successfully transitioning from one stage to the next, and the opportunity cost of capital using the approach developed by DiMasi, et al. (2016). For the purpose of this analysis, we broke down the overall development of a drug as shown in Figure 3, into six distinct stages, including 1—non-clinical, which includes all steps in between target discovery (Phase A) and FDA IND approval (Phase F), 2—Phase 1, 3—Phase 2, 4—Phase 3, 5—FDA review, and 6—Phase 4. If the cash outlay (aka development and approval cost) associated with a given phase i is C_i, then the expected cost, $E(C)$, that incorporates failures can be computed by dividing this cost by the transition success probability from phase i to launch, p_i, i.e.,

$$E(C_i) = \frac{C_i}{p_i} \tag{1}$$

Assuming that phase costs are distributed uniformly over the length of the phase, t_i, the capitalized cost, CC, that accounts for the opportunity cost of the investment in the drug, i.e., the rate of return (net of inflation) that the sponsor would otherwise be able to earn at the same risk level as the investment in the new drug that has been selected (see Section 4.2.9), is given by:

$$CC_i = \int_{t_i^e}^{t_i^b} \left(\frac{C_i}{t_i}\right) e^{rt} dt \tag{2}$$

where r is the opportunity cost of capital that captures the time value effect; t_i^b is the time from the beginning, b, of the given phase to product launch, and t_i^e is the time from the end, e, of the given phase to product launch. Equation 2 then becomes:

$$CC_i = \frac{(C_i/t_i)}{r}\left(e^{rt_i^b} - e^{rt_i^e}\right) \tag{3}$$

Given equations 1 and 3, we can then compute the expected capitalized cost of phase i that accounts for the cost of failures as well as the opportunity cost of capital as:

$$E(CC_i) = \frac{CC_i}{p_i} \tag{4}$$

Then the total expected capitalized cost of development for a drug, $E(CC)$, is the sum of the expected capitalized cost of each phase i,

$$E(CC) = \sum_{i=1}^{n} E(CC_i) \tag{5}$$

where i = non-clinical, Phase 1, Phase 2, Phase 3, FDA BLA/NDA review, and Phase 4 for drugs.

The following sections describe the data sources utilized in operationalizing the above framework and the specific model parameters and assumptions.

4.1 DATA SOURCES

We describe the primary data sources used in the modeling in the following sections. In addition to these data sources, we also used published studies to support our parameter estimates and assumptions. We note these in the applicable sections. As noted above, all data collected on each drug are presented in Appendix A.

4.1.1 Clinicaltrials.gov Data

Clinicaltrials.gov is a registry launched in September 2008 to provide protocol and results information on clinical trials conducted in the U.S. and around the world. Clinicaltrials.gov data are

updated daily and provide information on such parameters as study start and end dates and number of patients enrolled for the registered studies that are relevant for our analysis. We used a snapshot of the clinicaltrials.gov data downloaded on June 24, 2020 through the Clinical Trials Transformation Initiative's (CTTI) Access to Aggregate Content of ClinicalTrials.gov (AACT) initiative.

Using SAS, we queried the AACT database for all clinical trials relevant to each drug selected. We then restricted our sample to only include trials that were not terminated or withdrawn and were interventional in nature, where the intervention was a drug or a biological. Further, we only kept Phase 1, 2, and 3 trials that began before the BLA/NDA submission date because we wanted to capture those trials that were supportive of the BLA/NDA or were Phase 4 post-approval studies. Table 8 summarizes the relevant attributes taken from the AACT database as well as any criteria that would determine whether a particular trial was in scope for the analysis. This query resulted in a total of 400 Phase 1 through 4 trials for the selected drugs across all three drug cohorts. This likely is an underestimate of the number of trials conducted for any given compound as early phase trials are often not registered in clinicaltrials.gov.

Table 8. Clinical Trial Attributes Recorded from the AACT Database and Drugs@FDA

Clinical Trial Attribute	In-scope Criteria
Trial Type	Interventional
Intervention Type	Drug or Biological
NCT ID	NA
Phase	Phases 1 and 2 must have a: start date < NDA submission date [a] AND completion date < NDA approval date* Phase 3 must have a: start date < NDA submission date* Phase 4 must have a: start date > NDA submission*
Start Date	NA
End Date (Primary Completion Date if Available)	NA
Trial Status	Status must not be 'Terminated' or 'Withdrawn'
Region Trial Took Place	NA
Enrollment	NA

NA = Not applicable
[a] Information obtained from Drugs@FDA.

4.1.2 Drugs@FDA and FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Drugs@FDA and FDA Orange Book are online publicly available resources containing applicable information on current FDA-approved drugs. Drugs@FDA is an online database that includes patient information, label, application reviews, and other documentation including any BLA/NDA approval documents for most CBER/CDER approved drug products since 1939. FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book) contains patent and exclusivity information on drug products approved by FDA under the Federal Food, Drug, and Cosmetic Act. The Orange Book also has an online database searchable by both drug and patent information.

Since Phase 1 trials are not required to be registered in Clinicaltrials.gov and other recording inconsistencies are known to be present within the database, we supplemented the automated query of the AACT database with a manual search of each drug's BLA/NDA available through the Drugs@FDA database for any additional trials. We applied the same criteria listed in

Table 8 above to these trials. We also recorded the drug investigational new drug (IND) application date, the BLA/NDA submission date, and the BLA/NDA approval date from this database. Finally, we queried the Orange Book database for all drugs in the cohort and recorded the United States Patent and Trademark Office (USPTO) filing date.

4.1.3 IQVIA GrantPlan®

IQVIA's GrantPlan is a large database of current clinical investigator budgets from 62 countries. The database contains cost data compiled from final negotiated budgets between sponsors and investigator sites at the procedure, cost per visit, and cost per patient levels from countries involved in drug testing throughout North America, Europe, Asia, and Latin America. The database includes cost information from 48 sponsors and 12 CROs that conduct 76 percent of all global clinical trials. We obtained a custom tabulation from this database that provided cost estimates by therapeutic area, phase, and country along with applicable overhead benchmarks covering the period from 2015 through 2019. These data served as the basis for estimating cost adjustment factors for clinical trials by world regions (i.e., Europe, North America, Central America, South America, Asia, Africa, Middle East, Oceania).

4.2 MODEL PARAMETERS AND ASSUMPTIONS

4.2.1 Phase Durations

The phase duration parameter refers to the time it takes to complete a given stage of development depicted in Figure 3. Using the clinical trials deemed in scope, we estimated the duration of Phase 1 – 4 trials as the total time from the start date of the earliest reported clinical trial for that phase to the end date of the latest clinical trial reported for that phase for each drug in our three cohorts. If there were no studies available for one phase of a particular drug's development, we imputed a value based on the average duration for that phase across all drugs in that cohort.

For the non-clinical stage, our estimate represents the time it takes from synthesis of the compound to the start of human trials, which includes early exploratory research for target discovery, hit generation and target identification; lead optimization; preclinical work involving animal testing to develop dosing and toxicity models; and obtaining an IND approval from FDA to begin testing in human subjects. To encompass this, we defined the non-clinical phase duration as the time between the USPTO Registration of Compound and the FDA IND submission date for each drug.

Finally, we set the duration of the NDA review phase to be the time between NDA submission and BLA/NDA approval.

4.2.2 Time from Phase Start to Next Phase Start

The start-to-start parameter refers to the elapsed time between the start of one development phase (e.g., Phase 2) supporting a BLA/NDA and the start of the next development phase (e.g., Phase 3) supporting the same application. For the non-clinical phase to Phase 1 estimate, we assumed that Phase 1 will begin immediately upon successful completion of the non-clinical development phase and notification from FDA that the proposed Phase 1 study in the submitted IND may proceed, (i.e., when the IND is in effect), which is the same as the total non-clinical phase duration.

For the clinical phases 1 – 3, work may overlap. In other words, the sponsor may begin one or more Phase 2 clinical trials before completing Phase 1 clinical trials. Therefore, the start-to-start duration was total time between the start date of the earliest reported clinical trial for one phase and the start date of the earliest reported clinical trial for the subsequent phase. We did not

compute the start-to-start time between Phase 3 and post approval Phase 4 studies, but instead recorded the elapsed time from the first Phase 3 trial to BLA/NDA submission, and from BLA/NDA submission to approval.

4.2.3 Phase Begin (Months Before Launch)

The phase begin parameter refers to the length of time from the start of each development phase to drug launch. We estimated this as the sum of all start-to-start durations between a specific phase and BLA/NDA approval (e.g., number of months Phase 2 began before launch = Phase 2 start to Phase 3 start + Phase 3 start to BLA/NDA submission + BLA/NDA submission to approval).

4.2.4 Phase End (Months Before Launch)

The phase end parameter refers to the length of time from the end of each development phase to drug launch. For each phase, we estimated this variable by subtracting the phase duration from each phase begin parameter (e.g., number of months Phase 2 ended before launch = number of months Phase 2 began before launch – Phase 2 duration in months).

Several drugs in our sample had Phase 3 trials that ended after BLA/NDA approval. In those cases, the Phase 3 study began before BLA/NDA submission and the manufacturer may have used preliminary results from these studies to support the BLA/NDA, but the trial was not fully completed until after drug approval. We accounted for this by splitting the Phase 3 studies into the portion leading up to approval and the portion constituting a 'Phase 3 follow-up study.' This is further described in our computations below.

4.2.5 Total Number of Patients Enrolled by Region and Phase

Number of patients enrolled in a study is the largest single factor driving study costs but the costs of conducting a study also varies by geographic region (Moore, et al., 2020). For each drug in our three cohorts, we estimated the total number of patients enrolled in supporting trials in each of the 8 regions around the world.

The trials we compiled from Clinicaltrials.gov and Drugs@FDA included the total enrollment as well as a list of countries where the various arms of the trial were conducted. The exact enrollment per country was not provided in these databases, so we mapped each country to its corresponding world region (Europe, North America, Central America, South America, Asia, Africa, Middle East, Oceania), and distributed the total trial enrollment proportionally based on the number of trial sites per region to estimate enrollment per region,[21] i.e.:

$$\text{Enrollment}_{\text{region}} = \frac{\text{\# of Sites in Region}}{\text{Total \# of Sites}} \times \text{Total Enrollment} \quad (9)$$

If no countries were specified, we divided the enrollment evenly amongst the 8 regions. Finally, we summed the regional enrollment for each drug and each phase.

4.2.6 Average Cost Per Patient for Clinical Trials by Therapeutic Area and Region

The total cost of a clinical trial for a given phase and therapeutic area, C_{total}, includes study-level costs (such as institutional review board approvals and source data verification costs), C_{study},

[21] It is unlikely that any given trial actually had proportionate enrollment across regions. We acknowledge that this is a simplifying assumption which may result in an over- or under-estimate of costs for those trials. However, given that only 15 percent (60 out of 400) of trials had missing trial site information in the data compiled, we expect that any error associated with assuming an equal apportionment would be relatively minor.

patient-level costs (such as recruitment and clinical procedure costs), $C_{patient}$, and site-level costs (such as monitoring and project management), C_{site} (Sertkaya, et al., 2016) i.e.:

$$C_{total} = C_{study} + C_{patient} + C_{site} \quad (10)$$

Then, the average cost per-patient, CPP, can be calculated by dividing the total cost of a clinical trial C_{total}, by the number of patients, $n_{patient}$, enrolled in that trial, i.e.:

$$CPP = \frac{C_{total}}{n_{patient}} \quad (11)$$

In a previous study, ERG (2020) used total clinical trial cost and enrolled patients data from Cutting Edge and Medidata Solutions as well as patient level costs from IQVIA to estimate average per-patient costs for biopharmaceutical clinical trials in the U.S. by therapeutic area and phase in 2018 dollars (Eastern Research Group, Inc., 2020). To be able to apply these per-patient costs to international studies, we devised scaling factors using the IQVIA per-patient costs for each geographic region and therapeutic area. To calculate the scaling factor, *S*, that could be used to scale U.S. per-patient trial costs to another regions, we divided the median per-patient cost for that therapeutic area and region by the median per-patient cost for that therapeutic area in North America, i.e.:

$$S_{region,TA} = \frac{CPP_{region,TA}}{CPP_{North\ America,TA}} \quad (12)$$

The scaling factors were only computed by region and therapeutic area and then applied to the U.S. per-patient cost estimates by therapeutic area and phase discussed above. This yielded average cost per patient estimates for each therapeutic area, phase, and world region.

4.2.7 FDA User Fees

FDA is authorized to collect application fees for the review of human drug and biological products, and prescription drug program fees for certain approved products by the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Prescription Drug User Fee Amendments of 2017 (PDUFA VI). These fees change yearly in accordance with congressional reauthorization of PDUFA every five years. For this analysis, we used the rates for the 2019 fiscal year, published in 2018: $2,588,478 for an application requiring clinical data, which does not include $304,162 in associated program fees (U.S. Food and Drug Administration, 2018).

4.2.8 Phase Transition Success Probability

The phase transition success probability parameter represents the probability of a sponsor successfully moving from one stage of drug development depicted in Figure 3 to the next. If, for example, out of 100 new drug candidates that make it to Phase 1, 30 successfully proceed to Phase 2, then the phase transition probability from Phase 1 to Phase 2 is 30 percent.

We used figures from published studies to estimate the transition probability of success of a drug between the pre/nonclinical phase and Phase 1; Phase 1 and Phase 2; Phase 2 and Phase 3; Phase 3 and BLA/NDA submission; and BLA/NDA submission and drug approval. Table 9 shows the average probability of success between each step for the relevant therapeutic areas.

Table 9. Transition Probability of Success by Phase and Therapeutic Area

Therapeutic Area	Data Source	Time Period	Pre/Nonclinical to Phase 1	Phase 1 to Phase 2	Phase 2 to Phase 3	Phase 3 to FDA BLA/NDA Submission	FDA BLA/NDA Submission to Approval
Anti-Infective	Wong et al, (2019)	2000 - 2015	NA	70.1%	58.3%	NA	NA
	DiMasi et al, (2010)	1993-2004	NA	58.2%	52.2%	78.6%	100.0%
	BiomedTracker, (2016)	2006-2015	NA	69.5%	42.7%	72.7%	88.7%
	BiomedTracker, 2017 [a]	2010-2016	NA	NA	45.0%	71.0%	NA
	Average		**68.0%[b]**	**65.9%**	**49.6%**	**74.1%**	**94.4%**
Cardiovascular	Wong et al, (2019)	2000 - 2015	NA	73.3%	65.7%		
	DiMasi et al, (2010)	1993-2004	NA	62.9%	32.4%	64.3%	66.7%
	BiomedTracker, (2016)	2006-2015	NA	58.9%	24.1%	55.5%	84.2%
	BiomedTracker, (2017) [a]	2010-2016	NA	NA	26.0%	53.0%	NA
	Average		**68.0%[b]**	**65.0%**	**37.1%**	**57.6%**	**75.5%**
Genitourinary System	Wong et al, (2019)	2000 - 2015	NA	68.7%	57.1%		
	BiomedTracker, (2016)	2006-2015	NA	57.1%	32.7%	71.4%	85.7%
	Average		**68.0%[b]**	**62.9%**	**44.9%**	**71.4%**	**85.7%**
Oncology	Wong et al, (2019)	2000 - 2015	NA	57.6%	32.7%	NA	NA
	DiMasi et al, (2010)	1993-2004	NA	71.8%	49.0%	55.3%	100.0%
	BiomedTracker, (2016)	2006-2015	NA	62.8%	24.6%	40.1%	82.4%
	BiomedTracker, (2016)	2006-2015	NA	64.1%	23.0%	34.2%	79.6%
	BiomedTracker, (2016)	2006-2015	NA	61.8%	28.7%	52.6%	86.4%
	BiomedTracker, (2017) [a]	2010-2016	NA	NA	27.0%	45.0%	NA
	Pharma Intelligence, Informa, (2016) [a]	2011-2015	NA	59.0%	21.0%	38.0%	84.0%
	Pharma Intelligence, Informa, (2016) [a]	2011-2015	NA	57.0%	20.0%	32.0%	83.0%
	Pharma Intelligence, Informa, (2016) [a]	2011-2015	NA	64.0%	26.0%	54.0%	84.0%
	Pharma Intelligence, Informa, (2016) [a]	2011-2015	NA	56.0%	18.0%	36.0%	77.0%
	Pharma Intelligence, Informa, (2016) [a]	2011-2015	NA	61.0%	25.0%	40.0%	93.0%
	Average		**68.0%[b]**	**61.5%**	**26.8%**	**42.7%**	**85.5%**
Respiratory System	DiMasi et al, (2010)	1993-2004	NA	72.5%	20.0%	85.7%	80.0%
	BiomedTracker, (2016)	2006-2015	NA	67.6%	32.5%	71.4%	93.8%
	BiomedTracker, (2016)	2006-2015	NA	65.3%	29.1%	71.1%	94.6%
	BiomedTracker, (2017) [a]	2010-2016	NA	NA	28.0%	74.0%	NA
	Average		**68.0%[b]**	**68.5%**	**27.4%**	**75.6%**	**89.5%**

NA = Not available/Not applicable

[a] From PAREXEL's biopharmaceutical R&D statistical yearbook (PAREXEL International Corp., 2017).

[b] Transition probability from preclinical phase to Phase 1 trials for All Therapeutic Areas calculated from PAREXEL International Corp. (2017)as no information was available for the therapeutic area.

All AM drugs in our cohort fall under the anti-infective therapeutic area and drugs from the remaining 2 drug cohorts fall under the cardiovascular, genitourinary system, oncology, and respiratory system therapeutic areas. Across all therapeutic areas, successfully transitioning from Phase 2 to Phase 3 generally has the lowest likelihood ranging from 26.8 percent for oncology to 49.6 percent for anti-infective drugs. Anti-infective drugs also have a higher overall development success probability compared to other types of drugs, with 4.1 percent of oncology drugs and 15.5 percent of anti-infective drugs successfully making it from non-clinical development to market. We used these probabilities to determine the expected development and approval costs for each drug (Equation 2), using the appropriate probabilities for each drug's therapeutic area.

4.2.9 Opportunity Cost of Capital Data

The opportunity cost of capital (OCOC) represents the rate of return (net of inflation) that the sponsor would otherwise be able to earn at the same risk level as the investment in the new drug that has been selected. The value of OCOC can vary significantly by sponsor-specific factors, such as product portfolio, venture capital funding, and size of company, as well as other exogenous factors, such as economic and regulatory climate for drug development projects.

There are numerous studies that have evaluated OCOC for both small and large firms in the biopharmaceutical market. Table 10 presents the different OCOC estimates available from the published literature for all sectors (biotechnology and pharmaceutical) and all firm sizes. These estimates were all made using the capital asset pricing model (CAPM) model. In our analysis, we used the average of these figures (11 percent) as the OCOC for drug development projects.

Table 10. Sources for Opportunity Cost of Capital Used in this Analysis

Data Source	Study Period	Sector	Firm Size	Type of Model	Opportunity Cost of Capital
DiMasi et al, (2003)	2000	Total	All	CAPM	11.9%
DiMasi et al, (2016)	2000	Total	All	CAPM	11.8%
DiMasi et al, (2016)	2005	Total	All	CAPM	10.8%
DiMasi et al, (2016)	2010	Total	All	CAPM	9.4%
Paul et al, (2010)	2007	Total	All	CAPM	11.0%
Mean					**11.0%**

4.2.10 Development and Approval Costs by Phase of Development

The development and approval cost parameter represents the cash outlay (not adjusted for failures or opportunity cost of capital) a sponsor incurs during a given drug development phase. Development and approval costs vary based on the number of patients enrolled as well as the countries where study arms take place. For this model, we estimated the development and approval costs for each drug for the following stages: preclinical/nonclinical, Phases 1 through 3, the FDA review period, and Phase 4 using the parameters discussed above. To calculate the development and approval costs, *C*, for Phases 1 – 3, we multiplied the total enrollment per region for each drug by the median cost per patient by region for the therapeutic area of that drug as shown $C = \text{Enrollment}_{region} \times CPP_{region,TA}\#(13)$ below.

$$C = \text{Enrollment}_{region} \times CPP_{region,TA} \quad (13)$$

To use the appropriate average cost per patient (CPP) figure, we matched each drug to its corresponding therapeutic area. All of the drugs in the AM cohorts were in the infectious disease therapeutic area and all of the drugs in the oncology cohort were in the oncology therapeutic area. The therapeutic areas varied by drug in the non-AM cohort as shown in Table 11.

Table 11. Therapeutic Areas of the Non-AM Cohort Drugs

Non-AM Drug	Therapeutic Area
Bridion	Pain and Anesthesia
Giapreza	Cardiovascular
Surfaxin	Respiratory System
Lokelma	Genitourinary System
Veltassa	Genitourinary System
Vistogard	Oncology

For all drugs with data on Phase 4 trials available, we applied the same method as we did for Phases 1 – 3, as summarized by equation 13 above to estimate the costs associated with Phase 4 post-approval studies. However, many drugs approved more recently, particularly in the AM and oncology cohorts, did not have any data available on Phase 4 trials. Using data from available Phase 4 trials, we estimated the average Phase 4 enrollment by region for the AM, non-AM comparator, and oncology cohorts. We then multiplied this enrollment by the CPP by region and phase to get *regional average Phase 4 development and approval costs.*[22] The sum of the average development and approval costs for all 8 regions yielded the *average total Phase 4 development and approval costs* for the AM, non-AM comparator, and oncology cohorts. We applied this average to any drug that did not have any Phase 4 data available. For costs associated with the non-clinical phase, we used the method from DiMasi et al. (2016) that estimated that the early work before IND submission would cost approximately 45% of the total clinical phase costs.[23] The development and approval costs for each drug and phase was then the simple sum of all 8 regional development and approval costs. We then calculated the total development and approval cost for every drug to get to market as the sum of the costs from the non-clinical phase, Phase 1, Phase 2, Phase 3 before BLA/NDA approval, the FDA BLA/NDA review period, and Phase 4. We calculated this total cost both with and without post-approval (Phase 4) costs.

4.3 RESULTS

From Table 12, the median development and approval costs including post-approval Phase 4 studies for AM drugs were nearly the same as the oncology cohort at $149.6 million and $149.8 million, respectively. These bottom-up estimates are significantly lower than those reported in Wouters, et al. (2020) (see Table 6) as they exclude operational expenditures—office rent, company staff salaries, utilities, etc.—as well as supply chain related activities—chemistry and manufacturing control (CMC) costs, plant build or redesign for manufacturing, etc.—which may be included in Wouters, et al. (2020). The median development and approval costs for the non-AM cohort were nearly half of the other two cohorts at $79.5 million. However, Figure 4 below shows how certain drugs with significantly higher development costs, such as Cyramza, which had very high enrollment during its clinical phase, skew the mean total development and approval costs for the oncology cohort ($195.8 million) to be higher than both the AM ($144.5 million) and the non-AM comparator cohorts ($104.2 million). The magnitude of development and approval costs were largely driven by patient enrollment in clinical studies as shown by similarly high average enrollments in AM and oncology Phase 1, 2, and 3 studies. The average number of patients enrolled for the clinical stage (i.e., Phase 1, 2, and 3 combined) for the AM cohort drugs was 2,413, which was comparable to those for the oncology cohort drugs at 2,314 (Table 7). The non-AM comparator

[22] We again used the infectious disease TA CPP by region and phase for the AM cohort and the oncology TA CPP by region and phase for the oncology cohort, but since Surfaxin was the only non-AM drug that did not have Phase 4 data available, we used the respiratory TA CPP by region and phase to find the *non-AM average Phase 4 development and approval costs by region*.

[23] Here, Phase 3 costs include costs incurred after approval.

cohort had many fewer participants on average (1,430) which is mirrored in the cohort's low average development and approval costs. Of the three cohorts, non-AM drugs also had the longest time from target identification to market at an average of 20.2 years (ranging from 11 to 28.4 years). It took oncology drugs the shortest amount of time to reach market at 13.2 years (ranging from 6.6 to 23.8 years) and AM drugs a little over 2 years longer to reach market at an average of 15.8 years (ranging from 10.4 to 25 years).

From the perspective of total development and approval costs, Phase 3 studies with high enrollments comprised the largest portion of the development costs for drugs across the three cohorts. However, the probability of success for a drug to get from the pre/nonclinical phase to approval is only 15.5 percent for AM drugs and even lower for the non-AM comparator drugs (8.6 percent) and oncology drugs (4.1 percent). This probability increases significantly if the new drug candidate has already cleared the pre/nonclinical, Phase 1, and Phase 2 stages. For our three cohorts the probability of approval for a drug that entered Phase 3 is much higher at 69.9 percent for the AM cohort, 54.6 percent for the non-AM cohort, and 36.5 percent for the oncology cohort drugs.

The very low transition success probabilities at the pre/nonclinical phase mean that once we account for the costs of failures and opportunity cost of capital in the expected capitalized development and approval costs, the pre/nonclinical phase ends up constituting the majority of the development costs and accounted for on average, 75.8 percent (oncology cohort) to 78.7 percent (AM cohort) of the total costs including post-approval Phase 4 costs. Across the three cohorts, the pre/nonclinical phase lasted on average between 55 (oncology) and 63 (non-AM comparator) months but varied greatly for the drugs in the AM cohort with Xerava only taking about a year and a half for the pre/nonclinical activities and Dalvance taking nearly 9 years. We used the approach by Beall, et al (2019) and calculated pre/nonclinical duration as the time from patenting of the compound in the U.S. to the filing of an investigational new drug (IND) application with the FDA to begin testing in humans. The approach may underestimate the time from discovery to clinical phase if the compound is initially patented outside of the United States, e.g., patented with the European Patent Office (EPO) first and later with the U.S. Patent and Trademark Office (USPTO). Given that this phase accounts for a sizable portion of overall costs and publicly available information on expenditures and duration are scarce, we present our costs estimates with and without this phase in Figure 4 and Figure 5 below.

We see that AM drugs have average to high development and approval costs when compared to our other two cohorts. However, once we account for cost of failures and opportunity cost of capital, AM drugs have the lowest expected capitalized development and approval costs with a mean cost, including Phase 4 costs incurred post-approval, of $1,508 million in comparison to those for non-AM drugs ($3,198 million) and oncology drugs ($6,293 million) (Figure 5). This estimate is comparable to the average expected capitalized cost of development and approval of $1,297 million (95 percent CI: $673 million to $1,859 million) reported in Wouters, et al. (2020) for anti-infectives for systemic use. Additionally, when we exclude failure costs, as these are likely borne by investors with investments in multiple early-stage companies rather than the small single-compound AM drug developers, the mean capitalized development and approval costs estimated are $332 million (Table 12) which exceed those recently reported by (Gandhi & Schulman, 2021) by over 60 percent.

Table 12. Total Development and Approval Costs for the AM, Non-AM Comparator, and Oncology Cohorts

Cost Type	Phase	AM Cohort			Non-AM			Oncology		
		Mean	Std. Dev	Median	Mean	Std. Dev	Median	Mean	Std. Dev	Median
Development and Approval Costs (in $ 2018)	Non-clinical Phase	$39.8	$21.0	$41.3	$20.1	$9.4	$18.9	$47.0	$49.8	$29.9
	Clinical Phase	$89.2	$47.1	$92.6	$45.2	$21.0	$42.4	$105.4	$111.7	$67.1
	FDA Review Phase	$2.6	$0.0	$2.6	$2.6	$0.0	$2.6	$2.6	$0.0	$2.6
	Post-Approval Phase	$12.9	$17.7	$10.6	$36.3	$62.9	$12.5	$40.9	$57.9	$7.7
	Total without Post-approval	$131.6	$68.1	$136.4	$67.9	$30.4	$63.9	$155.0	$161.4	$99.6
	Total with Post-approval	$144.5	$70.5	$149.6	$104.2	$68.6	$79.5	$195.8	$174.7	$149.8
Expected Development and Approval Costs (in $ 2018) – Accounts for cost of failures	Non-clinical Phase	$256.0	$135.2	$265.6	$258.0	$130.0	$235.4	$1,146.5	$1,214.7	$729.8
	Clinical Phase	$151.5	$73.8	$164.0	$148.6	$70.0	$162.1	$632.8	$573.7	$500.9
	FDA Review Phase	$23.6	$0.0	$23.6	$23.6	$0.0	$23.6	$23.6	$0.0	$23.6
	Post-Approval Phase	$12.9	$17.7	$10.6	$36.3	$62.9	$12.5	$40.9	$57.9	$7.7
	Total without Post-approval	$431.1	$208.2	$456.2	$430.1	$194.8	$421.0	$1,802.9	$1,768.5	$1,248.4
	Total with Post-approval	$444.1	$208.8	$473.0	$466.4	$197.3	$466.1	$1,843.8	$1,774.5	$1,329.2
Capitalized Development and Approval Costs to Date of Launch (in $ 2018) – Accounts for time value of money	Non-clinical Phase	$189.2	$112.7	$183.9	$168.2	$111.1	$137.4	$214.8	$300.2	$112.6
	Clinical Phase	$140.3	$105.5	$130.8	$126.8	$56.3	$128.1	$143.8	$171.5	$74.3
	FDA Review Phase	$2.7	$0.2	$2.7	$3.2	$0.7	$2.9	$2.7	$0.0	$2.7
	Post-Approval Phase	$8.8	$10.6	$8.0	$21.0	$31.9	$9.4	$14.7	$14.6	$5.9
	Total without Post-approval	$332.3	$206.7	$358.5	$298.2	$163.8	$269.2	$361.3	$458.5	$165.3
	Total with Post-approval	$341.1	$206.8	$362.8	$319.2	$155.5	$310.7	$376.0	$464.8	$181.7
Expected Capitalized Development and Approval Costs to Date of Launch (in $ 2018) – Accounts for costs of failures and opportunity cost of capital	Non-clinical Phase	$1,218.5	$725.7	$1,183.9	$2,661.3	$2,816.7	$1,365.0	$5,242.7	$7,328.0	$2,748.5
	Clinical Phase	$255.6	$167.9	$249.8	$486.7	$398.9	$356.6	$1,010.8	$1,052.8	$718.4
	FDA Review Phase	$25.0	$1.7	$24.5	$29.4	$6.6	$26.4	$24.3	$0.3	$24.2
	Post-Approval Phase	$8.8	$10.6	$8.0	$21.0	$31.9	$9.4	$14.7	$14.6	$5.9
	Total without Post-approval	$1,499.0	$869.1	$1,502.8	$3,177.4	$3,142.0	$1,754.5	$6,277.9	$8,304.9	$3,104.7
	Total with Post-approval	$1,507.8	$869.9	$1,507.0	$3,198.3	$3,130.0	$1,796.1	$6,292.6	$8,311.7	$3,123.6

Figure 4. Development and Approval Costs with and without Pre/Nonclinical Phase Costs for AM, Non-AM Comparator, and Oncology Cohort Drugs (in 2018 $ Million)

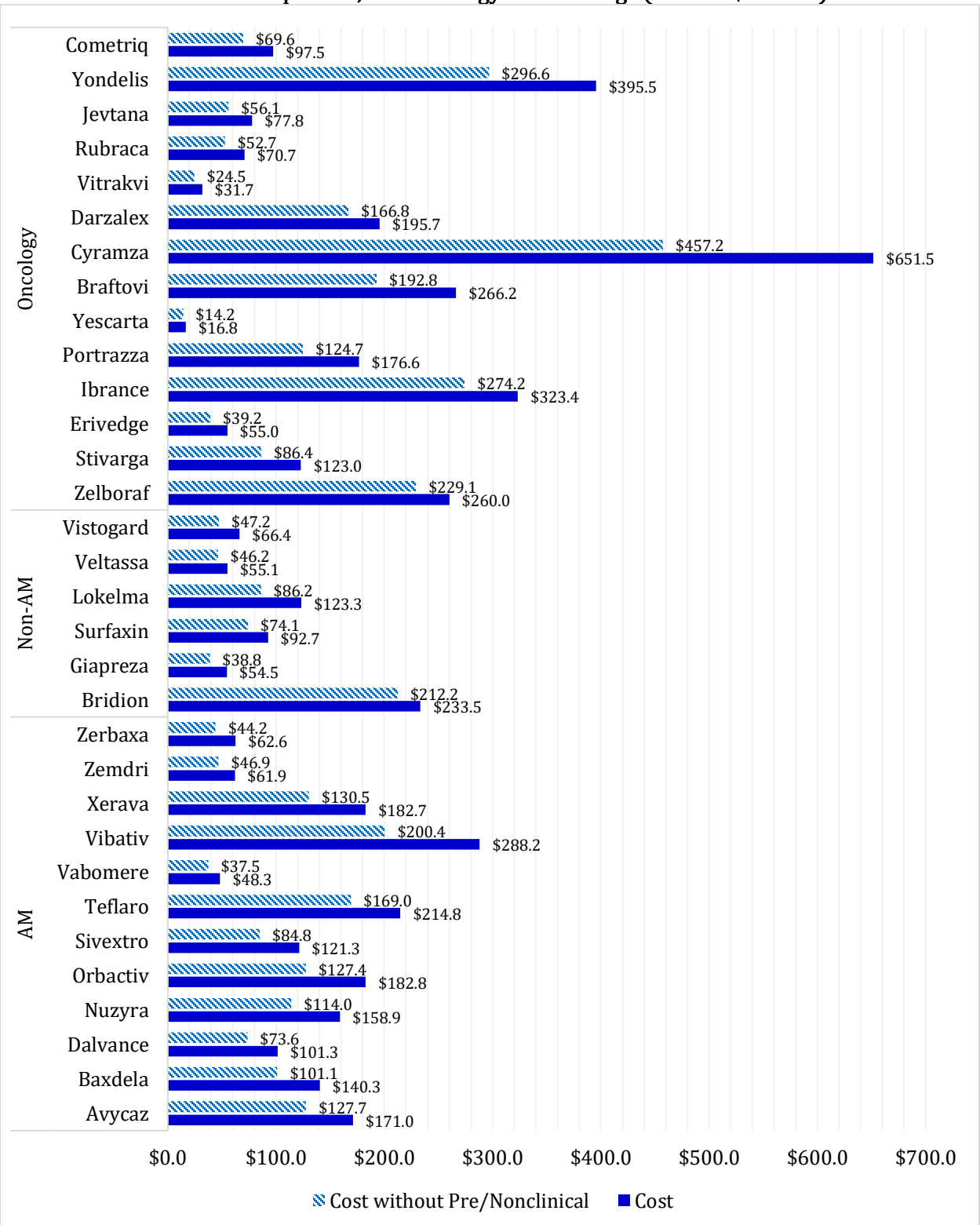
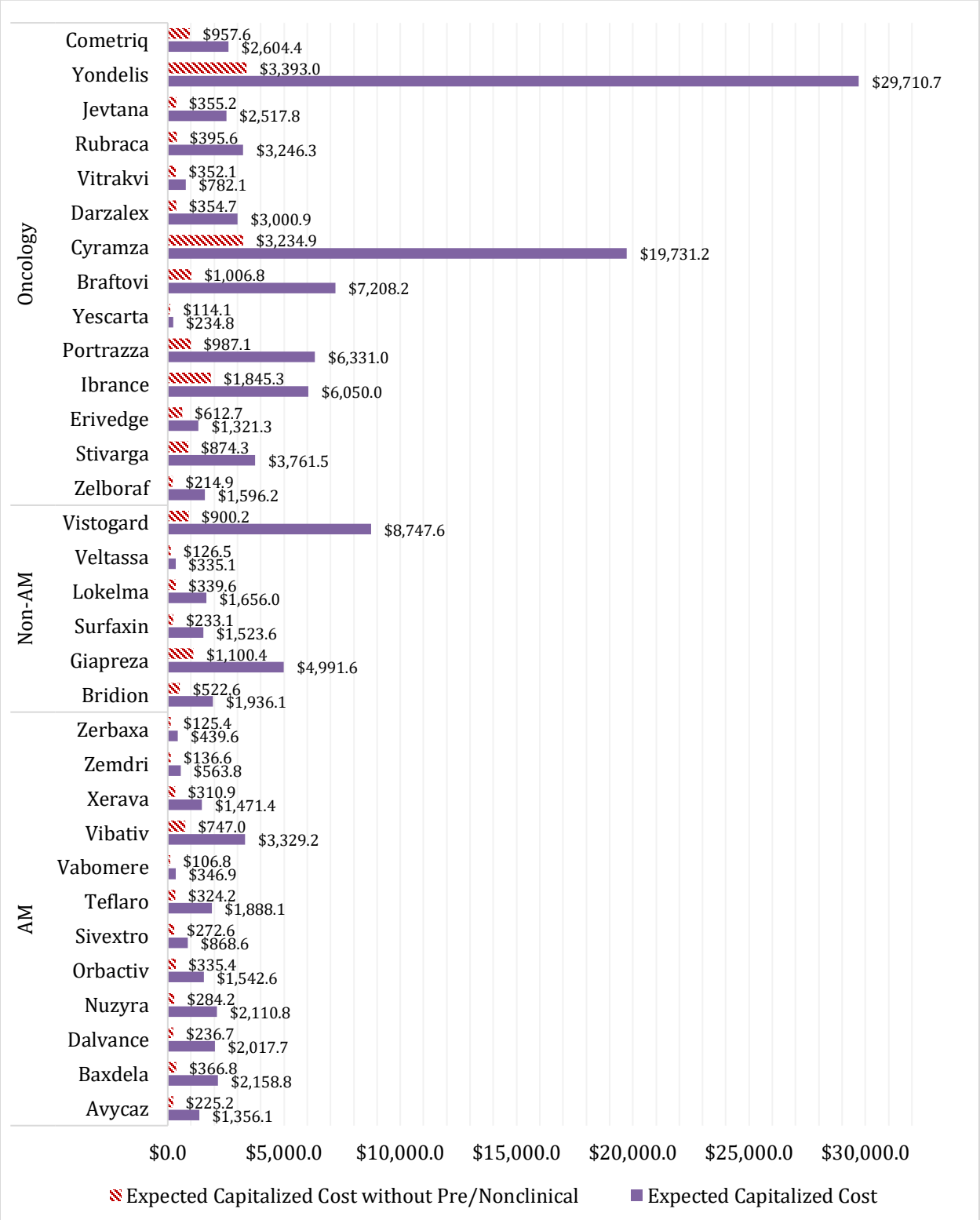


Figure 5. Expected Capitalized Development and Approval Costs with and without Pre/Nonclinical Phase Costs for AM, Non-AM Comparator, and Oncology Cohort Drugs (in 2018 $ Million)



Note: The resulting values for Yondelis and Cyramza are due to the high number of clinical studies involving large patient populations conducted for these drugs.

4.4 LIMITATIONS

There are several limitations to the development cost analysis. First, the costs presented currently do not account for those expenditures related to supply chain activities; chemistry, manufacturing, and controls (CMC) processes; plant design and/or build; marketing and commercialization; or other post approval activities, such as pharmacovigilance, pediatric studies, etc. These activities have a significant burden after a drug is launched in the U.S. market (Table 13). However, with the exception of AST development ($7 million) and resistance monitoring costs ($3 - $5 million) shown in Table 13, these costs are applicable to not just AM drugs but all drugs in our non-AM comparator and oncology cohorts. Thus, they do not alter the comparative results across the three drug cohorts to any significant extent.

Table 13. Expected Five-year Expenses in $ Million for a New AM Drug for the U.S. Market Post Launch from Krause (2019)

Commitment	Single Indication, Minimum Requirements	Two Indications, Some safety Signals	Several Indications, Expected Broad Use
Pediatric Pharmacokinetic (PK) and Safety Studies	$25	$50	$75
Additional Phase 3 Study	NA	$50	$75
Pharmacokinetic in Special Adult Populations	$2	$3	$5
Surveillance	$3	$5	$5
Pharmacovigilance	$5	$5	$5
Medical Affairs	$50	$50	$50
AST	$7	$7	$7
Drug Manufacturing	$150	$250	$400
Total	**$242**	**$420**	**$622**

NA = Not applicable

Second, the costs presented also do not account for the U.S. and non-U.S. government investment in these drugs that were intended to offset portions of the applicable drugs' R&D expenses that would have been incurred by the drug developers. In that sense, they potentially overestimate the costs incurred by drug developers. For example, there are several drugs within the AM cohort (Zemdri, Vabomere, Orbactiv, Xerava, and Nuzyra) that have received sizable U.S. government grant funding for R&D according to public records available via the Federal procurement database. We estimated the U.S. grant funding received by Zemdri at $220 million, by Nuzyra at $157 million, by Xerava at $61.5 million, and by Vabomere and Orbactiv combined at $59 million,[24] which amounts to around $498 million for the 5 AM drugs overall. While we have not been able to track U.S. government funding for the drugs in the non-AM comparator or the oncology cohorts due to company name changes resulting from mergers and acquisitions, it is possible that some of these drugs have also benefited from U.S. government funding, especially in early stages of R&D. Table 14 presents an analysis of the effects of a hypothetical $1 million in grant funding a company receives on the expected capitalized cost of drug development and approval by development phase. From the table, an early R&D grant of $1 million during pre/nonclinical development has the largest impact on mean overall development costs (-1.5 to -4.4 percent

[24] The reported funding figure in FPDS-NG of around $88 million was applicable to three drugs, Vabomere, Orbactiv, and Minocin, originally developed by the Medicines Company. Since Minocin is not a part of the AM cohort, the reported $465 million overall spending likely overestimates the spending on Zemdri, Vabomere, Orbactiv, and Nuzyra by roughly $29 million assuming a third of the $88 million funding was for Minocin.

reduction) across the three cohorts. The offsetting impact of the funding on overall development costs borne by the drug developer reduces as it gets applied to later development stages.

Table 14. Change in Expected Capitalized Costs Inclusive of Post-approval Costs due to a Hypothetical $1 Million in Government Grant Funding for a Development Phase [a]

Drug Cohort	Development Phase	Change in Mean Expected Capitalized Costs Including Post-approval Costs (in 2018 $ Million)		Change in Median Expected Capitalized Costs Including Post-approval Costs (in 2018 $ Million)	
		$	%	$	%
AM	Pre/Nonclinical	-$30.7	-2.0%	-$22.0	-1.5%
	Phase 1	-$23.4	-1.6%	-$22.6	-1.5%
	Phase 2	-$19.0	-1.3%	-$15.9	-1.1%
	Phase 3	-$15.6	-1.0%	-$11.7	-0.8%
Non-AM Comparator	Pre/Nonclinical	-$141.7	-4.4%	-$51.0	-2.8%
	Phase 1	-$78.8	-2.5%	-$27.9	-1.6%
	Phase 2	-$93.8	-2.9%	-$34.5	-1.9%
	Phase 3	-$68.6	-2.1%	-$26.3	-1.5%
Oncology	Pre/Nonclinical	-$93.3	-1.5%	-$124.9	-4.0%
	Phase 1	-$74.0	-1.2%	-$101.2	-3.2%
	Phase 2	-$56.5	-0.9%	-$72.9	-2.3%
	Phase 3	-$40.5	-0.6%	-$57.9	-1.9%

[a] To calculate the change in expected capitalized costs of a hypothetical $1 million grant funding for a given drug, we decreased the development and approval cost of a selected phase by the grant amount for each drug and re-calculated the expected capitalized costs using equations 1 through 5. We then compared this value to the expected capitalized cost previously calculated for each drug to compute the difference, The figures in the table represent the average difference across all drugs in a given cohort for that phase.

It is difficult to discern to which development stages the total U.S. government grant funding we identified for the four AM drugs would have applied. However, the amount of grant funding received for these drugs would likely have been sufficient to offset at least the sum of pre/nonclinical, Phase 1, and Phase 2 costs we estimated for Zemdri ($23 million), Nuzyra ($55 million), Xerava ($60 million) and Vabomere ($14 million) and around half of pre/nonclinical costs for Orbactiv ($55 million). This would have significantly reduced the estimated expected capitalized costs inclusive of post-approval costs incurred by the developers of those drugs. For example, a complete offset of pre/nonclinical, Phase 1, and Phase 2 costs would have reduced the expected capitalized costs inclusive of post-approval Phase 4 costs by 85 percent (from $564 to $82 million) for Zemdri, by 80 percent (from $347 to $69 million) for Vabomere, by 91 percent (from $2,111 to $199 million) for Nuzyra, by 83 percent (from $1,471 to $249 million) for Xerava, and by 39 percent (from $1,543 to $939 million) for Orbactiv.

Third, as shown in Figure 4 and Figure 5, the pre/nonclinical phase of development is a big driver of overall development costs. However, there are no publicly available estimates of pre/nonclinical costs. In modeling the expenditure associated with this stage, we used the methodology by DiMasi, et al. (2016) and assumed that the overall costs for the pre/nonclinical stage was around 45 percent of the total clinical phase (i.e., Phase 1, Phase 2, and Phase 3) costs for all drugs across the three drug cohorts. This results in allocating a sizeable amount to the pre/nonclinical stage in the modeling; $40 million for AM drugs, $20 million for non-AM comparator drugs, and $47 million for oncology drugs on average. The resulting pre/nonclinical stage cost estimates for AM drugs are, as a result, significantly higher than what we heard from an industry expert during our interviews who reported $2 million in pre/nonclinical research to find a molecule with clinical and market potential, but this is highly variable depending on the compound.

Given how sensitive the overall development costs are to the expenditure associated with this stage, better information is needed to improve estimates.

Fourth, as noted above, several more recently approved drugs did not have any information on Phase 4 trials available. Therefore, we had to use an average Phase 4 cost for 5 out of the 12 AM drugs, but these costs varied greatly from $400,000 (Sivextro) to $63.6 million (Teflaro). We similarly had to apply an average Phase 4 cost to 7 out of the 14 oncology drugs, with costs ranging from $1.2 million to $19.6 million.

Finally, it was difficult to find publicly available information on early phase (Phase 1 and Phase 2) clinical trials. Some companies may have conducted these trials outside of the U.S. and thus may not have had to register them in clinical trial registries such as clinicaltrials.gov or EU Clinical Trials Register. While FDA requires companies to submit summary information on all clinical trials conducted for a compound that is the subject of an NDA, information on early phase trials were either completely or partially lacking based on our review of the statistical information packages and other publicly available information on Drugs@FDA. This would have resulted in an underestimate of R&D costs given our bottom-up methodology. Despite the missing information, however, our expected capitalized development and approval cost estimates are in line with other recently published estimates that have utilized different methodologies.

5 EVALUATION OF COMPARATIVE ADDED CLINICAL BENEFIT

Clinical efficacy measures whether a drug treated patients as intended in a clinical trial. In contrast, comparative clinical effectiveness, which is the added clinical benefit of the drug over existing treatments, is revealed once the drug demonstrates improved health outcomes over existing treatments with widespread use after approval and accounting for 'real-world' conditions such as patients with multiple co-morbidities who may be taking multiple medications (Institute for Clinical and Economic Review, 2020). Real-world evidence, which FDA defines as health care data that is taken from sources outside traditional clinical settings, such as evidence generated from post-approval studies in more typical clinical settings and expanded patient populations, is revealed through a multitude of sources in the years after drug approval including consumer data, electronic health records and mortality data, and disease registries (Forum on Drug Discovery, Development, and Translation, 2016).

Prior to marketing approval, the added clinical benefit of a drug can be evaluated using pivotal clinical trials designed to demonstrate superiority (i.e., the drug is <u>better than</u> the standard therapy) rather than one designed to demonstrate non-inferiority (i.e., the drug is <u>not worse than</u> the standard therapy). For any drug, superiority trials require larger patient enrollment which makes them more costly to conduct. In some cases, such as an AM drug designed to treat highly resistant infections, superiority trials might be infeasible or unethical to conduct due to lack of patients or knowingly providing inferior treatments. In the absence of superiority trials, the evidence for the added clinical benefit of a drug, as defined here, is accumulated through actual use over time post approval. Since demonstration of superiority is not mandatory for regulatory approval, all of the Phase 3 trials submitted in support of an NDA for the drugs in our AM cohort have used noninferiority designs.

After clinical efficacy has been demonstrated in Phase 3 trials and the drug enters the market upon regulatory approval, real-world data may be collected over the following years that can be used to inform future clinical and policy decisions. However, public and private insurers, physicians, hospital pharmacy and therapeutics committees, and others need to make decisions regarding the drug's use, reimbursement, and formulary placement either at or soon after drug approval when there is still limited evidence of the drug's added clinical benefit. In the absence of standardized comparative drug evidence generation and assessments, these decisions may rely on

individual practitioner's idiosyncratic experience with and perceptions of the drugs (Forum on Drug Discovery, Development, and Translation, 2016). To combat this, several organizations, primarily non-U.S. government agencies, currently conduct health technology assessments, also referred to as clinical value assessments, to aid their decision making around drug policy or pricing. These assessments basically add an economic and treated population estimate overlay on the regulatory efficacy data by compiling existing information but do not generate any new data.

To gain a better understanding of the methods used in such assessments, we conducted a focused review of literature related to clinical value assessments and real-world effectiveness that was completed on February 1, 2021. For the review, we queried PubMed using search terms, such as "clinical effectiveness assessment," "real-world effectiveness assessment," "added clinical benefit, " and "clinical added value." To target our search, we limited the search query to the title and/or abstract of papers with these key words and applied further search filters to only return literature published between 2010 and 2021 and only search within these article types[25]: Books and Documents; Journal Article; Meta-Analysis; Practice Guideline; Research Support, NIH Extramural; Research Support, NIH Intramural; Research Support, Non-U.S. Government; Research Support, U.S. Government, Non-Public Health Service (PHS); Research Support, U.S. Government, PHS; Research Support, U.S. Government; Review; and Systematic Review.

Our literature search yielded 155 studies. We supplemented these studies with The International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) Value Assessment Frameworks Initiative Reports, as well as through a forward citation search of the literature results. From this set of literature, we reviewed the study abstracts to narrow down the collection to only the most relevant studies that described existing clinical value assessments or provided theoretical discussion of value assessment frameworks. This review resulted in 30 relevant studies that merited further in-depth review. Of these, 11 studies were either deemed irrelevant or did not have full study texts available. Many of the remaining 19 studies discussed the use of clinical value assessments to aid pricing and reimbursement decision-making for pharmaceuticals. The following discussion summarizes the findings of these 19 studies.

Many international assessments employed what they referred to as Relative Effectiveness (RE) Assessments, which compared the achieved health outcomes of a drug to comparator treatment options (Kleijnen, et al., 2014b). These assessments consequently both measured the real-world effectiveness of a drug, and, as we try to capture in our assessment, whether the drug is valuable relative to other therapy options, i.e., whether the drug has added clinical benefit over existing treatments. Our assessment methodology below places explicit value on drugs that either fill an unmet need or achieve better outcomes than the standard therapy.

In Europe, clinical value assessments are primarily addressed using the Health Technology Assessment (HTA) Core Model®. The HTA Core Model®, was originally developed by stakeholders including patients, providers, payers, and the European Commission to facilitate standardized value assessments for new health technologies in Europe. It consists of a set of generic questions that fall into the categories: 1) health problem and current use of the technology, 2) description and technical characteristics of the technology, 3) safety, 4) clinical effectiveness, 5) costs and economic evaluation, 6) ethical analysis, 7) organizational aspects, 8) patient and social aspects, and 9) legal aspects. The model is designed to allow assessors, who may be drug reimbursement or other therapy decision makers, to choose the questions most relevant to their assessment from the 136 provided. The model then provides methodological guidance so the assessors can answer each question and summarize the findings into 'result cards.' These results are structured to highlight

[25] We elected to not search for 'Clinical Trial' or 'Randomized Controlled Trial' articles to avoid literature on clinical efficacy studies conducted during clinical research.

information on the value of the technology of interest that is most useful for decision making (Kleijnen, et al., 2014a; Kleijnen, et al., 2014b; Kristensen, et al., 2017).

Another pervasive theme in other value assessment approaches in use was that the challenges assessing added clinical benefit for orphan drugs appeared similar to those for AM drugs in that both types of drugs usually target small populations; there often is limited added clinical benefit evidence at time of marketing authorization and developing; and using these drugs is often not cost-effective (Denis, et al., 2010; Zelei, et al., 2016; Van Wilder, et al., 2013). For example, a general clinical value assessment may not assign a high score to an AM drug approved for a relatively rare indication (i.e., MDR pneumonia) because the assessment may find it to be too expensive, especially in the presence of stewardship measures that result in infrequent prescriptions.

A selection of the literature also suggested methods to assess added clinical benefit more accurately in orphan drugs. The most common method from the literature reviewed was the use of reflective multicriteria decision analysis (MCDA). MCDA refers to an analytical method that uses input from a wide set of data metrics, or criteria, and is useful for contextualizing a set of disparate data elements. For example, cost effectiveness may be one criterion, but the full analysis may include many other criteria, such as unmet clinical need, that provide more context from different perspectives. Since MCDAs allow for a multitude and variety of criteria, this methodology has been shown to be responsive to rare disease issues (Wagner, et al., 2016; Guarga, et al., 2019). Other strategies to assess orphan drugs included weighing certain factors, such as the treatment innovation and unmet need, more highly than others, such as the patient population size, the cost effectiveness, the quality of evidence and clinical practice guidelines (Guarga, et al., 2019; Zelei, et al., 2016; Denis, et al., 2010).

5.1 METHODOLOGY AND DATA SOURCES

We developed a comparative added clinical benefit evaluation methodology that draws on publicly available data and encapsulates factors such as the clinical effectiveness in real world settings, the drugs' added clinical benefit over the standard available therapy at market entry, as well as pricing, accessibility, and affordability of the therapy. Our methodology described below draws from 22 different international metrics, which we refer to as evaluation metrics, that reveal some aspect of added clinical benefit of a drug over existing treatments. We also take patient population size and cost-effectiveness (to the extent that it is included in health technology assessment scores) into account but construct a weighting routine that reflects some of the key aspects of added clinical benefit for AM, non-AM comparator, and oncology drugs, employing a multicriteria decision analysis approach.

5.1.1 Evaluation Metrics

To assess a given drug's comparative added clinical benefit within each cohort, we collected different types of information that are likely to correlate with some aspect of added clinical benefit. We treated the information collected as metrics, where data were available, to garner a more comprehensive view of added clinical benefit and to rank the drugs by their relative added clinical benefit within each cohort. Some of the evaluation metrics we compiled were only applicable to AM drugs and hence were not used in the assessments for the non-AM comparator and oncology drug cohorts. We describe each evaluation metric used in our assessment in detail in the following sections.

5.1.1.1 Select Drug Characteristics

We compiled information on whether the drug was a New Molecular Entity (NME), a New Chemical Entity (NCE) and what the drug's route of administration (i.e., intravenous, oral) is for all

drugs across the three cohorts. This information was largely gathered from the drug profiles on Drugs@FDA.

Additionally, we estimated the market size for each drug in the non-AM comparator and oncology cohorts using two metrics: the approximate number of annual cases for the drug's indication as well as an estimate of the number of other drugs for that indication on the market. If a drug was approved for more than one indication, we added the approximate number of annual cases for each indication together. We only used the original indication(s) for approval. Similarly, we gathered information from Medscape's Diseases and Medication inventory on how many drugs were approved for a certain indication and added the number of drugs together if a drug was approved for more than one indication.

For the AM cohort, we used Carr & Stringer's (2019) estimates for estimated inpatient treatment courses for each infection from their 2019 Antibiotic and Antifungal Update, instead of the number of annual cases, along with the number of other drugs on the market for that indication as measure of approximate market size and anticipated patient population. For AM drugs, we also compiled information about the drug's expected activity against CDC urgent pathogens, WHO critical threat pathogens, and ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species).

5.1.1.2 European Health Technology Assessments

Countries around the world have devised systems and organized bodies that regulate drug and other therapeutics' quality and efficacy. Many of them are part of the International Network of Agencies for Health Technology Assessment (INAHTA), which defines an HTA as "*a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle*," the purpose of which "*is to inform decision-making in order to promote an equitable, efficient, and high-quality health system*" (The International Network of Agencies for Health Technology Assessment, 2020a).

We reviewed the health technology assessments conducted from France, the United Kingdom, and Germany. Such assessments were available for some but not all of the drugs included in this analysis.

France

The Haute Autorité de Santé (HAS) based out of Paris, France is a consulting body whose goal is to evaluate health products from a medical and economic viewpoint. HAS releases assessments that rate the actual clinical benefit (ACB) as well as the clinical added value (CAV) of medicinal products. The ACB rates the benefit of a drug based on its clinical efficacy and the condition treated by levels: substantial, moderate, low, or insufficient. The CAV rates the benefit in comparison with existing treatments, ranking the improvement in treatment on a scale from I (major) to IV (minor), with V indicating "no clinical added value" (Haute Autorité de santé, 2019; The International Network of Agencies for Health Technology Assessment, 2020b).

United Kingdom

The National Institute for Health and Care Excellence (NICE) out of Manchester, United Kington is a public body responsible for providing national guidance on various health products. NICE carries out HTAs and publishes corresponding guidance for the public and health professionals for prescribing certain drugs. Both clinical efficacy as well as acquisition cost data are considered in the summarized evidence and recommendations (The International Network of Agencies for Health Technology Assessment, 2020c).

Germany

The Institute for Quality and Efficiency in Health Care (IQWiG), out of Cologne, Germany, is a private foundation which conducts and publishes assessments on the quality and efficiency of health services. One product IQWiG provides is dossier assessments, in which IQWiG assesses dossiers submitted by manufacturers to determine whether new drugs at market entry provide any additional benefit to the standard therapy. The added benefit is classified as considerable, minor, non-quantifiable, or not proven (IQWiG, n.d.; The International Network of Agencies for Health Technology Assessment, 2020d).

5.1.1.3 Institute for Clinical and Economic Review Value Assessments

The Institute for Clinical and Economic Review (ICER) is an organization that assesses the clinical and economic value of prescription drugs and other health technologies. ICER conducts value assessments based on clinical data and input from stakeholders such as patients, doctors, private insurers, and the government. A drug's value takes into consideration both the *long- term value for money* and the *short-term affordability*. ICER considers *long-term value for money* the primary consideration for clinical value and determines this based on comparative clinical effectiveness, incremental cost-effectiveness, as well as other benefits and disadvantages to the drug. ICER determines the secondary consideration, *short-term affordability*, through looking at the potential budget impact for health care providers that would arise from introducing this new drug (Institute for Clinical and Economic Review, 2020). ICER ranks comparative clinical effectiveness based on the net health benefit of the new therapy as well as the level of certainty of the assessment. The evidence rating matrix ICER uses is depicted in Figure 6.

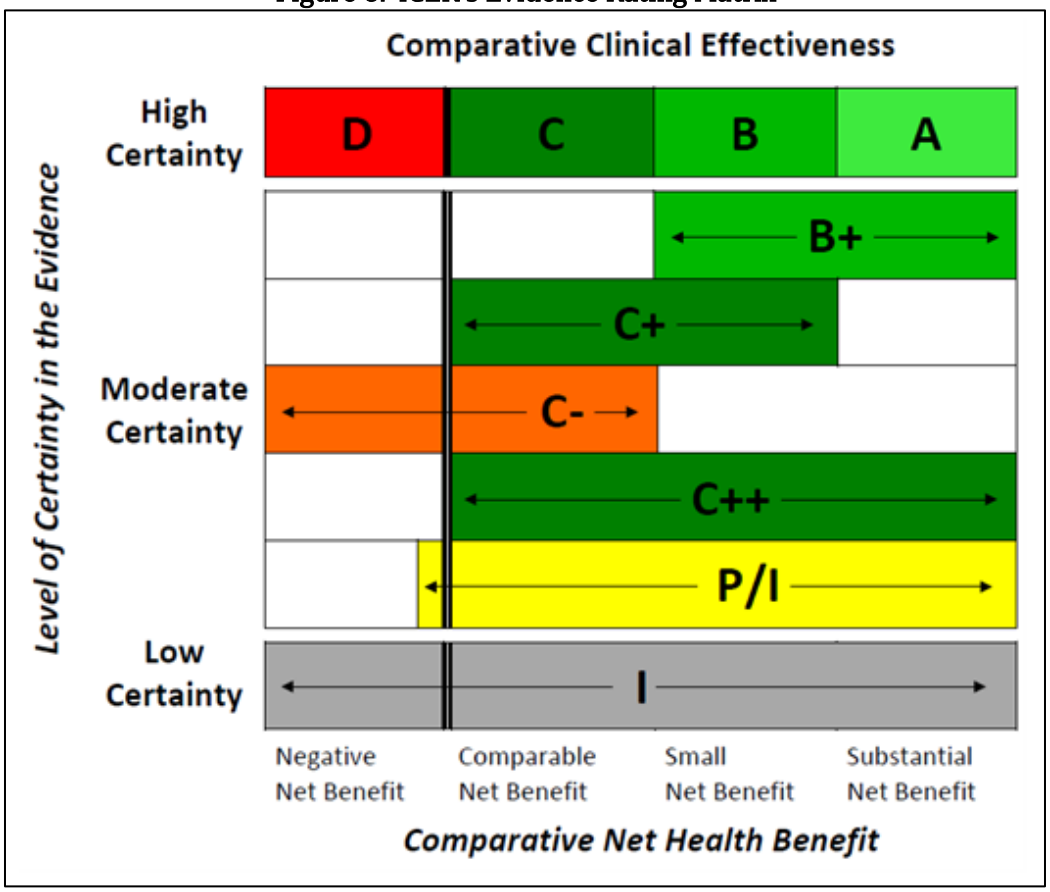
ICER conducts assessments for specific therapeutic areas, and accordingly rates the therapies in that area; for example, the broader CAR-T therapies assessment included a specific assessment of the FDA-approved drug axicabtagene ciloleucel or Yescarta™. In this assessment, ICER also issued an Affordability and Access Alert, which is another value rating tool that makes note of whether "added health care costs may be difficult for the system to absorb over the short term" (Institute for Clinical and Economic Review, 2018). ICER clinical value assessments were only available for drugs in our oncology cohort.

5.1.1.4 Trinity Drug Index

In 2016, Trinity began publishing comprehensive evaluations of FDA approved drugs. Trinity has published Drug Indices in 2016, 2017, 2018, and 2019, rating novel drugs that were approved in 2013, 2014, 2015, and 2016, respectively. Trinity reviews each drug and assigns a score in three categories: commercial performance, therapeutic value, and research and development (R&D) complexity. Each drug also receives an overall composite score based on the three categories on a scale from 1 to 5 (Fitzhenry, et al., 2016).

The *commercial performance score* rates how well the drug has performed and how it is predicted to perform in the future. These are determined based on cumulative sales to date and projected sales. The *therapeutic score* rates the drug's novelty, if it filled an unmet need, and how the drug compared to the standard of care when it was released. Trinity determines the additional value provided by the drug through surveys of life sciences experts and practicing physicians. The *R&D score* rates how long the clinical development took and how many patients participated in the trials in comparison with the cost of the process. Finally, the *overall score* combines the commercial (40 percent), therapeutic (40 percent), and R&D (20 percent) scores for a composite look at each novel drug. Across all four publications, only a subset of drugs in our sample were included in Trinity's assessments.

Figure 6. ICER's Evidence Rating Matrix



Source: Institute for Clinical and Economic Review *(2022)*
A = "Superior" – High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" – High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D= "Negative"- High certainty of an inferior net health benefit
B+= "Incremental or Better" – Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Incremental" – Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit
C- = "Comparable or Inferior" – Moderate certainty that the net health benefit is either comparable or inferior, with high certainty of at best a comparable net health benefit
C++ = "Comparable or Better" – Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" – Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit
I = "Insufficient" – Any situation in which the level of certainty in the evidence is low

5.1.1.5 Inclusion in Guidelines and Recommendations

We reviewed available guidelines and recommendation documents from the Infectious Diseases Society of America (IDSA) and Pharmacy & Therapeutics (P&T) Community to see if a given drug in our sample is included in their recommendations.

Infectious Diseases Society of America (IDSA) Guidelines

The Infectious Diseases Society of America (IDSA) is an organization made up of physicians, scientists, and public health experts who specialize in infectious diseases and promote infectious disease research and patient care. As part of improving infectious disease care, IDSA publishes practice guidelines for both patients and physicians. These guidelines review clinical evidence as well as extensive data from literature and provide treatment guidelines for specific therapeutic areas or clinical circumstances such as guidelines for skin and soft tissue infections or for outpatient parenteral antimicrobial therapy. The guidelines provide recommendations for a range of clinical situations from diagnosis to treatment (Infectious Diseases Society of America, 2020).

We reviewed the IDSA guidelines if they included one of our selected drugs in their therapy recommendations. As these guidelines are only for infectious disease therapies, the recommendations only included select drugs from the AM and non-AM comparator cohorts.

Pharmacy & Therapeutics (P&T) Community Decisions

The Pharmacy & Therapeutics (P&T) Community and their online journal, P&T® Journal provide key information on new drugs and therapies for pharmacy and therapeutics committee members. Experts in the field author articles in this journal so that P&T committees may make more informed formulary and medication-related policy decisions. For each drug that P&T® covers, experts describe the indications and usage, pharmacology, clinical trials, dosage, specific warnings and precautions, and the cost of the therapy. Taking all of these sections into considerations, P&T® then offers a conclusion on the drug's recommended place in therapy i.e., a first-line option or a last-line choice.

5.1.1.6 Medicaid Coverage

We compiled information from the Medicaid formularies for the ten states with the largest Medicaid markets: California, New York, Texas, Pennsylvania, Florida, Ohio, Illinois, Massachusetts, Michigan, and New Jersey using the searchable medical reference for clinicians, Epocrates® that allows querying each state's Medicaid formulary for specific drugs.[26] With narrow exceptions, Medicaid is required to cover all FDA-approved medications from manufacturers participating in the Medicaid Drug Rebate Program. For each drug, the formulary indicates the level of coverage for a drug under Medicaid in that state. Different levels of coverage include Y: Covered – No Prior Authorization Required, PPA: Preferred – Prior Authorization Required, PA: Prior Authorization Required, NPA: Non-Preferred – Prior Authorization Required, and N: Not Covered.[27] However, each state has slightly different reimbursement methodologies for determining at what level a drug is covered which reflects the state-specific ingredient costs and pharmacy dispensing fees. Thus, the category 'N' appears to align with 'NPA' in that these products are not preferred, but prescribers would need to go through different processes to access products in the 'N' category versus in the 'NPA' category. Products may also be designated 'N' because the state has not yet made a coverage determination (that is, the P&T Committee has not met yet to develop coverage criteria), or because the manufacturer has not hit the mandatory effective date for state coverage yet. The 'N' category may also indicate that the company may not have a rebate agreement in place yet. Nonetheless, we judged that a drug having a covered or preferred prior authorization status in a state's Medicaid program is an indicator of drug accessibility. Hence, we counted how many states out of ten either

[26] A similar analysis was not feasible for Medicare coverage because Medicare Part A, B, D formularies are not publicly available.

[27] A 'Not Covered' designation indicates that a drug is not on the state's Medicaid formulary. An individual may request an exemption if a drug is not on the Medicaid formulary.

covered or denoted 'preferred prior authorization' for each drug as an assessment of drug accessibility.

5.1.1.7 Automated Antimicrobial Susceptibility Test (AST) Device Incorporation

Antimicrobial Susceptibility Tests (ASTs) are testing methods used in hospitals and laboratories to determine whether a certain microorganism is susceptible or resistant to an AM drug. Automated AST systems test panels of tens of drugs at a time against a sample. However, AST device companies must first decide which drugs to incorporate onto the test panels for each system. We conducted a series of interviews with stakeholders in the AST industry and heard from an expert at one such automated AST device company that these companies tend to carry out thorough vetting analyses when deciding whether to incorporate a newly FDA-approved AM drug into their systems. This analysis factors in efficacy, resistance patterns and unmet need, customer demand, as well as predicted economic success. There also are additional considerations, e.g., the physical properties of certain AM compounds that may preclude their inclusion in these devices.

We compiled data on whether a given drug in the AM cohort was incorporated onto the two leading AST devices, bioMérieux's *Vitek® 2* and Beckman Coulter's *MicroScan*, that together comprise roughly 90 percent of the device market.[28] Since these two large AST manufacturers control the market, they can decide which AM drugs get incorporated onto their devices and when with little competition. We assumed that incorporation on to one or both of these devices indicates the automated AST device companies' internal evaluations of the added clinical benefit as well as the anticipated market demand for the new AM drug.

5.1.1.8 FDA Qualified Infectious Disease Product (QIDP) Classification

According to the GAIN Act provisions, under section 505E of the 34 Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355f), development of antibacterial and antifungal drugs for human use to treat serious or life-threatening infections is incentivized in several ways. First, those drug products that have been designated as a Qualified Infectious Disease Product (QIDP) and approved under section 505 of the FD&C Act are granted a 5-year exclusivity extension which is added to any exclusivity the application qualifies for upon approval. Additionally, FDA gives priority review to the first application submitted for approval for a QIDP. The application can also receive fast track designation if requested by the application sponsor (U.S. Food and Drug Administration, 2018). All of the drugs in the AM cohort, except for Teflaro and Vibativ that were approved prior to the passage of the GAIN Act, had received QIDP designations from FDA.

5.1.1.9 Receipt of Funding from HHS Biomedical Advanced Research and Development Authority (BARDA)

The Biomedical Advanced Research and Development Authority (BARDA) is part of the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) and was established in part to protect the country from emerging infectious diseases as well as chemical and biological threats. BARDA therefore supports specific drugs, vaccines, and diagnostics that contribute to their mission. In particular, one of BARDA's goals is to incentivize antibacterial research and development in order to reduce antimicrobial resistant bacterial infections that may follow a public health emergency. BARDA has subsequently provided funding to several AM drugs to support preclinical and clinical development through FDA approval. Thus, we recorded which drugs in the AM cohort received funding from BARDA as another metric of added clinical benefit.

[28] BD Phoenix™, commands less than 5 percent of the market with the remaining market share spread over those systems manufactured by smaller companies.

5.1.2 Evaluating Comparative Added Clinical Benefit

Based on the information available for each metric, we ranked each drug with 1 being the highest rank compared to the others in the cohort. The Trinity Drug Index, for example, assigned scores on a scale from 1 to 5 for five out of the twelve drugs in the AM cohort. We ranked the drug with the highest score "1," the second highest "2," and so on. We did this using MS Excel's rank function for all of the drugs in the cohort. However, many metrics did not have quantitative scoring or numerical data available. For those metrics, we qualitatively assigned rankings based on context and best professional judgment. For example, the French HTAs rated a drug's actual clinical benefit from "substantial" to "insufficient." For these, we ranked "substantial" as the highest and assigned rankings sequentially based on the assessment ratings.

We determined that each metric likely did not reveal added clinical benefit to the same extent. For example, ten out of twelve AM drugs received QIDP designation. While an important metric in identifying drugs that will treat serious or life-threatening infections, QIDP designation will not be able to effectively differentiate the relative added clinical benefit of each drug within the AM cohort. For this reason, we devised a weighting system that would place metrics in "added clinical benefit categories" that would allow us to synthesize the data on more equal footings (see Table 15). We also wanted the categories to be applicable to all three cohorts of drugs to allow for parallel comparative added clinical benefit analyses.

Based on input from HHS, we classified several metrics as key, i.e., that would be most revealing of a drug's added clinical benefit. For all three cohorts, we treated the Trinity Drug Index and other countries' assessments (HAS, NICE, IQWiG) as key indicators of the added clinical benefit of those drugs assessed. Here we treated the Trinity Drug Index as one metric and only incorporated the overall score. Another key metric for all cohorts was the drug's route of administration. We ranked all drugs with oral formulations higher than those with intravenous or other formulations to reflect the value created by allowing for outpatient prescriptions. For oncology drugs, we also included ICER's assessment as a key metric. While not applicable to the non-AM comparator and oncology cohorts, we also designated activity against CDC/WHO pathogens as well as automated AST device incorporation as key metrics for AM drugs.

For each cohort, we first sorted all of the metrics into different added clinical benefit categories. Next, we averaged the rank score of metrics comprising an added clinical benefit category for each drug. For example, under the Market Performance added clinical benefit category, if drug X had a rank score of 1 for the automated AST device incorporation metric and a 3 for the Trinity Drug Index commercial score metric, then we calculated the Market Performance added clinical benefit category score for drug X as 2 (= [1+3] / 2). This is equivalent to a weighting routine that assigns a weight of 0.5 to the automated AST device incorporation and the Trinity Drug Index commercial score metrics.

We repeated this process five times for each cohort, such that the metrics were sorted into different combinations of added clinical benefit categories each time, i.e., added clinical benefit category sets 1 through 5 (Table 15), and no single added clinical benefit category has a disproportionate influence on the overall comparative added clinical benefit assessment. The intent of the iteration was to minimize any impact from the manner in which these metrics were grouped on the overall ranking of each drug. For example, if a given drug consistently receives a lower rank score across the different added clinical benefit category divisions, then this increases the degree of confidence in the robustness of the relative ranking of that drug generated by this approach. For each set of added clinical benefit category set 1 through 5, we then computed the

aggregate added clinical benefit score for each drug, which is the simple sum of the calculated added clinical benefit category set scores.[29]

Table 15. Added Clinical Benefit Category Sets Used in Analysis

Added Clinical Benefit Category Set	Added Clinical Benefit Category	Metric
Set 1 - All Metrics (Unweighted)	All Metrics Unweighted	New Molecular Entity
		New Chemical Entity
		Route of Administration
		Annual Number of U.S. Cases (non-AM & oncology)
		Estimated Market Size (AM)
		Number of Drugs for Indication
		Activity against ESKAPE Pathogens (AM)
		Activity against CDC urgent WHO critical pathogens (AM)
		Trinity Drug Index Therapeutic Score
		Trinity Drug Index Commercial Score
		Trinity Drug Index R&D Score
		HAS ACB
		HAS CAV
		NICE
		IQWiG
		AST Device Incorporation (AM)
		QDIP Designation (AM)
		BARDA Funding (AM)
		P&T Community Decision
		IDSA Guideline Inclusion
		ICER Assessment
		Medicaid Coverage
Set 2 - Most Revealing Metrics (Key Metrics)	Most Revealing Metrics (Key Metrics)	Activity against CDC urgent WHO critical pathogens (AM)
		Trinity Drug Index Overall Score
		HAS ACB
		HAS CAV
		NICE
		IQWiG
		AST Device Incorporation (AM)
		ICER Assessment
Set 3 - Non-key, European HTA, Trinity Drug Index, Accessibility, and AM Key Metrics Combination	Non-Key Metrics	Annual Number of U.S. Cases (non-AM & oncology)
		Number of Drugs for Indication
		Estimated Market Size (AM)
		New Molecular Entity
		New Chemical Entity
		Activity against ESKAPE Pathogens (AM)
		QDIP Designation (AM)
		IDSA Guideline Inclusion
		BARDA Funding (AM)
		Medicaid Coverage
		P&T Community Decision
	European HTA	HAS ACB
		HAS CAV
		NICE

[29] Note that in one case we only factored the metrics we found most revealing, or 'key' metrics, into the aggregate score.

Added Clinical Benefit Category Set	Added Clinical Benefit Category	Metric
		IQWiG
	Trinity Drug Index	Trinity Drug Index Overall Score
	Accessibility	ICER Assessment
		Route of Administration
	AM Key Metrics	AST Device Incorporations (AM)
		Activity against CDC urgent WHO critical pathogens (AM)
Set 4 - Market Size, Unmet Need/Novelty, AM Drug Activity, Cost, European HTA, Market Performance, and Guideline/Recommendation Inclusion Metrics Combination	Market Size	Annual Number of U.S. Cases (non-AM & oncology)
		Number of Drugs for Indication
		Estimated Market Size (AM)
	Unmet Need/Novelty	New Molecular Entity
		New Chemical Entity
		Trinity Drug Index Therapeutic Score
		Route of Administration
	AM Drug Activity	QDIP Designation (AM)
		Activity against ESKAPE Pathogens (AM)
		Activity against CDC urgent WHO critical pathogens (AM)
		BARDA Funding (AM)
	Cost	Medicaid Coverage
		Trinity Drug Index R&D Score
		ICER Assessment
	European HTA	HAS ACB
		HAS CAV
		NICE
		IQWiG
	Market Performance	AST Device Incorporation (AM)
		Trinity Drug Index Commercial Score
	Inclusion in Recommendations	IDSA Guideline Inclusion
		P&T Community Decision
Set 5 - Market Value, Pre-approval Assessment, Added Value to Therapy, Clinical Efficacy, Accessibility, and Post-approval Use Metrics Combination	Market Value	Trinity Drug Index Commercial Score
		Estimated Market Size (AM)
		Annual Number of U.S. Cases (non-AM & oncology)
		Number of Drugs for Indication
	Pre-approval Assessment	Trinity Drug Index R&D Score
		BARDA Funding (AM)
		New Molecular Entity
		New Chemical Entity
		QDIP Designation (AM)
	Added Value to Therapy	Trinity Drug Index Therapeutic Score
		HAS CAV
		ICER Assessment
		IQWiG
	Clinical Efficacy	NICE
		HAS ACB
	Accessibility	Medicaid Coverage
		AST Device Incorporation (AM)
		Route of Administration
	Post-approval Use	IDSA Guideline Inclusion
		P&T Community Decision
		Activity against ESKAPE Pathogens (AM)
		Activity against CDC urgent WHO critical pathogens (AM)

Finally, summing the five *aggregate scores*, we arrived at an *overall score* for each drug that allowed us to rank order the drugs in each cohort. This sum is not intended to be a quantitative measure of added clinical benefit, rather a way to reveal which drugs were often ranked high, as represented by smaller sums, and which were ranked low, as represented by larger sums. Table 16 presents this analysis for the AM cohort.

Using the overall score for each drug, we categorized the drugs in each cohort as *high* added clinical benefit, *intermediate* added clinical benefit, or *indeterminate* added clinical benefit. For the drugs with the least number of available metrics, we determined that there was insufficient data for a reliable added clinical benefit assessment. Therefore, we categorized these drugs with insufficient data as having an *indeterminate* added clinical benefit. For the drugs with more metrics available, those with the highest overall scores were placed in the *high* added clinical benefit group, and others were placed in the *intermediate* added clinical benefit group. The analysis implicitly uses the availability of a particular metric as a measure of added clinical benefit in and of itself. In other words, if a drug has an HTA, has been incorporated into an automated AST device, assigned a Trinity Drug Index score, etc., it must have a higher added clinical benefit than one that lacks these types of assessments. However, lack of these assessments may not necessarily be due to lower added clinical value if the drug has not been on the market for an extended period to allow for the assessments to be performed.

Table 16. Evaluation of Comparative Added Clinical Benefit - Detailed Results for the AM Drug Cohort

Added Clinical Benefit Category Set 1		Added Clinical Benefit Category Set 2		Added Clinical Benefit Category Set 3		Added Clinical Benefit Category Set 4		Added Clinical Benefit Category Set 5		Sum Across All Category Sets		
Trade Name	Aggregate Score 1 [a]	Trade Name	Aggregate Score 2 [a]	Trade Name	Aggregate Score 3 [a]	Trade Name	Aggregate Score 4 [a]	Trade Name	Aggregate Score 5 [a]	Trade Name	Overall Score [a]	Number of Metrics Available
Zerbaxa	55	Vabomere	15	Sivextro	22	Zerbaxa	13	Zerbaxa	17	Zerbaxa	123	31
Sivextro	58	Zerbaxa	15	Zerbaxa	23	Avycaz	14	Avycaz	19	Avycaz	135	33
Avycaz	62	Avycaz	16	Orbactiv	23	Sivextro	16	Sivextro	19	Vabomere	142	28
Orbactiv	63	Sivextro	31	Avycaz	24	Vabomere	16	Vabomere	20	Sivextro	146	28
Vabomere	65	Dalvance	33	Dalvance	25	Orbactiv	20	Orbactiv	21	Orbactiv	162	28
Dalvance	66	Xerava	33	Vabomere	26	Baxdela	20	Dalvance	21	Dalvance	165	28
Baxdela	80	Teflaro	34	Teflaro	32	Dalvance	20	Baxdela	28	Baxdela	194	21
Nuzyra	82	Baxdela	34	Baxdela	32	Nuzyra	21	Teflaro	28	Nuzyra	203	21
Xerava	87	Orbactiv	35	Nuzyra	34	Xerava	23	Nuzyra	29	Xerava	209	25
Teflaro	92	Nuzyra	37	Xerava	36	Teflaro	23	Xerava	31	Teflaro	210	23
Zemdri	107	Zemdri	40	Vibativ	42	Vibativ	28	Vibativ	36	Zemdri	256	21
Vibativ	113	Vibativ	45	Zemdri	43	Zemdri	29	Zemdri	37	Vibativ	264	22

[a] Lower scores indicate higher rank.

5.1.3 Sensitivity Analysis Involving European HTAs

Drug industry experts noted that only drugs that explicitly apply for approval in Europe are included on European HTAs (HAS, NICE, and IQWiG above). Additionally, small U.S. drug makers must have partners to sponsor marketing in Europe, meaning that it is possible for a drug to gain approval in Europe but not have any marketing or sales on the continent. Since the developers of those drugs that were not included on HTAs either did not apply for European approval or the drugs have not been on the market long enough for inclusion, we repeated the full clinical effectiveness assessment, excluding the European HTA-related metrics to gauge the robustness of our clinical effectiveness divisions as well as the sensitivity of our overall results to this metric. We then compared the relative drug rankings of the original analysis to the results of the sensitivity analysis. This sensitivity analysis is presented in the following section.

5.2 RESULTS

The three added clinical benefit groups, i.e., high, intermediate, and indeterminate, reveal overall comparative added clinical benefit but are not intended for a quantitative ranking of drugs within each group. The comparative added clinical benefit of the drugs in the three cohorts based on this methodology is presented in Table 17 along with the results from the sensitivity analysis discussed in Section 5.1.3. Our discussions with federal experts and individuals with prescribing experience largely corroborate these results.

While the year of approval was not part of the ranking process, it is nonetheless an important factor to consider in interpreting these results. From Table 16 and Table 17, we can see that all 3 AM drugs approved in 2018 did not have enough available information for reliable results, placing them in the indeterminate category. More recently approved drugs may not have had enough time on the market to be considered in guidance or HTAs, meaning the methodology may tend to favor AM drugs that were approved earlier and thus have more data available. We note however, that this problem did not appear as prevalent in the non-AM comparator and oncology cohorts, where drugs from 2018 were placed in the high value division in either the baseline or sensitivity analysis.

Even though only a select number of drugs may have applied for approval in Europe, our sensitivity analysis produced comparable results to the baseline analysis. Without the European clinical assessment data, the majority of drugs remained in the same comparative added clinical benefit group, with only a few moving from intermediate to high or vice versa. The stability of the ranking for drugs such as Zerbaxa and Avycaz, Veltassa and Lokelma, and Rubraca and Ibrance that are at the top in both analyses for the three cohorts, respectively, suggests that the methodology is fairly robust to changing underlying metrics and/or how metrics are grouped to form added clinical benefit category sets.

Many of the metrics used in this assessment, such as European HTAs and the Trinity Drug Index Therapeutic score, are designed to assess the added clinical benefit of a drug using information either at or a few years after market approval. In cases where antimicrobial stewardship and limited numbers of difficult-to-treat infections may make Phase 3 superiority trials difficult or not possible, the developed methodology integrates readily available public information to provide a quick, transparent, and consistent means of assessing comparative added clinical benefit.

5.3 LIMITATIONS

The methodology has several limitations. First, due to insufficient public health metric data for more recently approved drugs, the results may skew towards rating older drugs higher because the methodology implicitly treats the availability of a particular metric as a measure of added

clinical benefit in and of itself. However, the absence of one or more metrics for a given drug may not necessarily be due to lower added clinical benefit of that drug if the drug has not been on the market long enough. There may also be other reasons, e.g., the physical properties of an AM compound may not allow it to be incorporated into automated AST devices. Second, the five added clinical benefit category sets were created using professional judgement and expert opinion but are not exhaustive of ways to categorize these metrics.

Table 17. Comparative Added Clinical Benefit Groups for AM, non-AM Comparator, and Oncology Drugs

Drug Cohort	Added Clinical Benefit Group	Baseline Assessment		Sensitivity Analysis	
		Trade Name	Approval Year	Drug Name	Approval Year
AM	High	Zerbaxa	2014	Avycaz	2015
		Avycaz	2015	Zerbaxa	2014
		Vabomere	2017	Sivextro	2014
		Sivextro	2014	Orbactiv	2014
	Intermediate	Orbactiv	2014	Dalvance	2014
		Dalvance	2014	Vabomere	2017
		Teflaro	2010	Teflaro	2010
	Indeterminate	Baxdela	2017	Baxdela	2017
		Xerava	2018	Xerava	2018
		Nuzyra	2018	Nuzyra	2018
		Zemdri	2018	Zemdri	2018
		Vibativ	2009	Vibativ	2009
Non-AM	High	Veltassa	2015	Veltassa	2015
		Lokelma	2018	Lokelma	2018
	Intermediate	Bridion	2015	Bridion	2015
		Giapreza	2017	Giapreza	2017
	Indeterminate	Surfaxin	2012	Surfaxin	2012
		Vistogard	2015	Vistogard	2015
Oncology	High	Rubraca	2016	Ibrance	2012
		Zelboraf	2011	Rubraca	2016
		Ibrance	2012	Erivedge	2012
		Erivedge	2012	Braftovi	2018
	Intermediate	Stivarga	2012	Zelboraf	2011
		Darzalex	2015	Stivarga	2012
		Jevtana	2010	Cyramza	2014
		Braftovi	2018	Darzalex	2015
		Yondelis	2015	Yondelis	2015
		Portrazza	2015	Jevtana	2010
		Yescarta	2017	Portrazza	2015
		Cyramza	2014	Yescarta	2017
	Indeterminate	Cometriq	2012	Cometriq	2012
		Vitrakvi	2018	Vitrakvi	2018

6 MARKET PERFORMANCE ANALYSIS

The last component to garnering a comprehensive view on the markets for the three drug cohorts was to investigate their relative commercial performance. After determining the comparative added clinical benefit of each drug, we hypothesized that in general, if markets function as expected, drugs with higher added clinical benefit relative to other drugs in the same cohort would perform better in the market upon launch and beyond.

As noted previously, AM drugs face unique challenges both before and after market entry. First, antimicrobial stewardship has resulted in decreased prescribing of AM drugs in general, but especially for newer drugs because they are often reserved for last-line treatment. Even among those that do get prescribed, many are only prescribed for short-term use, stifling any significant market returns (Duke Margolis Center for Health Policy, 2019; Rex, et al., 2014; Piddocck, 2012). Moreover, physicians often prefer prescribing less expensive generic drugs, especially when new AM drugs are approved based on noninferiority instead of superiority trials (Duke Margolis Center for Health Policy, 2019; Luepke & Mohr, 2017). The diagnostic-related group (DRG) based reimbursement system in the inpatient setting further incentivizes the use of older cheaper generic versions of the AM drugs.

All of these factors have contributed to the reported slow market uptake for new AM drugs in recent years. In their most recent report, Carr and Stringer (2019) referred to the sales of several AM drugs that entered the market in 2018 as being mostly 'disappointing'. In the analysis described below, we pull international sales data on all of the drugs to analyze whether the sales for the drugs in the AM cohort are lower than the other cohorts and not reflective of their comparative added clinical benefit.

6.1 METHODOLOGY AND DATA SOURCES

6.1.1 IQVIA MIDAS Database

We used IQVIA MIDAS data to examine the global sales of each drug selected. The IQVIA MIDAS database includes estimates of all drugs sold (in dollars and units) directly from drug manufacturers and indirectly through wholesalers into retail and non-retail channels of distribution in over 90 countries' healthcare markets. The database is considered the industry standard for measuring pharmaceutical sales. The data measures sales at actual transaction prices but does not capture off-invoice discounts, such as rebates to plans or pharmacy benefit managers (PBMs) in the U.S., that reduce the amount of money received by manufacturers. IQVIA uses a proprietary algorithm that relies on regional-, sectoral-, and distribution-channel-specific factors to project total global sales volume from the sample of data that they collect on a regular basis.

We obtained a custom tabulation from the MIDAS database for each drug in our cohorts, querying by generic name to identify any international sales under a different trade name. The data included quarterly sales (in $ US, kilograms, and units) for each drug by country from Q1 2007 through Q1 2021. Some products had sales in Europe before FDA approval for the U.S. market, meaning that some products had sales before 2010, the earliest starting in Q1 of 2007. However, most drugs saw U.S. sales one to two quarters after obtaining FDA approval.

6.1.2 Comparing Sales Against Overall Added Clinical Benefit Score

After collecting all relevant sales data for the drugs, we aimed to test our hypothesis that drugs with higher comparative added clinical benefit scores would generally have better market sales by plotting the sales of each drug against its overall comparative added clinical benefit score. While the overall comparative added clinical benefit score is not a stand-alone measure of the real-world clinical benefit of a drug over other therapies, the score embodies the comparative clinical value of each drug, based on our added clinical benefit framework, to compare to sales. We note that the added clinical benefit scores are not comparable across the three cohorts.

Given that each drug has been on the market for a different length of time, we needed to normalize sales using a standard length of time to appropriately compare the drugs in a given cohort. The duration for those drugs that have been on the market for the shortest amount of time as of Q1 2021 (Nuzyra and Yescarta) among all drugs included in this analysis was 9 quarters. Thus, we calculated each drug's first 9 quarters of sales to normalize our sales variable before

comparing this value to the drug's overall comparative added clinical benefit score. There are a variety of factors, such as the number of countries the drug is approved and marketed in, that influence a drug's market uptake, and hence its market success during the initial couple of years post launch. To smooth out those differences, the ideal comparison is between a drug's peak-year sales, the level at which the sales plateau, to its overall comparative added clinical benefit score. An example of peak-year sales can be seen for Teflaro in Figure 7 below. The first 16 quarters of sales show growth in each quarter, and then after Q17, the sales appear to even out and fluctuate between $36 and $42 million. Since data were unavailable for peak-year sales for all of the drugs selected, we used total first 9 quarter sales as a proxy. Table 18 presents the mean and median 9 quarter sales values as well as their range across the drugs in each cohort. On average, the sales are similar for the drugs in the non-AM comparator cohort and the AM cohort drugs. In contrast, oncology cohort drug first 9 quarter sales are exponentially higher on average than the drugs in the AM and non-AM comparator cohorts.

Table 18. Descriptive Statistics of First 9 Quarters IQVIA MIDAS Sales (in $ Million) for AM, Non-AM Comparator, and Oncology Cohort Drugs

Drug Cohort	Mean ($ millions)	Median ($ millions)	Range ($ millions)
AM	$34.43	$28.07	$1.24 (Zemdri) - $75.79 (Avycaz)
Non-AM Comparator	$34.49	$33.07	$0.57 (Surfaxin) - $88.02 (Lokelma)
Oncology	$587.89	$271.80	$18.21 (Rubraca) - $3,551.16 (Ibrance)

After plotting the total of the first 9 quarters of sales against the overall comparative added clinical benefit score for each cohort of drugs, we fit an exponential line to the data. Similar to the sensitivity analysis related to European HTAs described in Section 5.1.3, we repeated the fit both with and without HTA data. These exponential fits are meant to serve as visual guides to help evaluate the relationship between sales and comparative added clinical benefit. Partly due to our small sample sizes, it is not feasible to conduct a rigorous statistical analysis to estimate this relationship. Thus, we only report the simple Pearson correlation coefficients between 9-quarter sales and overall comparative added clinical benefit scores in the graphical displays.

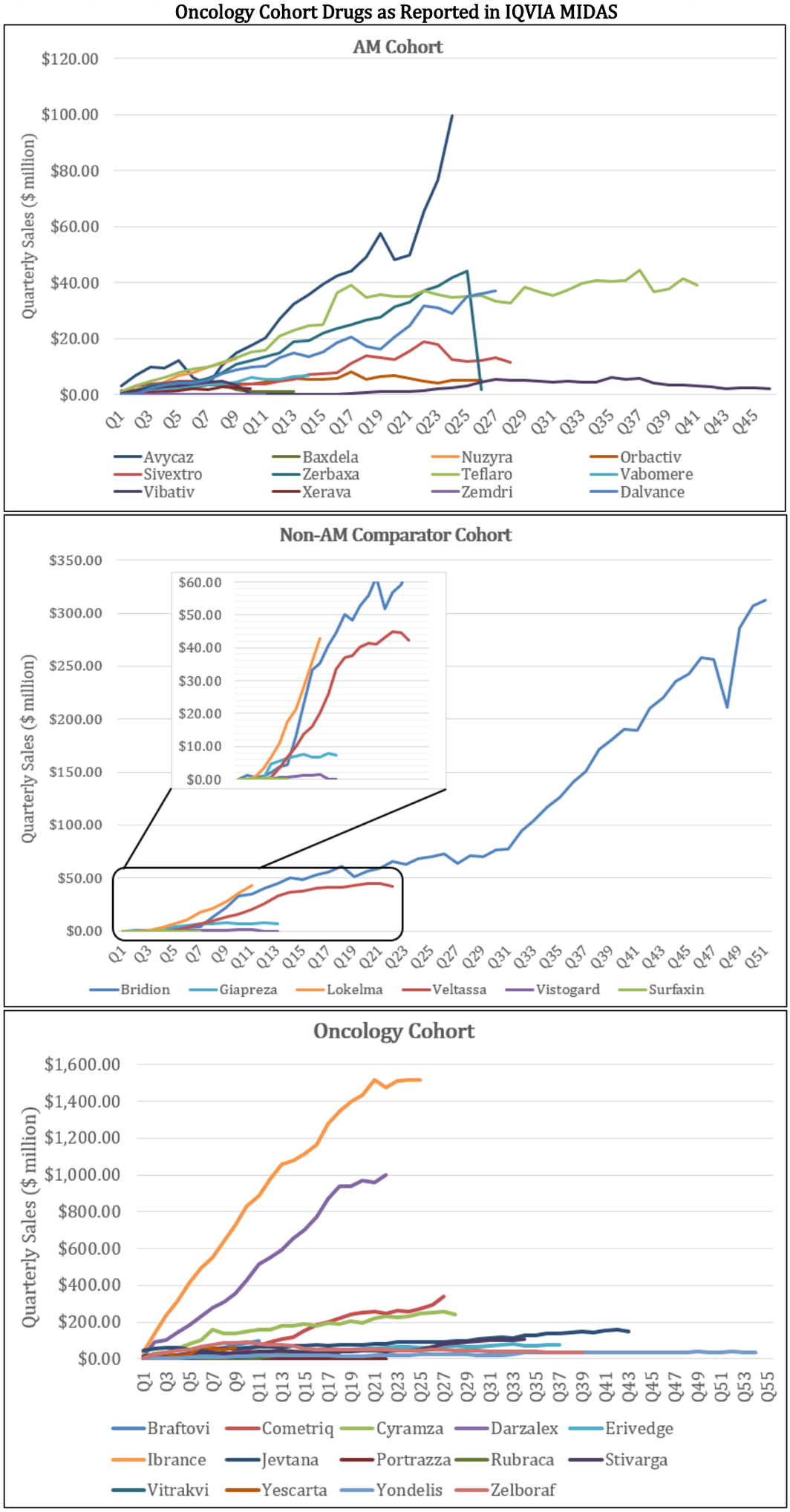
6.2 RESULTS

6.2.1 Quarterly Global Sales Since Launch

The quarterly sales, summed globally, are shown in Figure 7 (not cumulative). Q1 represents the first quarter the drug was on the market, so drugs approved more recently will have fewer quarters of data available.

The first thing to note about these three figures is the differences in scales on the y-axis. The highest sales in one quarter for the AM cohort were $99.54 million for Avycaz in its 24th quarter on the market, which was Q1 2021. Most other AM drugs reached between $5 and $10 million in quarterly sales after 1-2 years and up to $10 to $40 million in quarterly sales after about 5 years on the market. While Avycaz's sales were still much lower than the non-AM comparator cohort drug Bridion's with $311.77 million in sales in its 51st quarter (i.e., Q1 2021), the rest of the non-AM comparator cohort had sales comparable to the AM cohort in the first 1-2 years on the market. However, the non-AM comparator cohort, excluding Bridion, have more recently approved drugs than the AM cohort and thus fewer years of data, but Veltassa does surpass $40 million in quarterly sales after its 4th year on the market. The sales for many drugs in the oncology cohort dwarf the sales for those in the other two cohorts. The highest quarterly sales for the oncology cohort were $1,515.75 million for Ibrance in its 21st quarter (i.e., Q1 2020). The first 1-2 years on the market for many oncology drugs saw quarterly sales up to $20 - $50 million while the top performing drugs soared up to $100 to $1000 million.

Figure 7. Quarterly Global Sales Since Launch (in $ Million) for AM, Non-AM Comparator, and Oncology Cohort Drugs as Reported in IQVIA MIDAS



Nearly all drugs in all three cohorts showed increasing sales by quarter through the end of the available years of data; indicating that these data likely miss the period of 'peak-year sales,' or the maximum annual sales a drug will reach before plateauing/decreasing as other drugs populate the market. Depending on the indication and the availability of other drugs for that indication, the peak-year sales may come a few years after approval, e.g., Vibativ, which stabilized at around $5 million 27 quarters after entering the market before decreasing around quarter 37. On the other hand, a drug may not reach peak-year sales for many years, as in the case of Bridion, which continue to increase sharply through 51 quarters on the market. Even though many of the drugs in this analysis have not reached their peak-year sales yet, the available data reveal the relative magnitude of average sales among the three cohorts. We also note that the effects of the COVID-19 pandemic in 2020, which may have affected the sales trajectories of not only AM but all drugs, were not considered for this analysis.

6.2.2 First 9 Quarters of Sales versus Overall Comparative Added Clinical Benefit Scores

Figure 8 through Figure 10 below present the cumulative 9 quarters of global sales since launch for each drug against the overall comparative added clinical benefit score we assigned in our analysis both with and without HTA data. We also fit a trend line to visually depict the relationship between sales and comparative added clinical benefit. The x-axis in Figure 8 through Figure 10 has been flipped for legibility because in our analysis, lower scores reflect higher added clinical benefit.

Within the AM cohort, drugs with higher overall comparative added clinical benefit scores tend to have higher early market sales. The trend lines for both analyses with and without HTA data show this correlation between overall comparative added clinical benefit score and cumulative sales from the first 9 quarters on the market. Given the small sample size, however, the estimated fits for all cohorts are not very robust and have large confidence bounds around the parameter estimates as expected. Both the non-AM and oncology cohorts followed the same trend observed for AM drugs. The trend lines for these cohorts both with and without HTA data show a positive correlation between higher comparative added clinical benefit (i.e., lower overall score) and higher cumulative sales during the first 9 quarters on the market, indicating that the HTA evaluation compared to our score did not provide additional explanatory power. The results show that the drug with the highest first 9 quarters of sales was consistently placed in the high comparative added clinical benefit group for all three cohorts and in all sensitivity analyses. However, while the overall trend was present when each cohort was analyzed collectively, there were still numerous outliers or drugs that did not display the relationship between added benefit and sales. For example, Veltassa and Rubraca had uncharacteristically low early market sales when compared to the rest of the non-AM and oncology cohorts, respectively. Rubraca and Ibrance are both ranked very highly in the oncology cohort, but these two drugs also represent the lowest and highest first 9 quarters of sales in the oncology cohort, respectively. We were not able to identify a definitive cause for Rubraca and Veltassa's low sales, but the case of Veltassa does highlight the limitations of using only the first 9 quarters of sales data. From Figure 7, Veltassa's quarterly sales start increasing at a faster rate after the first year, while Vistogard, with the lowest overall comparative clinical benefit score, continues to have very low sales for the next few years.

6.3 LIMITATIONS

This analysis was limited by lack of sales data over sufficiently long time period. From Figure 7, we see that most drugs take a few years for their sales to stabilize in the market. Even then, many of the drugs in our cohorts do not appear to have reached their peak-year sales within the years of available data from IQVIA. Therefore, since we were only able to use data from the first 9 quarters of sales, any trends in the data should be viewed with this caveat.

Figure 8. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – AM Cohort

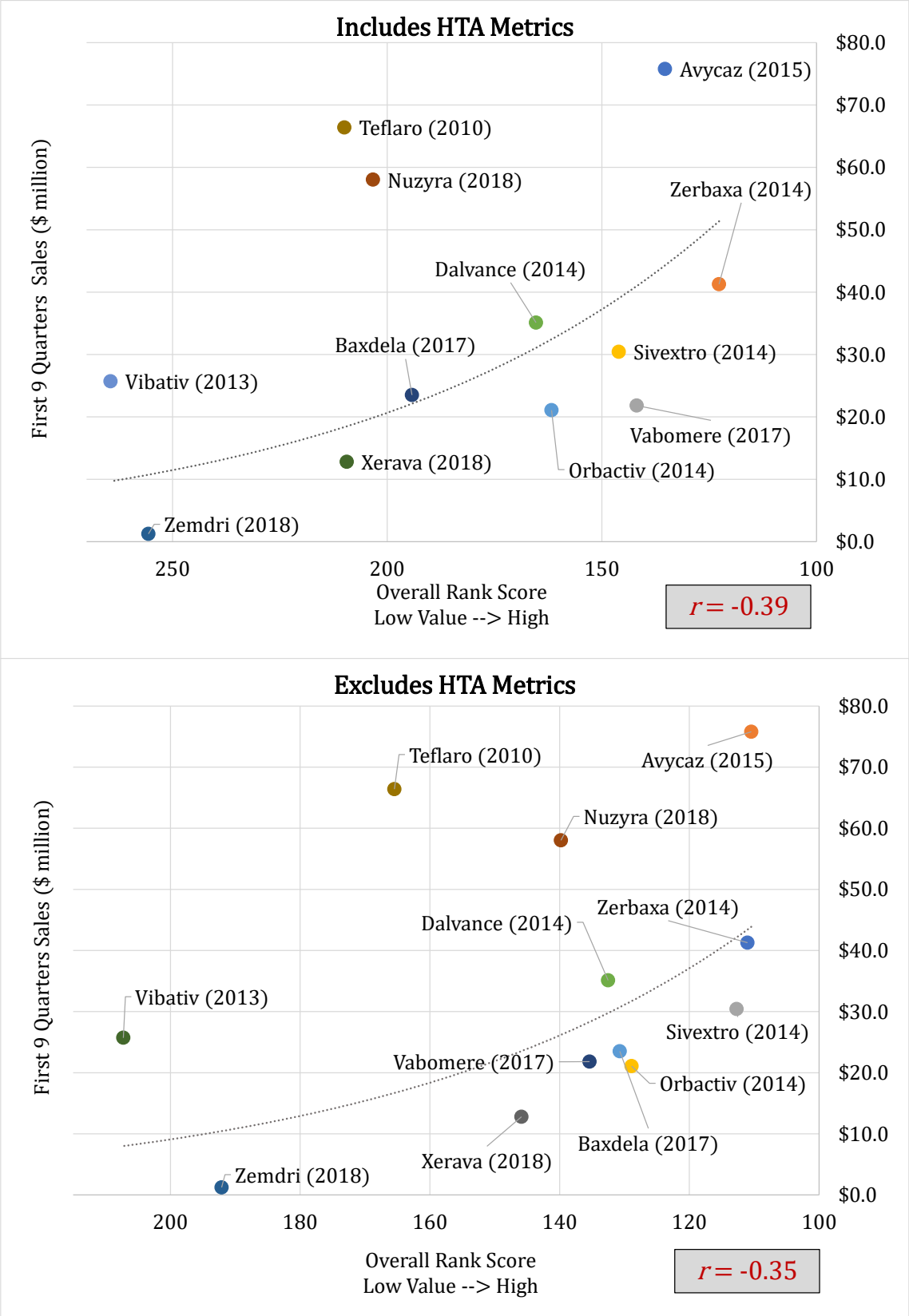
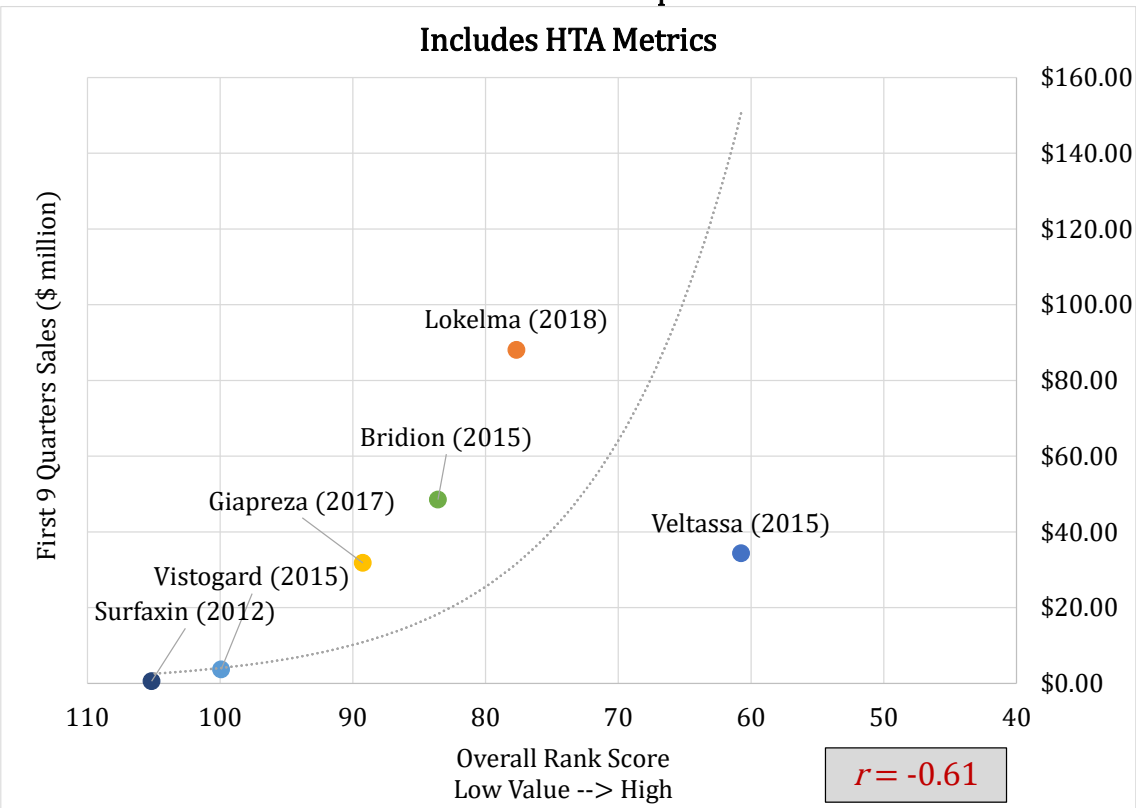


Figure 9. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – Non-AM Comparator Cohort



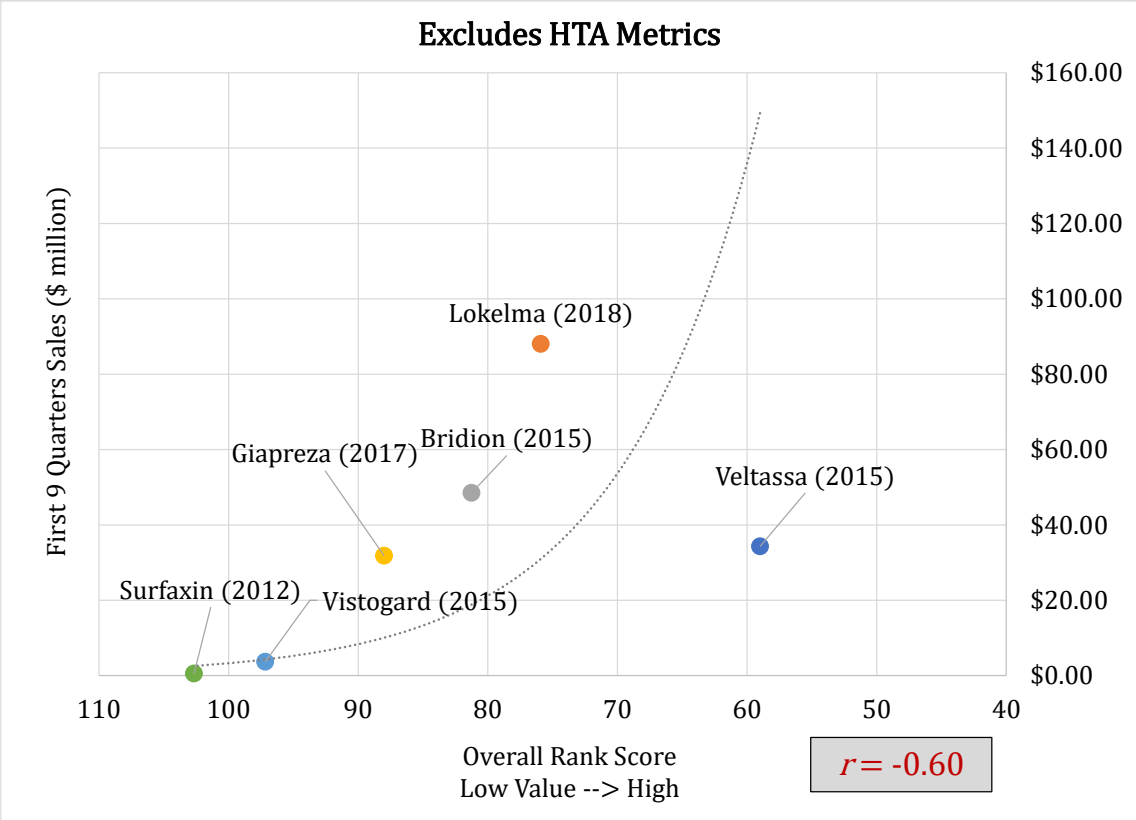
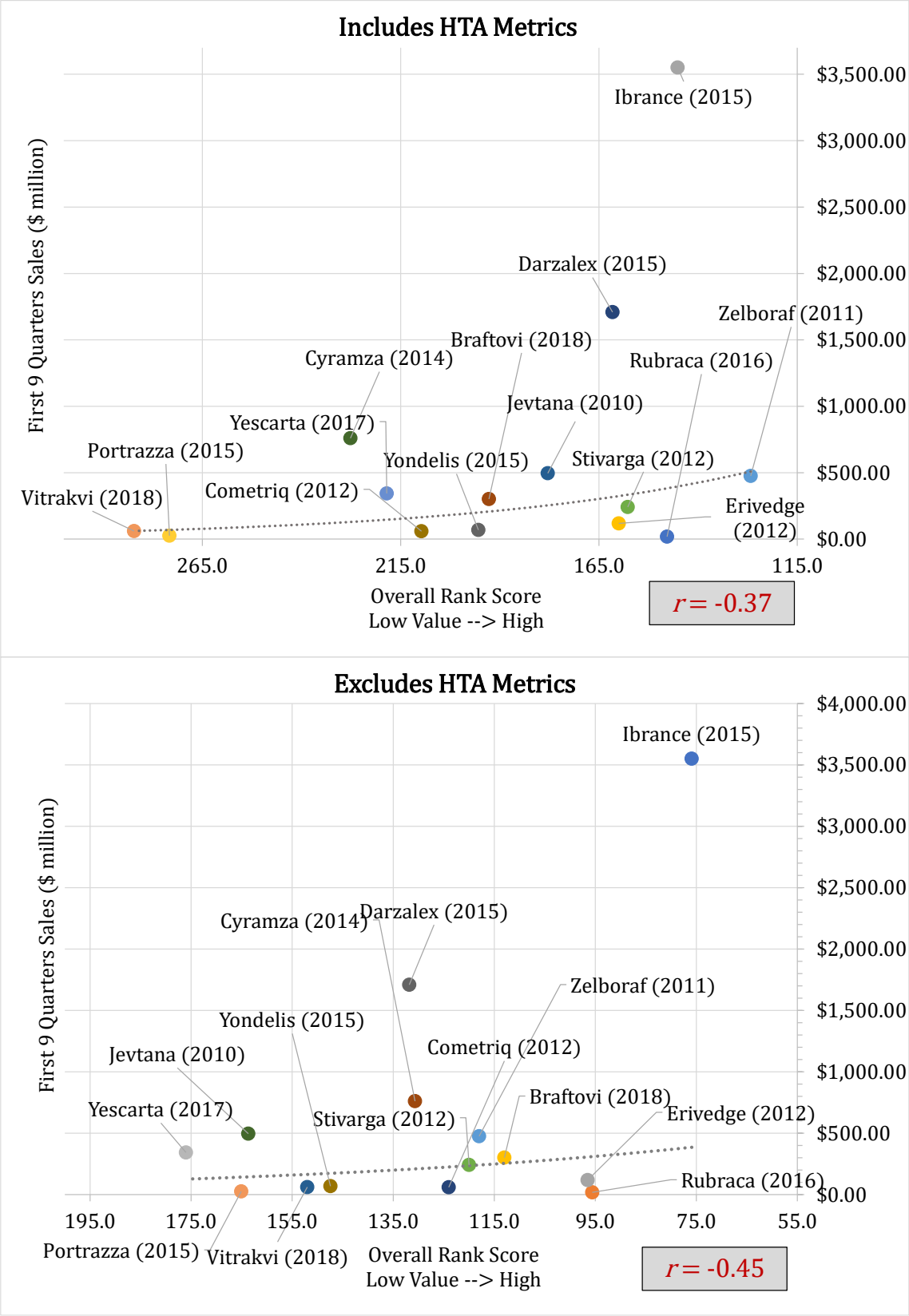


Figure 10. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – Oncology Cohort



6.4 SENSITIVITY ANALYSIS

Several researchers noted that drugs marketed by large biotechnology companies tend to have better sales than those marketed by small companies. Large companies have significantly more financial resources, well-trained large sales teams, global presence, and knowhow to navigate marketing and reimbursement requirements in different regions of the world. All of these factors can affect market uptake of new drugs. A recent analysis by McKinsey & Company (2021) evaluated the success of product launches between 101 experienced and 28 first-time launchers for drugs approved by FDA from 2014 through 2017. They found that 39 percent of first-time launchers exceed analysts' prelaunch sales forecasts, compared to 49 percent of experienced launchers. While this difference is not sizable, it could be significant. Therefore, we conducted a sensitivity analysis to see if company size alters the relationship between overall comparative added clinical benefit score and first 9-quarters sales across all three drug cohorts. For the oncology cohort, we performed an additional sensitivity analysis where we examined whether orphan drug designation influences this relationship. Drugs that receive orphan status receive seven years of marketing exclusivity, waiver of PDUFA fees, and a 25 percent tax credit for clinical costs incurred for the development of the drug. A study by America's Health Insurance Plans (2019) found that orphan drugs were 25 times more expensive than other drugs. Since 9 out of the 13 drugs in the oncology cohort were orphan drugs, we wanted to see if we would observe a different relationship between overall comparative added clinical benefit score and first 9 quarters of sales within this subset.

Figure B - 1 through Figure B - 6 in Appendix B present the results of our sensitivity analysis. We find that the relationship between overall comparative added clinical benefit score and first 9 quarters of sales is fairly robust; drugs with higher overall comparative added clinical benefit scores tend to have higher early market sales on average.

7 DISCUSSION AND CONCLUSION

Looking at the results of the development cost, comparative added clinical benefit, and market performance analyses can help us form a picture of the overall market returns for current and future AM drugs.

We see that the development costs in each cohort vary significantly by drug, but the median expected capitalized development and approval costs were highest for oncology drugs ($3,123.6 million dollars) and lowest for AM drugs ($1,507.0 million). However, the mean and median of the cumulative first 9 quarters of sales for drugs in the oncology cohort were $587.89 and $271.80 million, but only $34.43 and $28.07 million for the AM cohort of drugs. If the cost of developing an AM drug is about a factor of 2 less than an oncology drug, but the returns are nearly a factor of 10 less than an oncology drug in the first year, this would corroborate the concern of many manufacturers and experts that the relatively poor returns on investment for AM drugs make it very difficult to sustainably bring new drugs to market (Rex 2014, Piddock 2011, Stergiopoulos 2018, Duke Margolis Center for Health Policy 2019). As discussed in Section 4.4, when we account for the variety of push incentives, such as R&D grants through U.S. government and other public-private partnership programs that several recent AM drug developers have benefited from, the estimated development and approval costs for select AM drugs are significantly lower than those drugs in the non-AM comparator and oncology cohorts, for which similar incentives are not available. If such incentives have the potential to reduce development costs incurred by the drug developers between 80 to 90 percent, then developing an AM drug, on average, is more than 13 (= $3,123.6 million / [(1- 0.85 percent) × $1,507.0 million]) times cheaper compared to an oncology drug to the developer. Then, one can also argue that the slow market uptake and low returns in early years of marketing may not be as detrimental from the same perspective. When evaluating

the cost of drug development from a societal perspective, the source of funding is irrelevant. That said, the goal of this study is to evaluate the returns to the drug manufacturer. In that sense, it does matter who incurs these costs. Grants that do not have to be paid back offset private costs and thereby improve drug developer returns significantly. However, this improvement in overall returns may still be insufficient to keep a small developer that is dependent on the revenues from a single marketed drug financially viable or desirable as an acquisition target by big pharma.

Interestingly, the viability of non-AM comparator cohort of drugs appears to be very similar to the AM cohort. The non-AM comparator cohort of drugs had, on average, higher development costs than the AM cohort, and low early market sales at $34.49 (average) and $33.07 million (median). It does, however, appear that AM drugs and non-AM comparator drugs that are used in inpatient settings and thus are subject to DRG-based reimbursement both suffer from low revenues compared to oncology drugs.

Due to limitations of only using the first 9 quarters of sales data and small sample sizes, the relationship between added clinical benefit and early market sales is not very robust. However, the data show that overall, drugs with higher overall comparative added clinical benefit scores tend to have higher early market sales compared to other drugs in the same cohort on average. There are, however, exceptions to this. For example, in the oncology cohort, Darzalex, a multiple myeloma drug, has an overall comparative clinical benefit score of 162 which is 14 points higher than that of Rubraca, a drug for recurrent ovarian and metastatic prostate cancers, but has first 9 quarter sales of $1,710 million which is $1,691million higher than that of Rubraca. This could partly be due to the ordinal ranking method we employed which accounts for whether a drug X ranks higher/lower than a drug Y in the same cohort but not by how much higher/lower. In other words, drug X with an annual patient population estimate of 100,000 could receive a rank of 3, followed by drug Y with a rank of 4 and an annual patient population estimate of 5,000, and drug Z with a rank of 5 and an annual patient population estimate of 1,000. In this example, even though drug X's market size is 20 and 100 times larger than that of drugs Y and Z, respectively, its ranking does not reflect the large difference in the evaluation metric estimates. Even with this limitation, however, we observed that in each cohort, the drug with the highest cumulative 9-quarter sales was categorized into the high comparative added clinical benefit group consistently (Table 17). This indicates that our comparative added clinical benefit assessment algorithm is relatively robust and informative.

Overall, our analysis shows that the early market returns do seem to reflect the overall comparative added clinical benefit of the drug compared to other drugs in the market within each cohort examined. There are exceptions to this, however, in all three cohorts as noted above. It is not, however, possible to infer whether oncology drugs have better market performance because they are of higher added clinical benefit than AM and non-AM comparator drugs. The notable difference in market performance for oncology drugs is likely due to several factors. First, oncology drugs are not subject to the DRG-based reimbursement that keeps pricing for drugs administered in the hospital setting (i.e., Part A drugs) such as the AM and non-AM comparator drugs, in check. Second, the treatment durations for oncology drugs are much longer than those for AM and non-AM comparator drugs with many patients remaining on these medications for years. Third, patient populations for most of the oncology drugs in this cohort also are larger than most AM drugs. For example, the estimated number of metastatic locally advanced basal cell carcinoma cases that Erivedge is approved to treat is close to 3 million annually whereas the number complicated urinary tract infections that can be treated by Zemdri is only around 30,000 per year.

There is significant heterogeneity in commercial market performance among different therapy areas that reflect differences in patient populations, treatment durations, where these drugs are used (outpatient versus inpatient), and DRG-based reimbursement that incentivizes cost containment in hospitals. Despite this heterogeneity, our analysis suggests that markets tend to

reward comparative added clinical benefit within each therapy area (e.g., bacterial infections, cancer, etc.) but that the value ascribed to that benefit per patient and per population vary by at least an order of magnitude between DRG price limited Part A drugs (AM and non-AM) and protected class, usually Part B, drugs (oncology).

Additional research following on this analysis could explore the post approval costs that developers incur to conduct additional studies in pediatric and special adult populations, surveillance, pharmacovigilance, marketing, and manufacturing , relative to the product sales revenues generated in the same time frame. Gaining a better understanding of the relationship between post approval costs and product sales revenues could help further inform the discussion of "pull" incentives for AM drugs. Another avenue for future research could be to extend the comparative added clinical benefit assessment methodology to additional types of products to test the robustness of the relationship between comparative added clinical benefit and product sales. Understanding the future economic burden of AMR would also help to evaluate the strengths and weaknesses of the existing pipeline of AM drugs, and the potential need for additional incentives.

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APPENDIX A: INFORMATION COMPILED ON DRUGS SELECTED FOR ANALYSIS

The following notes apply to all tables in this appendix.

[a] ESKAPE pathogens include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species

[b] CDC urgent threat pathogens are: *Clostridioides difficile*, carbapenem-resistant *Enterobacteriaceae* (CRE), and drug-resistant *Neisseria gonorrhoeae*.

[c] WHO critical threat pathogens are: carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant ESBL-producing *Enterobacteriaceae*.

[d] Therapeutic value was based on an evaluation of the incremental clinical value in comparison to the standard of care (SOC) at the time of launch, the fulfillment of unmet need, and level of innovation.

[e] Commercial performance was determined by the cumulative sales to date, projected future sales, and performance relative to analyst forecasts.

[f] The R&D investment was based on the cost of randomized clinical trials (RCTs) and duration of clinical development. Trial cost was estimated based on the total number of enrolled patients (from the drug's NDA or BLA filing with approximate patient numbers from Post Market Requirements drawn from clinicaltrials.gov) and then adjusted for per-patient trial costs using Parexel's biopharmaceutical statistical sourcebook. Clinical development duration was calculated based on time from the first clinical study on clinicaltrials.gov until FDA approval.

[g] The overall score represents the weighted average of therapeutic value, commercial performance, and R&D investment scores, where the weights are 40 percent, 40 percent, and 20 percent, respectively.

[h] Based on Carr and Stringer, (2019).

[i] The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low, or insufficient for reimbursement for hospital use.

[j] The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value"

[k] Inpatient treatment course estimates from Alan Carr's (2019) Antibiotic and Antifungal Update.

[l] The information presented for Vibativ (telavancin) is for the HABP/VABP indication and does not include that for cSSSI for which the drug received initial FDA approval for in September 2009 (outside of our study period). Thus, development and approval costs presented are underestimated as they do not incorporate the clinical work that the company would have had to undertake for initial FDA approval for cSSSI.

[m] The physical properties of Orbactiv (oritavancin) preclude incorporation into an automated AST device.

Table A - 1. Avycaz (ceftazidime-avibactam) Information

Drug Name	**Avycaz (ceftazidime-avibactam)**		
Study Cohort	Antimicrobial		
Label Indications	Indicated for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus spp.*, and *Pseudomonas aeruginosa* in patients 18 years or older. Also indicated for the treatment of complicated intra-abdominal infections (cIAI) in combination with metronidazole and complicated urinary tract infections (cUTI) in pediatric patients 3 months and older.		
Original Company	Actavis		
Current Company	Allergan		
FDA Approval Date	February 2015		
FDA Submission Classification	Type 1 - New Molecular Entity and Type 4 - New Combination		
Type	Small molecule		
Class	Cephalosporin/beta-lactamase inhibitor		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Both		
Preclinical Information	Duration (in Months)		89
Clinical Information	Phase 1	Number of Studies	8
		Total Enrollment (All Studies)	310
		Total Phase Duration (in Months)	44.9
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	204
		Total Phase Duration (in Months)	8.0
	Phase 3	Number of Studies	6
		Total Enrollment (All Studies)	3,532
		Total Phase Duration (in Months)	45.9
FDA Review Information	Duration (in Months)		8.0
Post-approval Information	Phase 4	Number of Studies	1
		Total Enrollment (All Studies)	12
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	No		Rank = 5
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 9
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	Yes		Rank = 1

Drug Name	Avycaz (ceftazidime-avibactam)		
Approximate Annual Number U.S. Cases	1.1 million		Rank = 3
Estimated Inpatient Market Size [k]	28,035		Rank = 8
Number of Drugs Available for Indication(s) in the U.S.	39		Rank = 10
Trinity Drug Index	Therapeutic Score [d]	4.2	Rank = 1
	Commercial Score [e]	1.2	Rank = 1
	R&D Score [f]	2.5	Rank = 2
	Overall Score [g]	2.7	Rank = 2
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	Minor (IV)	Rank = 3
British Health Assessment (NICE) *	Currently developing guidelines		Rank = 4
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	Yes	Rank = 1
	MicroScan	Yes	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	HAP/VAP Guidelines Active against Pseudomonas, effectiveness against VAP yet to be determined		Rank = 3
P&T Community Decision *	Appropriate choice for last-line treatment / high cost		Rank = 5
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	PA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$171.0
	Expected Capitalized Cost (in $ Million 2018)		$1,356.1
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		135
	Without European Health Technology Assessment (HTA) Scores		110
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$75.79		

Table A - 2. Zemdri (plazomicin) Information

Drug Name	Zemdri (plazomicin)		
Study Cohort	Antimicrobial		
Label Indications	ZEMDRI is an aminoglycoside antibacterial indicated for the treatment of patients 18 years of age or older with Complicated Urinary Tract Infections (cUTI) including Pyelonephritis. As only limited clinical safety and efficacy data are available, reserve ZEMDRI for use in patients who have limited or no alternative treatment options. To reduce the development of drug-resistant bacteria and maintain effectiveness of ZEMDRI and other antibacterial drugs, ZEMDRI should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms.		
Original Company	Achaogen		
Current Company	Cipla USA		
FDA Approval Date	June 2018		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Aminoglycoside		
Spectrum (Broad/Narrow)	Narrow spectrum		
Gram -negative, gram-positive, or Both	Gram-negative		
Preclinical Information	Duration (in Months)		93.1
Clinical Information	Phase 1	Number of Studies	6
		Total Enrollment (All Studies)	189
		Total Phase Duration (in Months)	104.0
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	145
		Total Phase Duration (in Months)	20.7
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	678
		Total Phase Duration (in Months)	24.2
FDA Review Information	Duration (in Months)		8.0
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	Yes		Rank = 1
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	No		Rank = 12
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	Yes		Rank = 1

Drug Name	Zemdri (plazomicin)		
Approximate Annual Number U.S. Cases	1 million		Rank = 6
Estimated Inpatient Market Size [k]	28,035		Rank = 8
Number of Drugs Available for Indication(s) in the U.S.	24		Rank = 6
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 6
	Commercial Score [e]	NA	Rank = 6
	R&D Score [f]	NA	Rank = 6
	Overall Score [g]	NA	Rank = 6
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 8
	Clinical Added Value [j]	NA	Rank = 8
British Health Assessment (NICE) *	NA		Rank = 5
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	No	Rank = 8
	MicroScan	No	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 8
P&T Community Decision *	NA		Rank = 6
Medicaid Coverage	CA	N	Rank = 11
	NY	N	
	TX	N	
	PA	N	
	FL	N	
	OH	N	
	IL	N	
	MA	PPA	
	MI	PA	
	NJ	N	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$61.9
	Expected Capitalized Cost (in $ Million 2018)		$563.8
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		256
	Without European Health Technology Assessment (HTA) Scores		192
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$1.24		

Table A - 3. Dalvance (dalbavancin) Information

Drug Name	Dalvance (dalbavancin)		
Study Cohort	Antimicrobial		
Label Indications	DALVANCE is indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms. To reduce the development of drug-resistant bacteria and maintain the effectiveness of DALVANCE and other antibacterial drugs, DALVANCE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria		
Original Company	Durata Therapeutics		
Current Company	Allergan		
FDA Approval Date	May 2014		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Glycopeptide		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Gram-positive		
Preclinical Information	Duration (in Months)		107.3
Clinical Information	Phase 1	Number of Studies	6
		Total Enrollment (All Studies)	218
		Total Phase Duration (in Months)	30.3
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	88
		Total Phase Duration (in Months)	27.9
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	1,312
		Total Phase Duration (in Months)	20.0
FDA Review Information	Duration (in Months)		7.8
Post-approval Information	Phase 4	Number of Studies	8
		Total Enrollment (All Studies)	917
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	No		Rank = 5
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	No		Rank = 8
Approximate Annual Number U.S. Cases	800,000		Rank = 8
Estimated Inpatient Market Size [k]	302,468		Rank = 2

Drug Name	Dalvance (dalbavancin)		
Number of Drugs Available for Indication(s) in the U.S.	24		Rank = 6
Trinity Drug Index	Therapeutic Score [d]	3	Rank = 4
	Commercial Score [e]	1	Rank = 4
	R&D Score [f]	1.5	Rank = 5
	Overall Score [g]	9	Rank = 5
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	No clinical added value (V)	Rank = 5
British Health Assessment (NICE) *	NA		Rank = 5
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	Yes	Rank = 5
	MicroScan	No	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	SSTI Guidelines, effective treatment; OPAT Guidelines, promising		Rank = 1
P&T Community Decision *	NA		Rank = 6
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	NPA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$101.3
	Expected Capitalized Cost (in $ Million 2018)		$2,017.7
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		165
	Without European Health Technology Assessment (HTA) Scores		133
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$35.11		

Table A - 4. Teflaro (ceftaroline fosamil) Information

Drug Name	Teflaro (ceftaroline fosamil)		
Study Cohort	Antimicrobial		
Label Indications	Teflaro® is a cephalosporin antibacterial indicated in adult and pediatric patients for the treatment of the following infection caused by designated susceptible bacteria: Acute bacterial skin and skin structure infections (ABSSSI) in adult and pediatric patients (at least 34 weeks gestational age and 12 days postnatal age); Community-acquired bacterial pneumonia (CABP) in adult and pediatric patients 2 months of age and older. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Teflaro and other antibacterial drugs, Teflaro should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.		
Original Company	Cerexa		
Current Company	Allergan		
FDA Approval Date	November 2010		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Cephalosporin		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Both		
Preclinical Information	Duration (in Months)		83.6
Clinical Information	Phase 1	Number of Studies	12
		Total Enrollment (All Studies)	237
		Total Phase Duration (in Months)	57.5
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	150
		Total Phase Duration (in Months)	5.0
	Phase 3	Number of Studies	4
		Total Enrollment (All Studies)	2,606
		Total Phase Duration (in Months)	22.0
FDA Review Information	Duration (in Months)		9.9
Post-approval Information	Phase 4	Number of Studies	13
		Total Enrollment (All Studies)	7,923
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	No		Rank = 11
BARDA Funding (Yes/No)	No		Rank = 5
Type of FDA Review	Standard		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 9
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1

Drug Name	Teflaro (ceftaroline fosamil)		
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	No		Rank = 8
Approximate Annual Number U.S. Cases	2.5 million		Rank = 1
Estimated Inpatient Market Size [k]	302,468		Rank = 2
Number of Drugs Available for Indication(s) in the U.S.	17		Rank = 1
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 6
	Commercial Score [e]	NA	Rank = 6
	R&D Score [f]	NA	Rank = 6
	Overall Score [g]	NA	Rank = 6
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial (ABSSSI), Insufficient (CAP)	Rank = 7
	Clinical Added Value [j]	Minor (IV)	Rank = 3
British Health Assessment (NICE) *	NA		Rank = 5
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	Yes	Rank = 1
	MicroScan	Yes	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	SSTI Guidelines, should be added to initial empiric regimen when vancomycin is not an option; HABP/VABP Guidelines, No evaluations		Rank = 3
P&T Community Decision *	NA		Rank = 6
Medicaid Coverage	CA	PA	Rank = 7
	NY	Y	
	TX	Y; OT	
	PA	Y	
	FL	PA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$214.8
	Expected Capitalized Cost (in $ Million 2018)		$1,888.1
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		210
	Without European Health Technology Assessment (HTA) Scores		165
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$66.41		

Table A - 5. Vabomere (meropenem and vaborbactam) Information

Drug Name	Vabomere (meropenem and vaborbactam)		
Study Cohort	Antimicrobial		
Label Indications	VABOMERE (meropenem and vaborbactam) is a combination of meropenem, a penem antibacterial, and vaborbactam, a beta-lactamase inhibitor, indicated for the treatment of patients 18 years and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by designated susceptible bacteria. To reduce the development of drug-resistant bacteria and maintain the effectiveness of VABOMERE and other antibacterial drugs, VABOMERE should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.		
Original Company	The Medicines Company		
Current Company	Melinta Therapeutics		
FDA Approval Date	August 2017		
FDA Submission Classification	Type 1 - New Molecular Entity and Type 4 - New Combination		
Type	Small molecule		
Class	Carbapenem/beta-lactamase inhibitor		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Both		
Preclinical Information	Duration (in Months)		29.8
Clinical Information	Phase 1	Number of Studies	5
		Total Enrollment (All Studies)	262
		Total Phase Duration (in Months)	20.9
	Phase 2	Number of Studies	0
		Total Enrollment (All Studies)	NA
		Total Phase Duration (in Months)	NA
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	627
		Total Phase Duration (in Months)	35.6
FDA Review Information	Duration (in Months)		8.0
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	Yes		Rank = 1
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 9
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	Yes		Rank = 1

Drug Name	Vabomere (meropenem and vaborbactam)		
Approximate Annual Number U.S. Cases	1 million		Rank = 6
Estimated Inpatient Market Size [k]	28,035		Rank = 8
Number of Drugs Available for Indication(s) in the U.S.	24		Rank = 6
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 6
	Commercial Score [e]	NA	Rank = 6
	R&D Score [f]	NA	Rank = 6
	Overall Score [g]	NA	Rank = 6
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial (resistant last resort for enterobacteria), Insufficient (otherwise)	Rank = 1
	Clinical Added Value [j]	Moderate (III)	Rank = 1
British Health Assessment (NICE) *	A potentially useful alternative for treating infections due to carbapenem-resistant enterobacteria/ may need a combination therapy which would add additional costs		Rank = 1
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	Yes	Rank = 1
	MicroScan	Yes	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 8
P&T Community Decision *	Important addition to CRE treatments		Rank = 2
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	NPA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$48.3
	Expected Capitalized Cost (in $ Million 2018)		$346.9
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		142
	Without European Health Technology Assessment (HTA) Scores		135
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$21.81		

Table A - 6. Orbactiv (oritavancin) Information

Drug Name	Orbactiv (oritavancin)		
Study Cohort	Antimicrobial		
Label Indications	ORBACTIV is a lipoglycopeptide antibacterial drug indicated for the treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms. To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORBACTIV and other antibacterial drugs, ORBACTIV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.		
Original Company	The Medicines Company		
Current Company	Melinta Therapeutics		
FDA Approval Date	August 2014		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Glycopeptide		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Gram-positive		
Preclinical Information	Duration (in Months)		30.4
Clinical Information	Phase 1	Number of Studies	2
		Total Enrollment (All Studies)	166
		Total Phase Duration (in Months)	1.9
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	294
		Total Phase Duration (in Months)	8.0
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	1,979
		Total Phase Duration (in Months)	29.9
FDA Review Information	Duration (in Months)		8.0
Post-approval Information	Phase 4	Number of Studies	3
		Total Enrollment (All Studies)	54
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	No		Rank = 5
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	No		Rank = 8
Approximate Annual Number U.S. Cases	800,000		Rank = 8

Drug Name	Orbactiv (oritavancin)		
Estimated Inpatient Market Size [k]	302,468		Rank = 2
Number of Drugs Available for Indication(s) in the U.S.	17		Rank = 1
Trinity Drug Index	Therapeutic Score [d]	3	Rank = 4
	Commercial Score [e]	1	Rank = 4
	R&D Score [f]	2.5	Rank = 2
	Overall Score [g]	2.1	Rank = 4
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	No clinical added value (V)	Rank = 5
British Health Assessment (NICE) *	NA		Rank = 5
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation [m]	Vitek® 2	No	Rank = 8
	MicroScan	No	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	OPAT Guidelines, Promising but not recommended		Rank = 6
P&T Community Decision *	A convenient one-dose treatment option		Rank = 3
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	PA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$182.8
	Expected Capitalized Cost (in $ Million 2018)		$1,542.6
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		162
	Without European Health Technology Assessment (HTA) Scores		129
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$21.09		

Table A - 7. Baxdela (delafloxacin) Information

Drug Name	Baxdela (delafloxacin)		
Study Cohort	Antimicrobial		
Label Indications	BAXDELA is a fluoroquinolone antibacterial indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. To reduce the development of drug-resistant bacteria and maintain the effectiveness of BAXDELA and other antibacterial drugs, BAXDELA should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.		
Original Company	Melinta Therapeutics		
Current Company	Melinta Therapeutics		
FDA Approval Date	June 2017		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Fluoroquinolone		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Both		
Preclinical Information	Duration (in Months)		29.3
Clinical Information	Phase 1	Number of Studies	10
		Total Enrollment (All Studies)	504
		Total Phase Duration (in Months)	176.7
	Phase 2	Number of Studies	2
		Total Enrollment (All Studies)	406
		Total Phase Duration (in Months)	40.9
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	1,510
		Total Phase Duration (in Months)	32.0
FDA Review Information	Duration (in Months)		8.0
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Oral & Intravenous		Rank = 1
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	No		Rank = 5
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	Yes		Rank = 1
Approximate Annual Number U.S. Cases	800,000		Rank = 8
Estimated Inpatient Market Size [k]	302,468		Rank = 2

Drug Name	Baxdela (delafloxacin)		
Number of Drugs Available for Indication(s) in the U.S.	17		Rank = 1
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 6
	Commercial Score [e]	NA	Rank = 6
	R&D Score [f]	NA	Rank = 6
	Overall Score [g]	NA	Rank = 6
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 8
	Clinical Added Value [j]	NA	Rank = 8
British Health Assessment (NICE) *	NA		Rank = 5
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	Yes	Rank = 5
	MicroScan	No	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 8
P&T Community Decision *	NA		Rank = 6
Medicaid Coverage	CA	PA	Rank = 8
	NY	NPA	
	TX	NPA	
	PA	NPA	
	FL	Y	
	OH	NPA	
	IL	Y	
	MA	PPA	
	MI	NPA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$140.3
	Expected Capitalized Cost (in $ Million 2018)		$2,158.8
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		194
	Without European Health Technology Assessment (HTA) Scores		131
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$23.51		

Table A - 8. Zerbaxa (ceftolozane + tazobactam) Information

Drug Name	Zerbaxa (ceftolozane + tazobactam)		
Study Cohort	Antimicrobial		
Label Indications	ZERBAXA is a combination of ceftolozane, a cephalosporin antibacterial, and tazobactam, a beta-lactamase inhibitor, indicated in patients 18 years or older for the treatment of the following infections caused by designated susceptible microorganisms: Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole; Complicated Urinary Tract Infections (cUTI), Including Pyelonephritis; Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZERBAXA and other antibacterial drugs, ZERBAXA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.		
Original Company	Cubist Pharmaceuticals		
Current Company	Merck		
FDA Approval Date	December 2014		
FDA Submission Classification	Type 1 - New Molecular Entity and Type 4 - New Combination		
Type	Small molecule		
Class	Cephalosporin/beta-lactamase inhibitor		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Both		
Preclinical Information	Duration (in Months)		79.9
Clinical Information	Phase 1	Number of Studies	9
		Total Enrollment (All Studies)	192
		Total Phase Duration (in Months)	33.0
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	122
		Total Phase Duration (in Months)	7.9
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	1,052
		Total Phase Duration (in Months)	27.4
FDA Review Information	Duration (in Months)		7.9
Post-approval Information	Phase 4	Number of Studies	2
		Total Enrollment (All Studies)	33
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	No		Rank = 5
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1

Drug Name	Zerbaxa (ceftolozane + tazobactam)		
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	Yes		Rank = 1
Approximate Annual Number U.S. Cases	1,100,000		Rank = 3
Estimated Inpatient Market Size [k]	28, 035		Rank = 8
Number of Drugs Available for Indication(s) in the U.S.	39		Rank = 10
Trinity Drug Index	Therapeutic Score [d]	4	Rank = 2
	Commercial Score [e]	1.2	Rank = 1
	R&D Score [f]	3.5	Rank = 1
	Overall Score [g]	2.8	Rank = 1
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	No clinical added value (V)	Rank = 5
British Health Assessment (NICE) *	A second-line option / high acquisition costs		Rank = 2
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	No	Rank = 5
	MicroScan	Yes	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	HAP/VAP Guidelines, Active against Pseudomonas, effectiveness against VAP yet to be determined		Rank = 3
P&T Community Decision *	NA		Rank = 6
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	PA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$62.2
	Expected Capitalized Cost (in $ Million 2018)		$439.6
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		123
	Without European Health Technology Assessment (HTA) Scores		111
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$41.27		

Table A - 9. Sivextro (tedizolid phosphate) Information

Drug Name	Sivextro (tedizolid phosphate)		
Study Cohort	Antimicrobial		
Label Indications	SIVEXTRO is an oxazolidinone-class antibacterial drug indicated in adult and pediatric patients 12 years of age and older for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. To reduce the development of drug-resistant bacteria and maintain the effectiveness of SIVEXTRO and other antibacterial drugs, SIVEXTRO should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.		
Original Company	Cubist Pharmaceuticals		
Current Company	Merck		
FDA Approval Date	June 2014		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Oxazolidinone		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Gram-positive		
Preclinical Information	Duration (in Months)		47.3
Clinical Information	Phase 1	Number of Studies	15
		Total Enrollment (All Studies)	507
		Total Phase Duration (in Months)	55.5
	Phase 2	Number of Studies	2
		Total Enrollment (All Studies)	392
		Total Phase Duration (in Months)	47.2
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	1,333
		Total Phase Duration (in Months)	28.8
FDA Review Information	Duration (in Months)		7.9
Post-approval Information	Phase 4	Number of Studies	3
		Total Enrollment (All Studies)	50
Route of Administration	Oral and Intravenous		Rank = 1
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	No		Rank = 5
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	No		Rank = 8
Approximate Annual Number U.S. Cases	800,000		Rank = 8

Drug Name	Sivextro (tedizolid phosphate)		
Estimated Inpatient Market Size [k]	302,469		Rank = 2
Number of Drugs Available for Indication(s) in the U.S.	17		Rank = 1
Trinity Drug Index	Therapeutic Score [d]	3.6	Rank = 3
	Commercial Score [e]	1.2	Rank = 1
	R&D Score [f]	2.5	Rank = 2
	Overall Score [g]	2.4	Rank = 3
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	No clinical added value (V)	Rank = 5
British Health Assessment (NICE) *	NA		Rank = 5
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	No	Rank = 8
	MicroScan	No	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	SSTI Guidelines, effective treatment		Rank = 1
P&T Community Decision *	A novel second-generation oxazolidinone; additional data are needed on the safety of this therapy when used in the setting of neutropenia		Rank = 3
Medicaid Coverage	CA	PA	Rank = 8
	NY	PA	
	TX	NPA	
	PA	Y	
	FL	NPA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$121.3
	Expected Capitalized Cost (in $ Million 2018)		$868.6
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		146
	Without European Health Technology Assessment (HTA) Scores		113
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$30.44		

Table A - 10. Nuzyra (omadacycline) Information

Drug Name	Nuzyra (omadacycline)		
Study Cohort	Antimicrobial		
Label Indications	NUZYRA is a tetracycline class antibacterial indicated for the treatment of adult patients with the following infections caused by susceptible microorganisms: Community-acquired bacterial pneumonia (CABP); Acute bacterial skin and skin structure infections (ABSSSI). To reduce the development of drug-resistant bacteria and maintain the effectiveness of NUZYRA and other antibacterial drugs, NUZYRA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.		
Original Company	Paratek Pharmaceuticals		
Current Company	Paratek Pharmaceuticals		
FDA Approval Date	October 2018		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Tetracycline		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Both		
Preclinical Information	Duration (in Months)		62.0
Clinical Information	Phase 1	Number of Studies	4
		Total Enrollment (All Studies)	156
		Total Phase Duration (in Months)	NA(?)
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	234
		Total Phase Duration (in Months)	5.7
	Phase 3	Number of Studies	3
		Total Enrollment (All Studies)	2,164
		Total Phase Duration (in Months)	22.8
FDA Review Information	Duration (in Months)		7.9
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Oral and Intravenous		Rank = 1
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	Yes		Rank = 1
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	Yes		Rank = 1
Approximate Annual Number U.S. Cases	2,500,000		Rank = 1

Drug Name	Nuzyra (omadacycline)		
Estimated Inpatient Market Size [k]	302,468		Rank = 2
Number of Drugs Available for Indication(s) in the U.S.	17		Rank = 7
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 6
	Commercial Score [e]	NA	Rank = 6
	R&D Score [f]	NA	Rank = 6
	Overall Score [g]	NA	Rank = 6
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 8
	Clinical Added Value [j]	NA	Rank = 8
British Health Assessment (NICE) *	NA		Rank = 5
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	No	Rank = 8
	MicroScan	No	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 8
P&T Community Decision *	NA		Rank = 6
Medicaid Coverage	CA	PA	Rank = 11
	NY	NPA	
	TX	NPA	
	PA	NPA	
	FL	Y	
	OH	NPA	
	IL	NPA	
	MA	NPA	
	MI	PA	
	NJ	PA	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$158.9
	Expected Capitalized Cost (in $ Million 2018)		$2,110.8
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		203
	Without European Health Technology Assessment (HTA) Scores		140
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$58.04		

Table A - 11. Xerava (eravacycline) Information

Drug Name	Xerava (eravacycline)		
Study Cohort	Antimicrobial		
Label Indications	XERAVA is a tetracycline class antibacterial indicated for the treatment of complicated intra-abdominal infections in patients 18 years of age and older. Limitations of Use XERAVA is not indicated for the treatment of complicated urinary tract infections (cUTI). To reduce the development of drug-resistant bacteria and maintain the effectiveness of XERAVA and other antibacterial drugs, XERAVA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.		
Original Company	Tetraphase Pharmaceuticals		
Current Company	Tetraphase Pharmaceuticals		
FDA Approval Date	August 2018		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Tetracycline		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Both		
Preclinical Information	Duration (in Months)		19.6
Clinical Information	Phase 1	Number of Studies	9
		Total Enrollment (All Studies)	227
		Total Phase Duration (in Months)	15.9
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	143
		Total Phase Duration (in Months)	15.9
	Phase 3	Number of Studies	4
		Total Enrollment (All Studies)	3,154
		Total Phase Duration (in Months)	51.9
FDA Review Information	Duration (in Months)		7.9
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	Yes		Rank = 1
BARDA Funding (Yes/No)	Yes		Rank = 1
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	Yes		Rank = 1
Approximate Annual Number U.S. Cases	100,000		Rank = 12

Drug Name	Xerava (eravacycline)		
Estimated Inpatient Market Size [k]	1,223,379		Rank = 1
Number of Drugs Available for Indication(s) in the U.S.	NA		Rank = 12
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 6
	Commercial Score [e]	NA	Rank = 6
	R&D Score [f]	NA	Rank = 6
	Overall Score [g]	NA	Rank = 6
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 8
	Clinical Added Value [j]	NA	Rank = 8
British Health Assessment (NICE) *	NA		Rank = 5
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	Yes	Rank = 1
	MicroScan	Yes	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 8
P&T Community Decision *	NA		Rank = 6
Medicaid Coverage	CA	N	Rank = 10
	NY	N	
	TX	N	
	PA	N	
	FL	Y	
	OH	N	
	IL	N	
	MA	PPA	
	MI	PA	
	NJ	N	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$182.7
	Expected Capitalized Cost (in $ Million 2018)		$1471.4
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		209
	Without European Health Technology Assessment (HTA) Scores		146
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$12.79		

Table A - 12. Vibativ (telavancin) Information

Drug Name	Vibativ (telavancin) [l]		
Study Cohort	Antimicrobial		
Label Indications	VIBATIV is a lipoglycopeptide antibacterial drug indicated for the treatment of the following infections in adult patients caused by designated susceptible bacteria: Complicated skin and skin structure infections (cSSSI); Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of Staphylococcus aureus. VIBATIV should be reserved for use when alternative treatments are not suitable. To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs VIBATIV should only be used to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.		
Original Company	Theravance		
Current Company	Theravance		
FDA Approval Date	June 2013		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Class	Glycopeptide		
Spectrum (Broad/Narrow)	Broad spectrum		
Gram -negative, gram-positive, or Both	Gram-positive		
Preclinical Information	Duration (in Months)		23.1
Clinical Information	Phase 1	Number of Studies	0
		Total Enrollment (All Studies)	NA
		Total Phase Duration (in Months)	NA
	Phase 2	Number of Studies	3
		Total Enrollment (All Studies)	430
		Total Phase Duration (in Months)	38.0
	Phase 3	Number of Studies	4
		Total Enrollment (All Studies)	3,429
		Total Phase Duration (in Months)	29.9
FDA Review Information	Duration (in Months)		52.8
Post-approval Information	Phase 4	Number of Studies	3
		Total Enrollment (All Studies)	62
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	No		Rank = 11
BARDA Funding (Yes/No)	No		Rank = 5
Type of FDA Review	Standard		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 9
Activity Against ESKAPE Pathogens (Yes/No) [a]	Yes		Rank = 1

Drug Name	Vibativ (telavancin) [l]		
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	No		Rank = 8
Approximate Annual Number U.S. Cases	1,100,000		Rank = 3
Estimated Inpatient Market Size [k]	NA		Rank = 12
Number of Drugs Available for Indication(s) in the U.S.	32		Rank = 9
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 6
	Commercial Score [e]	NA	Rank = 6
	R&D Score [f]	NA	Rank = 6
	Overall Score [g]	NA	Rank = 6
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 8
	Clinical Added Value [j]	NA	Rank = 8
British Health Assessment (NICE) *	Should only be used in situations where it is known or suspected that other alternatives are not suitable		Rank = 3
German Dossier Assessment (IQWiG)	NA		NA
AST Device Incorporation	Vitek® 2	No	Rank = 8
	MicroScan	No	
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	HAP/VAP Guidelines, Similar outcomes to vancomycin but higher mortality rates; SSTI Guidelines, May be effective but lack clinical data		Rank = 6
P&T Community Decision *	Exceptional benefits compared with conventional therapies		Rank = 1
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	NPA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$288.2
	Expected Capitalized Cost (in $ Million 2018)		$3,329.2
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		264
	Without European Health Technology Assessment (HTA) Scores		207
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$25.71		

Table A - 13. Bridion (sugammadex sodium) Information

Drug Name	Bridion (sugammadex sodium)		
Study Cohort	Non-Antimicrobial Comparator		
Label Indications	BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery		
Original Company	Merck		
Current Company	Merck		
FDA Approval Date	December 2015		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		44.9
Clinical Information	Phase 1	Number of Studies	6
		Total Enrollment (All Studies)	208
		Total Phase Duration (in Months)	NA
	Phase 2	Number of Studies	8
		Total Enrollment (All Studies)	770
		Total Phase Duration (in Months)	45.6
	Phase 3	Number of Studies	12
		Total Enrollment (All Studies)	1,438
		Total Phase Duration (in Months)	32.0
FDA Review Information	Duration (in Months)		97.3
Post-approval Information	Phase 4	Number of Studies	74
		Total Enrollment (All Studies)	8,615
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	NA		Rank = 5
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	NA		Rank = 5
Trinity Drug Index	Therapeutic Score [d]	4.8	Rank = 1
	Commercial Score [e]	2.8	Rank = 1
	R&D Score [f]	3	Rank = 2
	Overall Score [g]	3.6	Rank = 1
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1

Drug Name	Bridion (sugammadex sodium)		
	Clinical Added Value [j]	Minor (IV)	Rank = 1
British Health Assessment (NICE) *	NA		Rank = 3
German Dossier Assessment (IQWiG)	NA		Rank = 2
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 2
P&T Community Decision *	NA		NA
Medicaid Coverage	CA	PA	Rank = 4
	NY	Y	
	TX	Y	
	PA	Y	
	FL	PA	
	OH	PA	
	IL	Y	
	MA	PA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$233.5
	Expected Capitalized Cost (in $ Million 2018)		$1,936.1
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		84
	Without European Health Technology Assessment (HTA) Scores		81
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$48.52		

Table A - 14. Giapreza (angiotensin II) Information

Drug Name	Giapreza (angiotensin II)		
Study Cohort	Non-Antimicrobial Comparator		
Label Indications	GIAPREZA is a vasoconstrictor to increase blood pressure in adults with septic or other distributive shock		
Original Company	La Jolla Pharmaceutical Company		
Current Company	La Jolla Pharmaceutical Company		
FDA Approval Date	December 2017		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		57.9
Clinical Information	Phase 1	Number of Studies	3
		Total Enrollment (All Studies)	168
		Total Phase Duration (in Months)	101.3
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	12
		Total Phase Duration (in Months)	35.9
	Phase 3	Number of Studies	5
		Total Enrollment (All Studies)	927
		Total Phase Duration (in Months)	231.6
FDA Review Information	Duration (in Months)		5.7
Post-approval Information	Phase 4	Number of Studies	1
		Total Enrollment (All Studies)	48
Route of Administration	Intravenous		Rank = 4
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	1,000,000		Rank = 4
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	21		Rank = 1
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 3
	Commercial Score [e]	NA	Rank = 3
	R&D Score [f]	NA	Rank = 3
	Overall Score [g]	NA	Rank = 3
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 3

Drug Name	Giapreza (angiotensin II)		
	Clinical Added Value [j]	NA	Rank = 3
British Health Assessment (NICE) *	NA		Rank = 3
German Dossier Assessment (IQWiG)	NA		Rank = 2
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	Chronic Kidney Disease in HIV Guidelines, Recommended when clinically feasible		Rank = 1
P&T Community Decision *	NA		NA
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	PA	
	OH	PA	
	IL	Y	
	MA	PA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$54.5
	Expected Capitalized Cost (in $ Million 2018)		$4,991.6
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		89
	Without European Health Technology Assessment (HTA) Scores		88
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$31.82		

Table A - 15. Surfaxin (lucinactant) Information (Discontinued in the U.S.)

Drug Name	Surfaxin (lucinactant)		
Study Cohort	Non-Antimicrobial Comparator		
Label Indications	SURFAXIN is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS		
Original Company	Discovery Laboratories		
Current Company	Discovery Laboratories		
FDA Approval Date	March 2012		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		54.9
Clinical Information	Phase 1	Number of Studies	2
		Total Enrollment (All Studies)	27
		Total Phase Duration (in Months)	NA
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	2
		Total Phase Duration (in Months)	NA
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	1,302
		Total Phase Duration (in Months)	26.9
FDA Review Information	Duration (in Months)		94.6
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Intratracheal		Rank = 4
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Standard		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 6
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	1,151,969		Rank = 3
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	4		Rank = 4
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 3
	Commercial Score [e]	NA	Rank = 3
	R&D Score [f]	NA	Rank = 3
	Overall Score [g]	NA	Rank = 3
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 3

Drug Name	Surfaxin (lucinactant)		
	Clinical Added Value [j]	NA	Rank = 3
British Health Assessment (NICE) *	NA		Rank = 3
German Dossier Assessment (IQWiG)	NA		Rank = 2
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 2
P&T Community Decision *	NA		NA
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	PA	
	OH	PA	
	IL	Y	
	MA	PA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$92.7
	Expected Capitalized Cost (in $ Million 2018)		$1,523.6
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		105
	Without European Health Technology Assessment (HTA) Scores		103
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$0.57		

Table A - 16. Lokelma (sodium zirconium cyclosilicate) Information

Drug Name	Lokelma (sodium zirconium cyclosilicate)		
Study Cohort	Non-Antimicrobial Comparator		
Label Indications	LOKELMA is a potassium binder indicated for the treatment of hyperkalemia in adults		
Original Company	AstraZeneca		
Current Company	AstraZeneca		
FDA Approval Date	May 2018		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		125.1
Clinical Information	Phase 1	Number of Studies	3
		Total Enrollment (All Studies)	367
		Total Phase Duration (in Months)	49.9
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	90
		Total Phase Duration (in Months)	6.0
	Phase 3	Number of Studies	4
		Total Enrollment (All Studies)	1,886
		Total Phase Duration (in Months)	47.9
FDA Review Information	Duration (in Months)		35.7
Post-approval Information	Phase 4	Number of Studies	1
		Total Enrollment (All Studies)	20
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Standard		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	3,700,000		Rank = 1
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	12		Rank = 2
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 3
	Commercial Score [e]	NA	Rank = 3
	R&D Score [f]	NA	Rank = 3
	Overall Score [g]	NA	Rank = 3
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 3
	Clinical Added Value [j]	NA	Rank = 3

Drug Name	Lokelma (sodium zirconium cyclosilicate)		
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	NA		Rank = 2
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		NA
Medicaid Coverage	CA	PA	Rank = 4
	NY	Y	
	TX	Y; OT	
	PA	PPA	
	FL	PA	
	OH	PA	
	IL	NPA	
	MA	PPA	
	MI	PA	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$123.3
	Expected Capitalized Cost (in $ Million 2018)		$1,656.0
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		78
	Without European Health Technology Assessment (HTA) Scores		76
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$88.02		

Table A - 17. Veltassa (patiromer) Information

Drug Name	Veltassa (patiromer)		
Study Cohort	Non-Antimicrobial Comparator		
Label Indications	Veltassa is a potassium binder indicated for the treatment of hyperkalemia. Limitation of Use: Veltassa should not be used as an emergency treatment for lifethreatening hyperkalemia because of its delayed onset of action.		
Original Company	Relypsa, Inc.		
Current Company	Vifor Pharma, Inc.		
FDA Approval Date	October 2015		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		44.3
Clinical Information	Phase 1	Number of Studies	3
		Total Enrollment (All Studies)	70
		Total Phase Duration (in Months)	NA
	Phase 2	Number of Studies	3
		Total Enrollment (All Studies)	507
		Total Phase Duration (in Months)	48.9
	Phase 3	Number of Studies	1
		Total Enrollment (All Studies)	243
		Total Phase Duration (in Months)	5.0
FDA Review Information	Duration (in Months)		12.0
Post-approval Information	Phase 4	Number of Studies	6
		Total Enrollment (All Studies)	2,222
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Standard		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	3,700,000		Rank = 1
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	12		Rank = 2
Trinity Drug Index	Therapeutic Score [d]	3.8	Rank = 2
	Commercial Score [e]	1.6	Rank = 2
	R&D Score [f]	4	Rank = 1
	Overall Score [g]	3	Rank = 2

Drug Name	Veltassa (patiromer)		
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	No clinical added value (V)	Rank = 2
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	No proof of added benefit		Rank = 1
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 2
P&T Community Decision *	NA		NA
Medicaid Coverage	CA	PA	Rank = 6
	NY	Y	
	TX	Y; OT	
	PA	PPA	
	FL	NPA	
	OH	PA	
	IL	NPA	
	MA	P; QL	
	MI	PA	
	NJ	P	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$55.1
	Expected Capitalized Cost (in $ Million 2018)		$335.1
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		61
	Without European Health Technology Assessment (HTA) Scores		59
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$34.32		

Table A - 18. Vistogard (uridine triacetate) Information

Drug Name	Vistogard (uridine triacetate)		
Study Cohort	Non-Antimicrobial Comparator		
Label Indications	VISTOGARD® is a pyrimidine analog indicated for the emergency treatment of adult and pediatric patients: following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration. Limitations of use: VISTOGARD is not recommended for the non-emergent treatment of adverse reactions associated with fluorouracil or capecitabine because it may diminish the efficacy of these drugs. The safety and efficacy of VISTOGARD initiated more than 96 hours following the end of fluorouracil or capecitabine administration have not been established.		
Original Company	Wellstat Therapeutics		
Current Company	Wellstat Therapeutics		
FDA Approval Date	December 2015		
FDA Submission Classification	NA		
Type	Small molecule		
Preclinical Information	Duration (in Months)		51.4
Clinical Information	Phase 1	Number of Studies	5
		Total Enrollment (All Studies)	88
		Total Phase Duration (in Months)	NA
	Phase 2	Number of Studies	2
		Total Enrollment (All Studies)	85
		Total Phase Duration (in Months)	70.9
	Phase 3	Number of Studies	4
		Total Enrollment (All Studies)	389
		Total Phase Duration (in Months)	230.5
FDA Review Information	Duration (in Months)		5.0
Post-approval Information	Phase 4	Number of Studies	1
		Total Enrollment (All Studies)	60
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority; Orphan		
New Molecular Entity (Yes/No)	No		Rank = 6
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA

Drug Name	Vistogard (uridine triacetate)		
Approximate Annual Number U.S. Cases	NA		Rank = 5
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	0		Rank = 5
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 3
	Commercial Score [e]	NA	Rank = 3
	R&D Score [f]	NA	Rank = 3
	Overall Score [g]	NA	Rank = 3
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 3
	Clinical Added Value [j]	NA	Rank = 3
British Health Assessment (NICE) *	NA		Rank = 3
German Dossier Assessment (IQWiG)	NA		Rank = 2
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		NA
IDSA Guideline Inclusion	NA		Rank = 2
P&T Community Decision *	NA		NA
Medicaid Coverage	CA	PA	Rank = 1
	NY	Y	
	TX	Y	
	PA	Y	
	FL	PA	
	OH	PA	
	IL	Y	
	MA	PA	
	MI	Y	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$66.4
	Expected Capitalized Cost (in $ Million 2018)		$8,747.6
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		100
	Without European Health Technology Assessment (HTA) Scores		97
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$3.66		

Table A - 19. Zelboraf (vemurafenib) Information

Drug Name	Zelboraf (vemurafenib)		
Study Cohort	Oncology		
Label Indications	ZELBORAF® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. ZELBORAF® is indicated for the treatment of patients with ErdheimChester Disease with BRAF V600 mutation. Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma.		
Original Company	Hoffmann-La Roche Inc.		
Current Company	Genentech Inc.		
FDA Approval Date	August 2011		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		32.4
Clinical Information	Phase 1	Number of Studies	2
		Total Enrollment (All Studies)	127
		Total Phase Duration (in Months)	NA
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	132
		Total Phase Duration (in Months)	11.9
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	2,894
		Total Phase Duration (in Months)	72.6
FDA Review Information	Duration (in Months)		3.7
Post-approval Information	Phase 4	Number of Studies	2
		Total Enrollment (All Studies)	510
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority; Orphan		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	96,480		Rank = 7
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	17		Rank = 4
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 7
	Commercial Score [e]	NA	Rank = 7

Drug Name	Zelboraf (vemurafenib)		
	R&D Score [f]	NA	Rank = 7
	Overall Score [g]	NA	Rank = 7
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	Moderate (III)	Rank = 1
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	Considerable added benefit		Rank = 1
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	P	Rank = 1
	NY	Y	
	TX	Y; OT	
	PA	PPA	
	FL	PPA	
	OH	Y	
	IL	NPA	
	MA	PPA	
	MI	Y	
	NJ	P	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$260.0
	Expected Capitalized Cost (in $ Million 2018)		$1,596.2
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		126.8
	Without European Health Technology Assessment (HTA) Scores		118.0
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$475.31		

Table A - 20. Stivarga (regorafenib) Information

Drug Name	Stivarga (regorafenib)		
Study Cohort	Oncology		
Label Indications	STIVARGA is a kinase inhibitor indicated for the treatment of patients with: Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy, an antiVEGF therapy, and, if RAS wild-type, an anti-EGFR therapy; Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate; Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.		
Original Company	Bayer HealthCare Pharmaceuticals, Inc.		
Current Company	Bayer		
FDA Approval Date	August 2011		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		90.0
Clinical Information	Phase 1	Number of Studies	8
		Total Enrollment (All Studies)	260
		Total Phase Duration (in Months)	33.9
	Phase 2	Number of Studies	4
		Total Enrollment (All Studies)	173
		Total Phase Duration (in Months)	49.9
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	959
		Total Phase Duration (in Months)	20.9
FDA Review Information	Duration (in Months)		5.0
Post-approval Information	Phase 4	Number of Studies	2
		Total Enrollment (All Studies)	131
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority; Orphan		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	192,630		Rank = 5
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	21		Rank = 6

Drug Name	Stivarga (regorafenib)		
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 7
	Commercial Score [e]	NA	Rank = 7
	R&D Score [f]	NA	Rank = 7
	Overall Score [g]	NA	Rank = 7
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial (with sorafenib tolerance), Insufficient (other clinical situations)	Rank = 8
	Clinical Added Value [j]	Minor (IV)	Rank = 4
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	Minor added benefit		Rank = 3
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	P	Rank = 2
	NY	Y	
	TX	Y; OT	
	PA	PPA	
	FL	NPA	
	OH	PA	
	IL	NPA	
	MA	PPA	
	MI	Y	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$123.0
	Expected Capitalized Cost (in $ Million 2018)		$3,761.5
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		163.5
	Without European Health Technology Assessment (HTA) Scores		120.0
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$241.91		

Table A - 21. Erivedge (vismodegib) Information

Drug Name	Erivedge (vismodegib)		
Study Cohort	Oncology		
Label Indications	ERIVEDGE (vismodegib) is a hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiation.		
Original Company	Genentech, Inc.		
Current Company	Genentech, Inc.		
FDA Approval Date	January 2012		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		24.8
Clinical Information	Phase 1	Number of Studies	4
		Total Enrollment (All Studies)	220
		Total Phase Duration (in Months)	46.5
	Phase 2	Number of Studies	3
		Total Enrollment (All Studies)	407
		Total Phase Duration (in Months)	31.0
	Phase 3	Number of Studies	0
		Total Enrollment (All Studies)	NA
		Total Phase Duration (in Months)	NA
FDA Review Information	Duration (in Months)		4.7
Post-approval Information	Phase 4	Number of Studies	2
		Total Enrollment (All Studies)	65
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	2,800,000		Rank = 1
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	7		Rank = 3
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 7
	Commercial Score [e]	NA	Rank = 7
	R&D Score [f]	NA	Rank = 7

Drug Name	Erivedge (vismodegib)		
	Overall Score [g]	NA	Rank = 7
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	Minor (IV)	Rank = 4
British Health Assessment (NICE) *	Not recommended		Rank = 11
German Dossier Assessment (IQWiG)	Added benefit not proven		Rank = 8
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	Important new therapy		Rank = 1
Medicaid Coverage	CA	P	Rank = 2
	NY	Y	
	TX	Y; OT	
	PA	PPA	
	FL	NPA	
	OH	PA	
	IL	P	
	MA	PPA	
	MI	Y	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$55.0
	Expected Capitalized Cost (in $ Million 2018)		$1,321.3
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		162.8
	Without European Health Technology Assessment (HTA) Scores		96.5
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$118.32		

Table A - 22. Ibrance (palbociclib) Information

Drug Name	Ibrance (palbociclib)		
Study Cohort	Oncology		
Label Indications	IBRANCE is a kinase inhibitor indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or fulvestrant in patients with disease progression following endocrine therapy.		
Original Company	Pfizer Inc.		
Current Company	Pfizer Inc.		
FDA Approval Date	December 2015		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		25.5
Clinical Information	Phase 1	Number of Studies	15
		Total Enrollment (All Studies)	454
		Total Phase Duration (in Months)	116.7
	Phase 2	Number of Studies	4
		Total Enrollment (All Studies)	294
		Total Phase Duration (in Months)	72.8
	Phase 3	Number of Studies	4
		Total Enrollment (All Studies)	3,033
		Total Phase Duration (in Months)	94.1
FDA Review Information	Duration (in Months)		5.7
Post-approval Information	Phase 4	Number of Studies	4
		Total Enrollment (All Studies)	1,623
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	271,270		Rank = 3
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	35		Rank = 11
Trinity Drug Index	Therapeutic Score [d]	4.6	Rank = 2
	Commercial Score [e]	4.8	Rank = 1

Drug Name	Ibrance (palbociclib)		
	R&D Score [f]	3.5	Rank = 2
	Overall Score [g]	4.5	Rank = 1
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial (no visceral involvement, pre-treated with endocrine therapy), Insufficient (others)	Rank = 8
	Clinical Added Value [j]	Minor (IV), No clinical added value (V)	Rank = 9
British Health Assessment (NICE) *	Recommended with an aromatase inhibitor		Rank = 1
German Dossier Assessment (IQWiG)	Added benefit not proven		Rank = 8
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	P	Rank = 2
	NY	Y	
	TX	Y; OT	
	PA	PPA	
	FL	NPA	
	OH	Y	
	IL	NPA	
	MA	PPA	
	MI	Y	
	NJ	P	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$323.4
	Expected Capitalized Cost (in $ Million 2018)		$6,050.0
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		148.2
	Without European Health Technology Assessment (HTA) Scores		75.9
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$3,551.16		

Table A - 23. Portrazza (necitumumab) Information

Drug Name	Portrazza (necitumumab)		
Study Cohort	Oncology		
Label Indications	PORTRAZZA™ is an epidermal growth factor receptor (EGFR) antagonist indicated, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous non-small cell lung cancer. Limitation of Use: PORTRAZZA is not indicated for treatment of non-squamous non-small cell lung cancer.		
Original Company	Eli Lilly and Company		
Current Company	Eli Lilly and Company		
FDA Approval Date	November 2015		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Large molecule		
Preclinical Information	Duration (in Months)		49.7
Clinical Information	Phase 1	Number of Studies	2
		Total Enrollment (All Studies)	75
		Total Phase Duration (in Months)	86.8
	Phase 2	Number of Studies	5
		Total Enrollment (All Studies)	382
		Total Phase Duration (in Months)	91.8
	Phase 3	Number of Studies	2
		Total Enrollment (All Studies)	1,726
		Total Phase Duration (in Months)	43.4
FDA Review Information	Duration (in Months)		11.7
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Intra-articular, intramuscular, intravitreal		Rank = 9
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	None		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	194,497		Rank = 4
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	37		Rank = 12
Trinity Drug Index	Therapeutic Score [d]	3.2	Rank = 4
	Commercial Score [e]	1	Rank = 6
	R&D Score [f]	2.5	Rank = 5

Drug Name	Portrazza (necitumumab)		
	Overall Score [g]	2.2	Rank = 6
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 12
	Clinical Added Value [j]	NA	Rank = 12
British Health Assessment (NICE) *	Not recommended in combination with gemcitabine and cisplatin		Rank = 11
German Dossier Assessment (IQWiG)	Minor added benefit in combination with gemcitabine and cisplatin		Rank = 3
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	P	Rank = 13
	NY	N	
	TX	N	
	PA	N	
	FL	NPA	
	OH	N	
	IL	N	
	MA	PPA	
	MI	N	
	NJ	P	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$176.6
	Expected Capitalized Cost (in $ Million 2018)		$6,331.0
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		273.3
	Without European Health Technology Assessment (HTA) Scores		165.1
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$25.31		

Table A - 24. Yescarta (axicabtagene ciloleucel) Information

Drug Name	Yescarta (axicabtagene ciloleucel)		
Study Cohort	Oncology		
Label Indications	YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of: Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Limitations of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approvedunder accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).		
Original Company	Kite Pharma Inc.		
Current Company	Kite Pharma Inc.		
FDA Approval Date	October 2017		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Large molecule		
Preclinical Information	Duration (in Months)		49.7
Clinical Information	Phase 1	Number of Studies	1
		Total Enrollment (All Studies)	8
		Total Phase Duration (in Months)	21.2
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	111
		Total Phase Duration (in Months)	21.2
	Phase 3	Number of Studies	0
		Total Enrollment (All Studies)	NA
		Total Phase Duration (in Months)	NA
FDA Review Information	Duration (in Months)		6.6
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Intravenous		Rank = 9
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	None		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA

Drug Name	Yescarta (axicabtagene ciloleucel)		
Approximate Annual Number U.S. Cases	74,200		Rank = 9
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	31		Rank = 10
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 7
	Commercial Score [e]	NA	Rank = 7
	R&D Score [f]	NA	Rank = 7
	Overall Score [g]	NA	Rank = 7
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	Moderate (III)	Rank = 1
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	NA		Rank = 13
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	B+ rating / net health benefit / Affordability and Access Alert		Rank = 1
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	PA	Rank = 14
	NY	N	
	TX	N	
	PA	PA	
	FL	N	
	OH	N	
	IL	N	
	MA	MB; OT	
	MI	N	
	NJ	N	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$16.8
	Expected Capitalized Cost (in $ Million 2018)		$234.8
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		218.5
	Without European Health Technology Assessment (HTA) Scores		176.0
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$343.33		

Table A - 25. Braftovi (encorafenib + Mektovi [binimetinib]) Information

Drug Name	Braftovi (encorafenib + Mektovi [binimetinib])		
Study Cohort	Oncology		
Label Indications	BRAFTOVI is a kinase inhibitor indicated: in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test; in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.		
Original Company	Array BioPharma Inc.		
Current Company	Pfizer Inc.		
FDA Approval Date	June 2018		
FDA Submission Classification	Type 1 - New Molecular Entity and Type 4 - New Combination		
Type	Small molecule		
Preclinical Information	Duration (in Months)		41.9
Clinical Information	Phase 1	Number of Studies	2
		Total Enrollment (All Studies)	117
		Total Phase Duration (in Months)	34.5
	Phase 2	Number of Studies	4
		Total Enrollment (All Studies)	219
		Total Phase Duration (in Months)	59.7
	Phase 3	Number of Studies	5
		Total Enrollment (All Studies)	2,889
		Total Phase Duration (in Months)	67.4
FDA Review Information	Duration (in Months)		11.9
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Standard; Orphan		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	96,480		Rank = 7
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	17		Rank = 4
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 7
	Commercial Score [e]	NA	Rank = 7

Drug Name	Braftovi (encorafenib + Mektovi [binimetinib])		
	R&D Score [f]	NA	Rank = 7
	Overall Score [g]	NA	Rank = 7
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Moderate	Rank = 10
	Clinical Added Value [j]	No clinical added value (V)	Rank = 10
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	Added benefit not proven		Rank = 8
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	PPA	Rank = 2
	NY	Y	
	TX	Y	
	PA	NPA	
	FL	Y; QL	
	OH	PA	
	IL	NPA	
	MA	PPA	
	MI	Y	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$266.2
	Expected Capitalized Cost (in $ Million 2018)		$7,208.2
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		192.8
	Without European Health Technology Assessment (HTA) Scores		113.0
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$301.69		

Table A - 26. Cyramza (ramucirumab) Information

Drug Name	Cyramza (ramucirumab)		
Study Cohort	Oncology		
Label Indications	CYRAMZA® is a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist indicated: as a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine-or platinum-containing chemotherapy; in combination with erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations; in combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA; in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine; as a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib.		
Original Company	Eli Lilly and Company		
Current Company	Eli Lilly and Company		
FDA Approval Date	April 2014		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Large molecule		
Preclinical Information	Duration (in Months)		49.7
Clinical Information	Phase 1	Number of Studies	6
		Total Enrollment (All Studies)	96
		Total Phase Duration (in Months)	93.8
	Phase 2	Number of Studies	17
		Total Enrollment (All Studies)	1613
		Total Phase Duration (in Months)	73.9
	Phase 3	Number of Studies	6
		Total Enrollment (All Studies)	5,054
		Total Phase Duration (in Months)	71.2
FDA Review Information	Duration (in Months)		7.9
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Injection		Rank = 9
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Orphan		
New Molecular Entity (Yes/No)	Yes		Rank = 1

Drug Name	Cyramza (ramucirumab)		
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	382,127		Rank = 2
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	83		Rank = 13
Trinity Drug Index	Therapeutic Score [d]	4.2	Rank = 3
	Commercial Score [e]	2.8	Rank = 3
	R&D Score [f]	3	Rank = 3
	Overall Score [g]	3.4	Rank = 3
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Moderate	Rank = 10
	Clinical Added Value [j]	No clinical added value (V)	Rank = 10
British Health Assessment (NICE) *	Not recommended		Rank = 11
German Dossier Assessment (IQWiG)	Minor added benefit		Rank = 3
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	Effective second-line treatment		Rank = 2
Medicaid Coverage	CA	P	Rank = 9
	NY	MB; 0T	
	TX	Y	
	PA	Y	
	FL	NP	
	OH	NPA	
	IL	Y	
	MA	PPA	
	MI	Y	
	NJ	P	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$651.5
	Expected Capitalized Cost (in $ Million 2018)		$19,731.2
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		227.7
	Without European Health Technology Assessment (HTA) Scores		130.7
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$760.30		

Table A - 27. Darzalex (daratumumab) Information

Drug Name	Darzalex (daratumumab)		
Study Cohort	Oncology		
Label Indications	DARZALEX is a CD38-directed cytolytic antibody indicated for the treatment of adult patients with multiple myeloma: in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy; in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant; in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant; in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy; in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor; as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.		
Original Company	Janssen Biotech, Inc.		
Current Company	Janssen Biotech, Inc.		
FDA Approval Date	November 2015		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Large molecule		
Preclinical Information	Duration (in Months)		49.7
Clinical Information	Phase 1	Number of Studies	1
		Total Enrollment (All Studies)	9
		Total Phase Duration (in Months)	17.0
	Phase 2	Number of Studies	2
		Total Enrollment (All Studies)	228
		Total Phase Duration (in Months)	81.3
	Phase 3	Number of Studies	4
		Total Enrollment (All Studies)	2,511
		Total Phase Duration (in Months)	52.0
FDA Review Information	Duration (in Months)		4.3
Post-approval Information	Phase 4	Number of Studies	1
		Total Enrollment (All Studies)	150
Route of Administration	Injection		Rank = 9
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Orphan		

Drug Name	Darzalex (daratumumab)		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	32,110		Rank = 10
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	23		Rank = 8
Trinity Drug Index	Therapeutic Score [d]	4.8	Rank = 1
	Commercial Score [e]	4.6	Rank = 2
	R&D Score [f]	3	Rank = 3
	Overall Score [g]	4.4	Rank = 2
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	Minor (IV)	Rank = 4
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	Non-quantifiable added benefit		Rank = 6
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	I rating / "reasonable" cost value/ Insufficient evidence for net health benefit		Rank = 3
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	P	Rank = 9
	NY	MB; OT	
	TX	Y	
	PA	Y	
	FL	NPA	
	OH	PA	
	IL	Y	
	MA	PPA	
	MI	N	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$195.7
	Expected Capitalized Cost (in $ Million 2018)		$3,000.9
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		164.3
	Without European Health Technology Assessment (HTA) Scores		131.8
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$1,709.53		

Table A - 28. Vitrakvi (larotrectinib) Information

Drug Name	Vitrakvi (larotrectinib)		
Study Cohort	Oncology		
Label Indications	VITRAKVI is a kinase inhibitor indicated for the treatment of adult and pediatric patients with solid tumors that: have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or that have progressed following treatment. Select patients for therapy based on an FDA-approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.		
Original Company	Loxo Oncology, Inc.		
Current Company	Bayer		
FDA Approval Date	November 2018		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		64.1
Clinical Information	Phase 1	Number of Studies	1
		Total Enrollment (All Studies)	75
		Total Phase Duration (in Months)	32.9
	Phase 2	Number of Studies	1
		Total Enrollment (All Studies)	174
		Total Phase Duration (in Months)	9.2
	Phase 3	Number of Studies	0
		Total Enrollment (All Studies)	NA
		Total Phase Duration (in Months)	NA
FDA Review Information	Duration (in Months)		8.1
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority; Orphan		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	NA		Rank = 13
Estimated Inpatient Market Size [k]	NA		NA

Drug Name	Vitrakvi (larotrectinib)		
Number of Drugs Available for Indication(s) in the U.S.	NA		Rank = 14
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 7
	Commercial Score [e]	NA	Rank = 7
	R&D Score [f]	NA	Rank = 7
	Overall Score [g]	NA	Rank = 7
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 12
	Clinical Added Value [j]	NA	Rank = 12
British Health Assessment (NICE) *	NA		Rank = 14
German Dossier Assessment (IQWiG)	Added benefit not proven		Rank = 8
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	PPA	Rank = 2
	NY	Y	
	TX	OT	
	PA	Y	
	FL	NPA	
	OH	PA	
	IL	NPA	
	MA	PPA	
	MI	Y	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$31.7
	Expected Capitalized Cost (in $ Million 2018)		$782.1
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		282.3
	Without European Health Technology Assessment (HTA) Scores		152.0
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$60.67		

Table A - 29. Rubraca (rucaparib) Information

Drug Name	Rubraca (rucaparib)		
Study Cohort	Oncology		
Label Indications	RUBRACA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated: for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy; for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA. It is also indicated for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA. This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.		
Original Company	Clovis Oncology		
Current Company	Clovis Oncology		
FDA Approval Date	December 2016		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		127.2
Clinical Information	Phase 1	Number of Studies	1
		Total Enrollment (All Studies)	85
		Total Phase Duration (in Months)	49.9
	Phase 2	Number of Studies	2
		Total Enrollment (All Studies)	97
		Total Phase Duration (in Months)	99.8
	Phase 3	Number of Studies	1
		Total Enrollment (All Studies)	564
		Total Phase Duration (in Months)	38.9
FDA Review Information	Duration (in Months)		5.9
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority; Orphan		
New Molecular Entity (Yes/No)	Yes		Rank = 1

Drug Name	Rubraca (rucaparib)		
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	22,530		Rank = 11
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	22		Rank = 7
Trinity Drug Index	Therapeutic Score [d]	3	Rank = 6
	Commercial Score [e]	2.2	Rank = 4
	R&D Score [f]	4.5	Rank = 1
	Overall Score [g]	3	Rank = 4
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	Moderate (III)	Rank = 1
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	Added benefit not proven		Rank = 8
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	C+; P/ would need to be discounted / Promising but inconclusive evidence		Rank = 2
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	PA	Rank = 2
	NY	Y	
	TX	Y; OT	
	PA	PPA	
	FL	Y; QL	
	OH	PA	
	IL	NPA	
	MA	PPA	
	MI	Y	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$70.7
	Expected Capitalized Cost (in $ Million 2018)		$3,246.3
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		124.3
	Without European Health Technology Assessment (HTA) Scores		95.6
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$18.21		

Table A - 30. Jevtana (cabazitaxel) Information

Drug Name	Jevtana (cabazitaxel)		
Study Cohort	Oncology		
Label Indications	JEVTANA is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.		
Original Company	sanofi-aventis U.S., LLC		
Current Company	sanofi-aventis U.S., LLC		
FDA Approval Date	June 2010		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		93.0
Clinical Information	Phase 1	Number of Studies	4
		Total Enrollment (All Studies)	92
		Total Phase Duration (in Months)	33.9
	Phase 2	Number of Studies	2
		Total Enrollment (All Studies)	104
		Total Phase Duration (in Months)	NA
	Phase 3	Number of Studies	1
		Total Enrollment (All Studies)	755
		Total Phase Duration (in Months)	31.9
FDA Review Information	Duration (in Months)		2.6
Post-approval Information	Phase 4	Number of Studies	4
		Total Enrollment (All Studies)	400
Route of Administration	Intravenous		Rank = 9
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	174,650		Rank = 6
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	23		Rank = 8
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 7
	Commercial Score [e]	NA	Rank = 7
	R&D Score [f]	NA	Rank = 7
	Overall Score [g]	NA	Rank = 7

Drug Name	Jevtana (cabazitaxel)		
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	Minor (IV)	Rank = 4
British Health Assessment (NICE) *	Recommended in combination with prednisone or prednisolone		Rank = 1
German Dossier Assessment (IQWiG)	Considerable added benefit over 65yo, not quantifiable added benedit under 65yo		Rank = 1
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	Effective second-line agent		Rank = 2
Medicaid Coverage	CA	P	Rank = 11
	NY	MB; OT	
	TX	Y	
	PA	Y	
	FL	NPA	
	OH	MB; OT	
	IL	Y	
	MA	PPA	
	MI	N	
	NJ	P	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$77.8
	Expected Capitalized Cost (in $ Million 2018)		$2,517.8
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		180.7
	Without European Health Technology Assessment (HTA) Scores		163.7
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$496.25		

Table A - 31. Yondelis (trabectedin) Information

Drug Name	Yondelis (trabectedin)		
Study Cohort	Oncology		
Label Indications	YONDELIS is an alkylating drug indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.		
Original Company	Janssen Products, L.P.		
Current Company	Janssen Products, L.P.		
FDA Approval Date	October 2015		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		49.7
Clinical Information	Phase 1	Number of Studies	6
		Total Enrollment (All Studies)	126
		Total Phase Duration (in Months)	225.6
	Phase 2	Number of Studies	18
		Total Enrollment (All Studies)	1370
		Total Phase Duration (in Months)	173.6
	Phase 3	Number of Studies	7
		Total Enrollment (All Studies)	3,107
		Total Phase Duration (in Months)	188.7
FDA Review Information	Duration (in Months)		10.9
Post-approval Information	Phase 4	Number of Studies	0
		Total Enrollment (All Studies)	NA
Route of Administration	Intravenous		Rank = 9
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority; Orphan		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	Yes		Rank = 1
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	NA		Rank = 13
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	2		Rank = 1
Trinity Drug Index	Therapeutic Score [d]	3.2	Rank = 4
	Commercial Score [e]	1.8	Rank = 5
	R&D Score [f]	1.5	Rank = 6
	Overall Score [g]	2.3	Rank = 5

Drug Name	Yondelis (trabectedin)		
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	Substantial	Rank = 1
	Clinical Added Value [j]	Minor (IV)	Rank = 4
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	NA		Rank = 13
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	P	Rank = 11
	NY	MB; OT	
	TX	Y	
	PA	Y	
	FL	NPA	
	OH	PA	
	IL	Y	
	MA	PA	
	MI	N	
	NJ	P	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$395.5
	Expected Capitalized Cost (in $ Million 2018)		$29,710.7
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		198.2
	Without European Health Technology Assessment (HTA) Scores		147.4
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$69.09		

Table A - 32. Cometriq (cabozantinib) Information

Drug Name	Cometriq (cabozantinib)		
Study Cohort	Oncology		
Label Indications	COMETRIQ is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).		
Original Company	Exelixis, Inc.		
Current Company	Exelixis, Inc.		
FDA Approval Date	November 2012		
FDA Submission Classification	Type 1 - New Molecular Entity		
Type	Small molecule		
Preclinical Information	Duration (in Months)		21.1
Clinical Information	Phase 1	Number of Studies	8
		Total Enrollment (All Studies)	291
		Total Phase Duration (in Months)	82.9
	Phase 2	Number of Studies	2
		Total Enrollment (All Studies)	241
		Total Phase Duration (in Months)	48.9
	Phase 3	Number of Studies	1
		Total Enrollment (All Studies)	330
		Total Phase Duration (in Months)	39.9
FDA Review Information	Duration (in Months)		6.3
Post-approval Information	Phase 4	Number of Studies	2
		Total Enrollment (All Studies)	358
Route of Administration	Oral		Rank = 1
QIDP Designation (Yes/No)	NA		NA
BARDA Funding (Yes/No)	NA		NA
Type of FDA Review	Priority; Orphan		
New Molecular Entity (Yes/No)	Yes		Rank = 1
New Chemical Entity (Yes/No)	No		Rank = 5
Activity Against ESKAPE Pathogens (Yes/No) [a]	NA		NA
Activity Against CDC Urgent or WHO Critical Threat Pathogens (Yes/No) [b][c]	NA		NA
Approximate Annual Number U.S. Cases	1,000		Rank = 12
Estimated Inpatient Market Size [k]	NA		NA
Number of Drugs Available for Indication(s) in the U.S.	2		Rank = 1
Trinity Drug Index	Therapeutic Score [d]	NA	Rank = 7
	Commercial Score [e]	NA	Rank = 7
	R&D Score [f]	NA	Rank = 7
	Overall Score [g]	NA	Rank = 7
French Health Assessment (Haute Autorité de Santé)	Actual Benefit [i]	NA	Rank = 12

Drug Name	Cometriq (cabozantinib)		
	Clinical Added Value [j]	NA	Rank = 12
British Health Assessment (NICE) *	Recommended		Rank = 1
German Dossier Assessment (IQWiG)	Non-quantifiable added benefit		Rank = 6
AST Device Incorporation	Vitek® 2	NA	NA
	MicroScan	NA	NA
ICER Assessment *	NA		Rank = 4
IDSA Guideline Inclusion	NA		NA
P&T Community Decision *	NA		Rank = 4
Medicaid Coverage	CA	P	Rank = 2
	NY	Y	
	TX	Y; OT	
	PA	PPA	
	FL	NPA	
	OH	PA	
	IL	NPA	
	MA	PPA	
	MI	Y	
	NJ	Y	
Estimated Development and Approval Cost	Cost (in $ Million 2018)		$97.5
	Expected Capitalized Cost (in $ Million 2018)		$2,604.4
Overall Clinical Value Score	With European Health Technology Assessment (HTA) Scores		209.8
	Without European Health Technology Assessment (HTA) Scores		124.0
First 9 Quarters IQVIA MIDAS Sales (in $ Million 2018)	$59.38		

APPENDIX B: SENSITIVITY ANALYSIS OF THE RELATIONSHIP BETWEEN OVERALL COMPARATIVE ADDED CLINICAL BENEFIT SCORE AND FIRST 9-QUARTER SALES

We evaluated the relationship between overall comparative added clinical benefit score and 9-quarter sales for the following cases:

- All AM drugs versus small company AM drugs with and without HTA metrics,
- All non-AM comparator drugs versus small company non-AM comparator drugs with and without HTA metrics,
- All oncology drugs versus large company oncology drugs with and without HTA metrics, and
- All oncology drugs versus those with orphan status with and without HTA metrics.

Figure B - 1 through Figure B - 6 present the results of this analysis.

Figure B - 1. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – All AM and Small Company AM Drugs (Includes HTA Metrics)

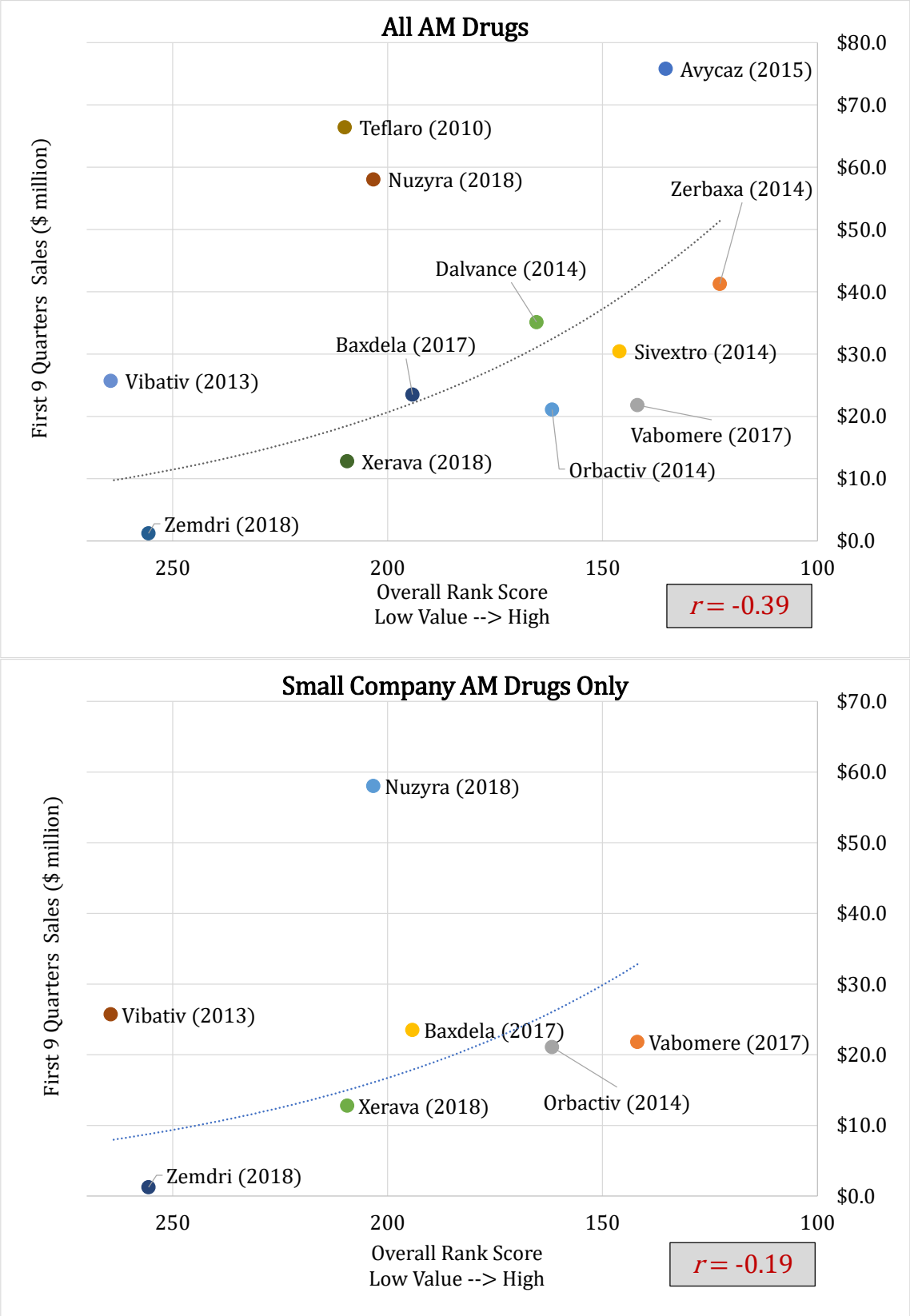
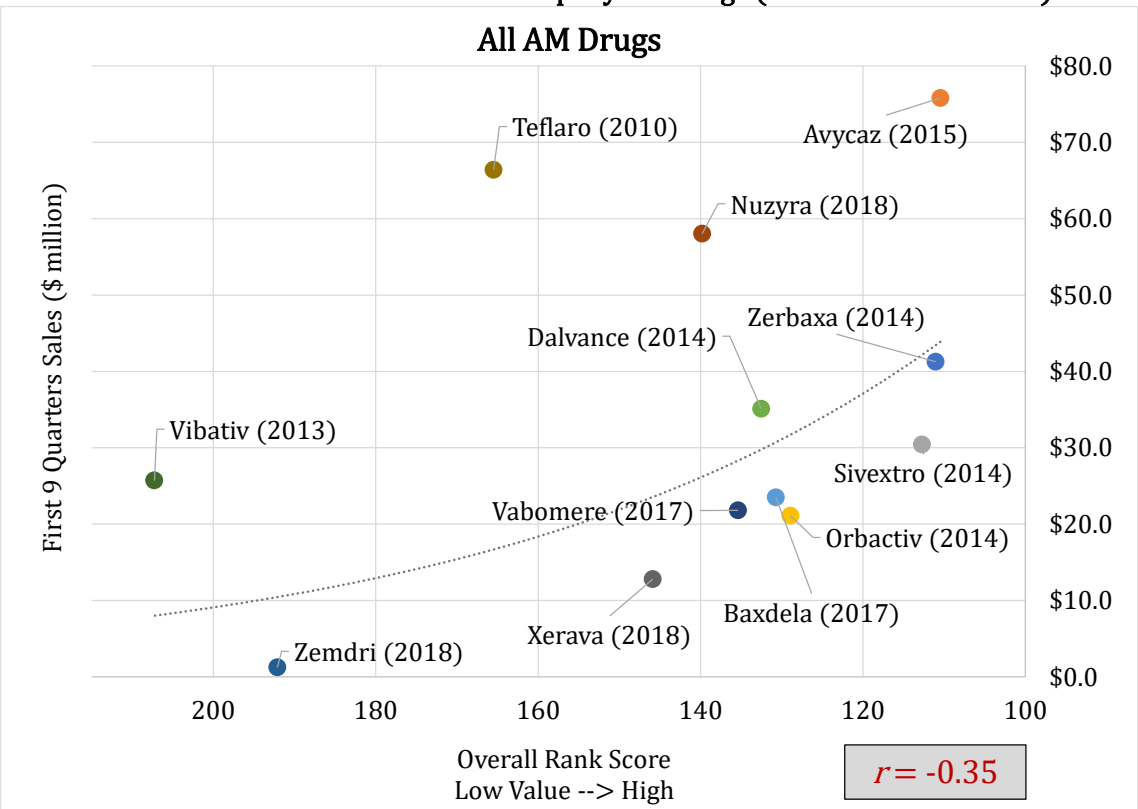


Figure B - 2. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – All AM and Small Company AM Drugs (Excludes HTA Metrics)



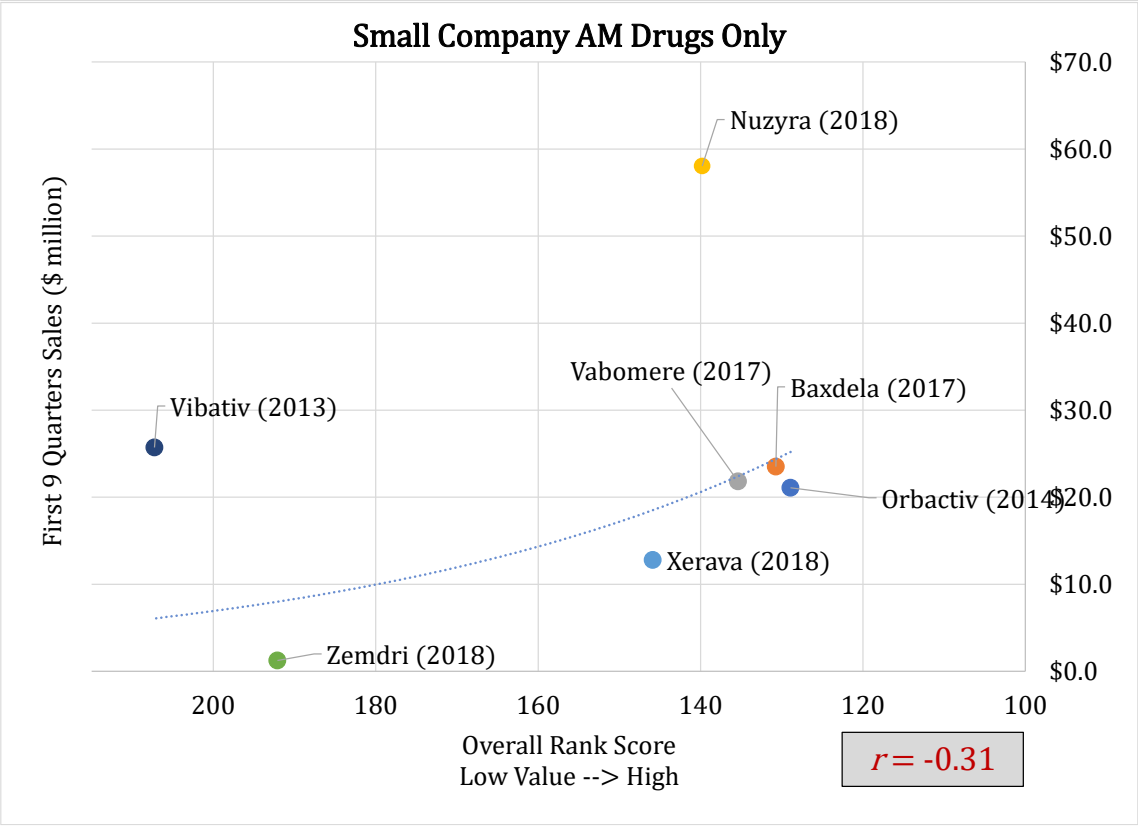
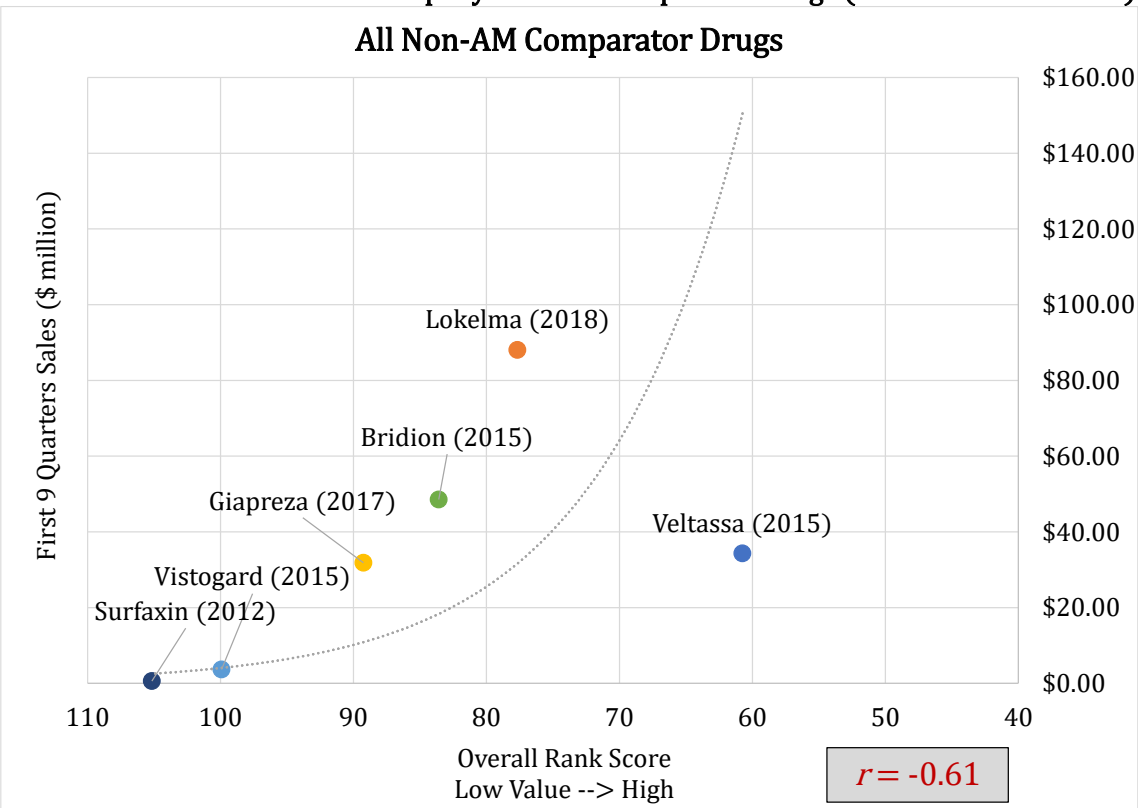


Figure B - 3. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – All and Small Company Non-AM Comparator Drugs (Includes HTA Metrics)



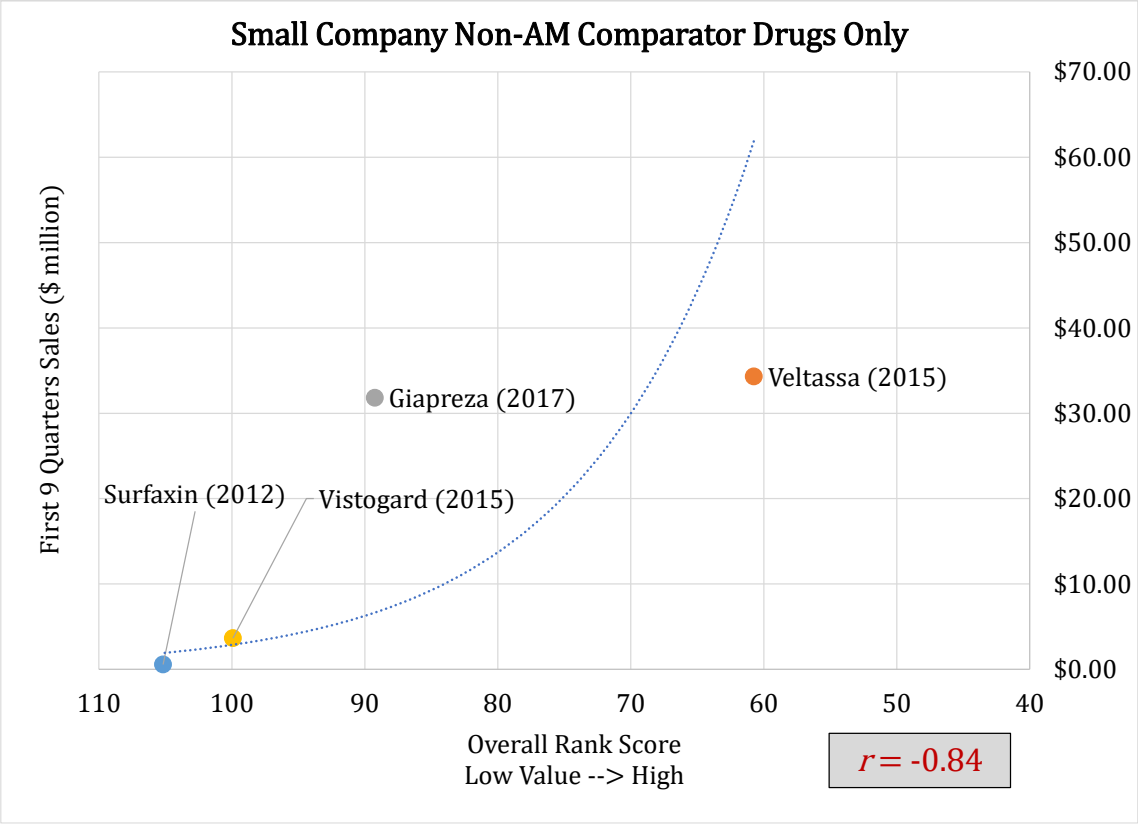


Figure B - 4. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – All and Small Company Non-AM Comparator Drugs (Excludes HTA Metrics)

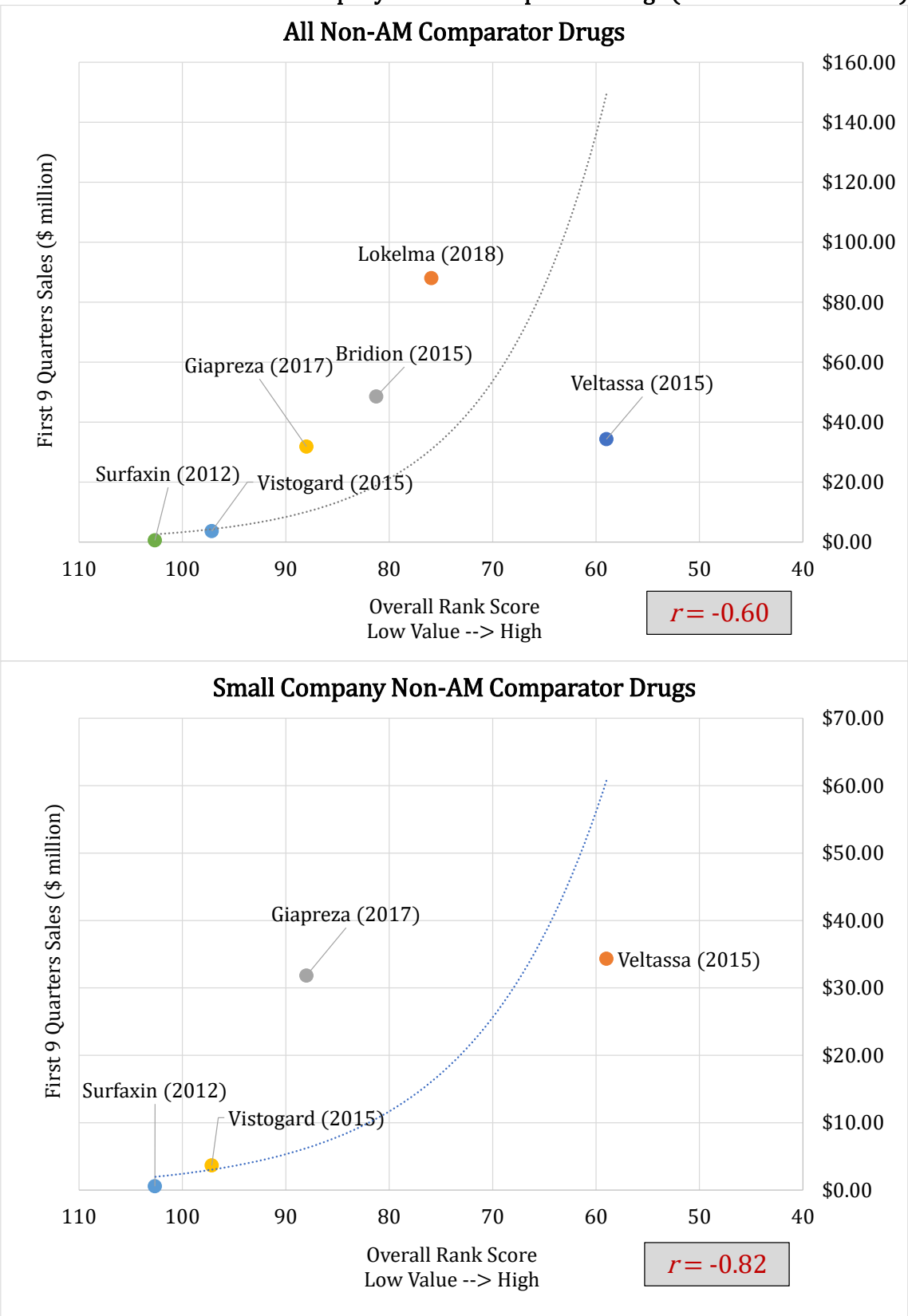


Figure B - 5. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – All Oncology, Large Company Oncology, and Orphan Status Oncology Drugs (Includes HTA Metrics)

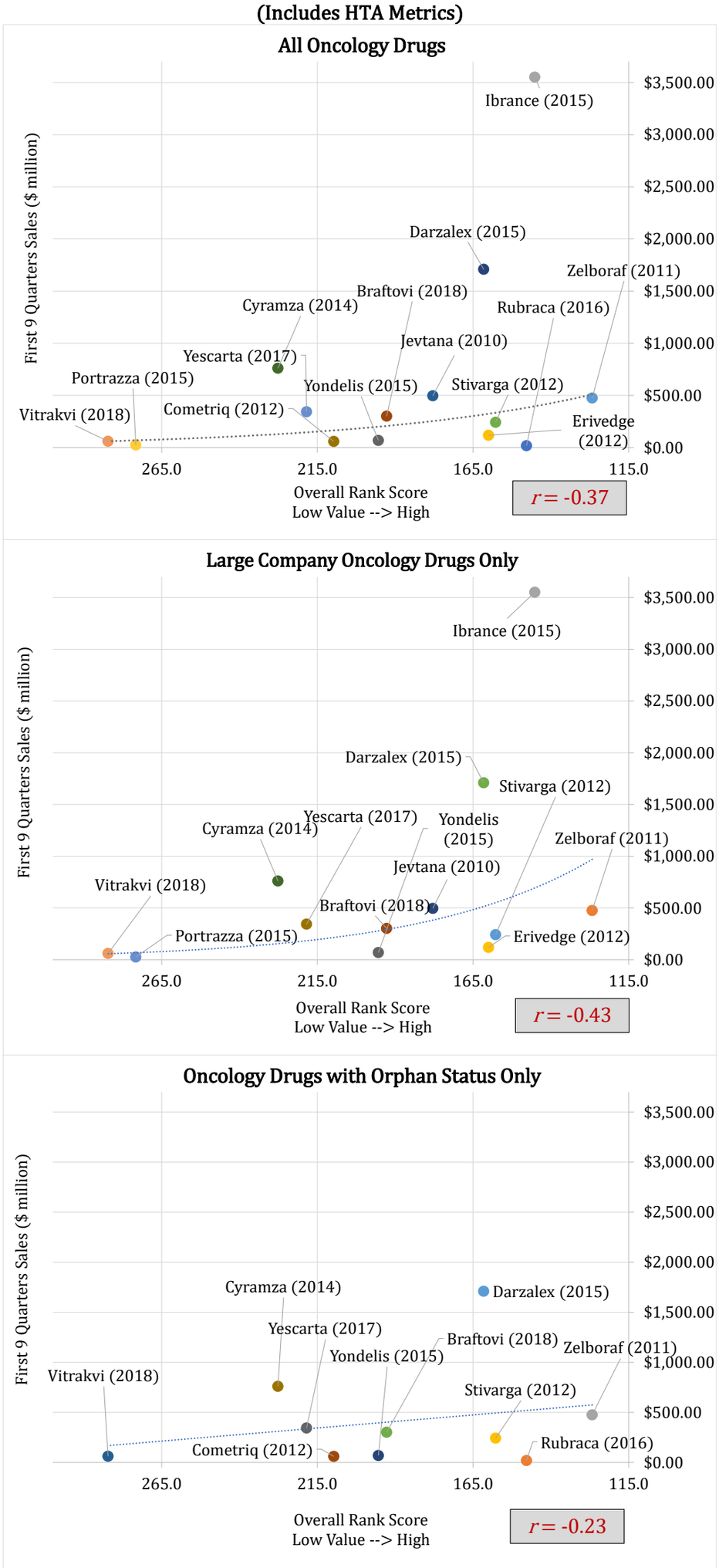


Figure B - 6. First 9 Quarters of IQVIA MIDAS Reported Sales versus Overall Comparative Clinical Benefit Score – All Oncology, Large Company Oncology, and Orphan Status Oncology Drugs (Excludes HTA Metrics)