Biotechnology

Antibiotic R&D Update 20

REPORT HIGHLIGHTS: Several new antibiotics reached the market in the last 12 months, but sales for the most part have been a disappointment. The polymyxins have only gradually been displaced by new safer and more effective antibiotics for serious infections, consistent with the notion that the current reimbursement framework in the hospital does not adequately reward innovation. Factoring in a few development and regulatory misses, investor sentiment toward nearly the entire space has deteriorated and cash is a concern for most companies. For investors willing to consider antibiotics, we believe there are underappreciated opportunities with companies focused on markets outside the hospital (e.g. Urinary Tract Infection, Community Pneumonia, and NTM Lung Disease), in particular Nabriva (NBRV, BUY) and Iterum (ITRM, BUY).

- **There is a sense of urgency among stakeholders to identify new mechanisms to support industry and drug development**. The two most prominent mechanisms under consideration are a Medicare add-on payment and a market entry reward. We detect a greater degree of collaboration and alignment among many U.S. government agencies, foundations, and the academic medical community, but we do not yet have conviction that anything meaningful will be implemented in 2019.
- CRE and related carbapenem-resistant pathogens have attracted the most attention from industry. We acknowledge better antibiotics are needed, but the number of patients in the U.S. appears to be modest, growth in the number of cases is small, and physicians have been slow to shift from older polymyxins. We are also concerned the market could become crowded given the size of the development pipeline. However, with reimbursement policy changes, the total U.S. market for carbapenem-resistant pathogens could be over $1.6B in 2030.
- **We believe lefamulin has the best profile to address the large unmet need in Community Pneumonia outside the hospital (Nabriva; PDUFA 8/19/19)**. Although there are many generic antibiotics available, several efficacy and safety vulnerabilities to standard of care have emerged. If coupled with a large sales group, we believe lefamulin has an opportunity to reach $1B U.S. sales.
- **Urinary Tract Infections represents another attractive target market.** There is no sufficiently potent oral antibiotic available (some patients require an IV antibiotic) and the market outside the hospital is large. **Iterum** is expected to announce Phase 3 results in 2H19, followed by Spero in 2020.
- ***C. difficile*: Guidelines Matter.** Dificid and Zinplava, the only drugs approved in the last 10 years for *C. difficile*, have not been commercially successful. However, we note that the first update to IDSA guidelines (2018) since approval of Dificid (2011) had a sudden +30-40% impact on sales. Prompt updates to guidelines may be needed to ensure that more effective new antibiotics are actually put to use when approved.

Companies Mentioned in Report:

- **AKAO: $0.46, PT: NA**
- **ITRM: $8.11, PT: $20.00**
- **TTPH: $1.20, PT: NA**
- **CDTX: $2.49, PT: $14.00**
- **NBRV: $2.39, PT: $15.00**

Topic of Discussion:

Review of the Antibiotic Space

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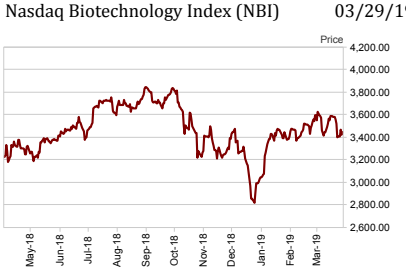
Sector Chart

Nasdaq Biotechnology Index (NBI) 03/29/19



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Investor sentiment continues to deteriorate, driven by disappointing launches, a few negative development and regulatory outcomes, and modest interest from Pharma.

For investors willing to consider the space, we suggest a focus on companies with a target market outside the hospital, an indication with a very clear unmet need, and minimal competitive development. We believe the most attractive opportunities are in 1) Urinary Tract Infections, where the most reliable remaining options can only be administered IV and 2) Community Pneumonia where macrolide resistance is remarkably high and fluoroquinolone use is increasingly discouraged. Infections that require longer-term treatment, such as Nontuberculous Mycobacteria (NTM) infections, are also attractive. Insmed recently launched Arikayce for NTM.

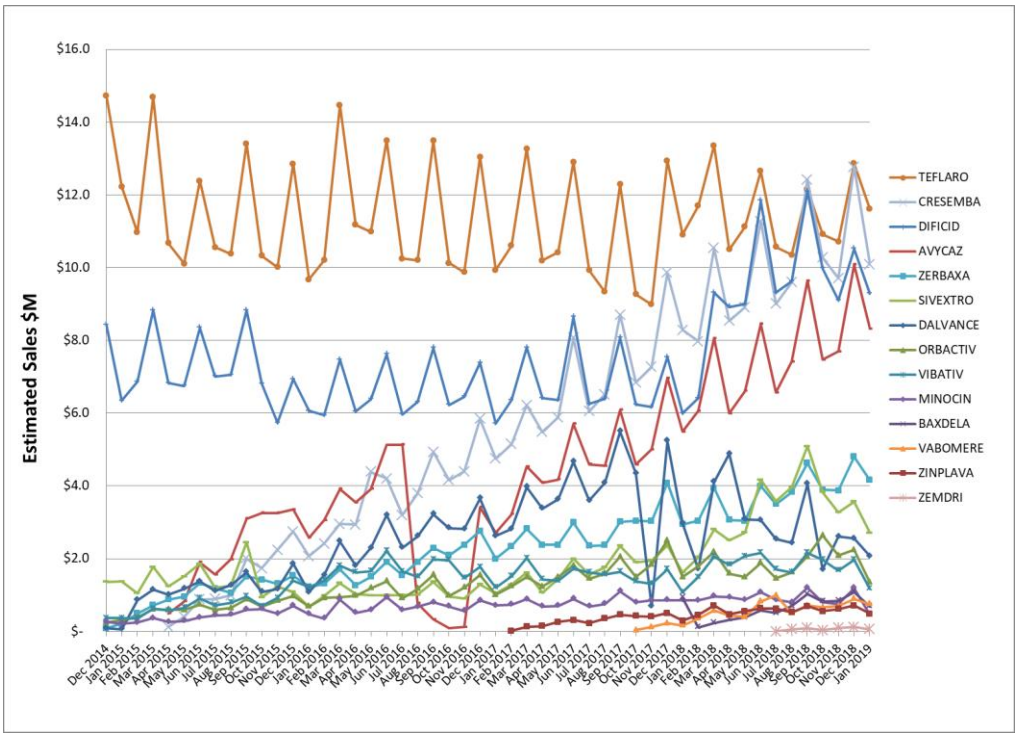
COMMERCIAL LANDSCAPE

Table 1: Branded Antibiotic and Antifungal Pricing and Sales (U.S Only)

Drug Company	Unit	WAC	Dosage	WAC/Course*	Price Change	U.S. Sales
Ambisome Astellas	1x50mg Vial	$247	3-5mg/kg qd	$25935 5mg/kg 14 days	9% increase 7/10/2018	4Q18 IMS sales: $32.9M 4Q18 Symphony: $75.0M 4Q18 Astellas Report $33M
Avycaz Allergan	1x2.5g Vial	$359	cIAI 2.5g q8h, 5-14 days cUTI 2.5g q8h, 7-14 days	$5387-15085	9.5% increase 1/1/2019	4Q18 IMS sales: $25.1M 4Q18 Symphony: $26.4M 4Q18 AGN Reported: $24.6M
Baxdela Melinta	10x300mg Vial	$1325	300mg q12h 5-14 days	$1325-3710	Launch price 10/20/2017	4Q18 IMS sales: $2.8M 4Q18 Symphony: $2.5M
	20x450mg Tablet	$1418	450mg q12h 5-14 days	$744-2084	5% increase 10/1/2018	
Cresemba Astellas	1x372mg Vial	$315	372mg q8h load 2days 372mg qd	$15400 45 days	6% increase 1/8/2019	4Q18 IMS sales: $32.8M 4Q18 Symphony: $35.7M 4Q18 Astellas Report $31M
	14x186mg Tablet	$1296	372mg q8h load 2days 372mg qd	$9257 45 days	6% increase 1/8/2019	
Dalvance Allergan	1x500mg Vial	$1535	1500mg or 1000mg followed one week later by 500mg	$4605	3% increase 7/1/2017	4Q18 IMS sales: $9.0M 4Q18 Symphony: $10.1M 4Q18 AGN Reported: $17.3M
Dificid Merck	20x200mg Tablet	$3865	200mg oral q12h 10-14 days	$3865 10 days	5% increase 1/4/2019	4Q18 IMS sales: $29.7M 4Q18 Symphony: $33.8M
Eraxis Pfizer	1x100mg Vial	$180	200mg load; 100mg qd 14 days after + culture	$2880 15 days	Launch price 10/26/2009	4Q18 IMS sales: $2.3M 4Q18 Symphony: $8.5M
Invanz Merck	1x1.0g Vial	$135	cIAI: 1g qd, 5-14 days cSSSI: 1g qd, 7-14 days cUTI: 1g qd, 10-14 days CAP: 1g, 10-14 days	$675-1890	9.8% increase 1/5/2018	4Q18 IMS sales: $16.9M 4Q18 Symphony: $26.2M 4Q18 MRK Reported: $1M Generic launch Aug 2018
Minocin Melinta	1x100mg Vial	$162	100mg q12h 10-14 days	$3240-4536	5% increase 7/2/2018	4Q18 IMS sales $2.8M 4Q18 Symphony: $2.9M
Mycamine Astellas	10x100mg Vial	$1870	Treat: 100mg qd Prophylaxis: 50mg qd	$2805 15 days	Launch price	4Q18 IMS sales: $28.4M 4Q18 Symphony: $62.3M 4Q18 Astellas Report $29M
Noxafil Merck	1x300mg Vial	$530	300mg BID Load; 300mg QD		Launch price 3/18/2014	4Q18 IMS sales: $91.6M 4Q18 Symphony: $94.3M 4Q18 MRK Reported: $96M
	60x100mg Tablet	$4112	300mg BID Load; 300mg QD	$16600 80 days	5% increase 1/4/2019	
Nuzyra Paratek	1x100mg Vial	$345	CABP: 200mg IV load 1 day 100mg IV or 300mg oral QD 7-14 days total ABSSSI: 200mg IV load 1 day or 450mg oral load 2 days 100mg IV or 300mg oral; 7-14 d	CABP 7-14days $2760-5825 ABSSSI 7-14day $2760-5925	Launch price 12/10/2018	
	6x150mg Tablet	$1185			Launch price 12/10/2018	
Orbactiv Melinta	1x400mg Vial	$996	1200mg single dose	$2988	3% increase 7/2/2018	4Q18 IMS sales: $7.1M 4Q18 Symphony: $8.4M
Sivextro Merck	10x200mg Vial	$2876	200mg qd 6 days	$1725	4% increase 1/4/2019	4Q18 IMS sales: $10.7M 4Q18 Symphony: $13.6M
	6x200mg Tablet	$2165	200mg qd 6 days	$2165	4% increase 1/4/2019	
Teflaro Allergan	10x600 mg Vial	$1921	600mg q12h 5-14 days	$1922-5381	9.5% increase 1/1/2019	4Q18 IMS sales: $34.6M 4Q18 Symphony: $40.3M 4Q18 AGN Reported: $30.0M
Vabomere Melinta	1x2.0g Vial	$165	4.0g q8h 5-14 days	$4950-13860	Launch price 9/25/2017	4Q18 IMS sales: $2.3M 4Q18 Symphony: $2.3M
Vibativ Cumberland Theravance	1x750mg Vial	$432	10mg/kg qd 7-14 days	$3024-6084	2.5% increase 7/1/2018	4Q18 IMS sales: $5.7M 4Q18 Symphony: $6.3M Sold to Cumberland 11/19
Xerava Tetraphase	1x50mg Vial	$44	1mg/kg q12h 4-14 days	$704-2464 4-14 days	Launch price 10/1/18	4Q18 TTPH Reported $0.2M
Zemdri Achaogen	1x500mg Vial	$315	15mg/kg qd 4-7 days cUTI	$3780-13230 4-14 days	Launch price 07/17/2018	4Q18 IMS sales: $0.2M 4Q18 AKAO Reported $0.5M
Zerbaxa Merck	10x1.5g Vial	$1086	cIAI 1.5g q8h, 4-14 days cUTI 1.5g q8h, 7 days Off Label HABP 3.0g q8h 14 days	$1300-9120 4-14 days	3% increase 1/4/2019	4Q18 IMS sales: $12.6M 4Q18 Symphony: $8.4M
Zinplava Merck	1x1000mg Vial	$3800	10mg/kg single dose	$3800	Launch price 12/8/2016	4Q18 IMS sales: $1.9M 4Q18 Symphony: $1.9M

*Source: Company reports; Needham & Company, LLC estimates; *Assume 75-80kg for weight-based dosing and batching; IMS/Iqvia, Symphony*

Branded Antibiotic Sales Trajectories (IQVIA data 1/31/19; Actual sales reported by company may differ—see Table 1)



Branded Antibiotic Sales Trajectories (3-month Moving Average; IQVIA Data through 1/31/19)

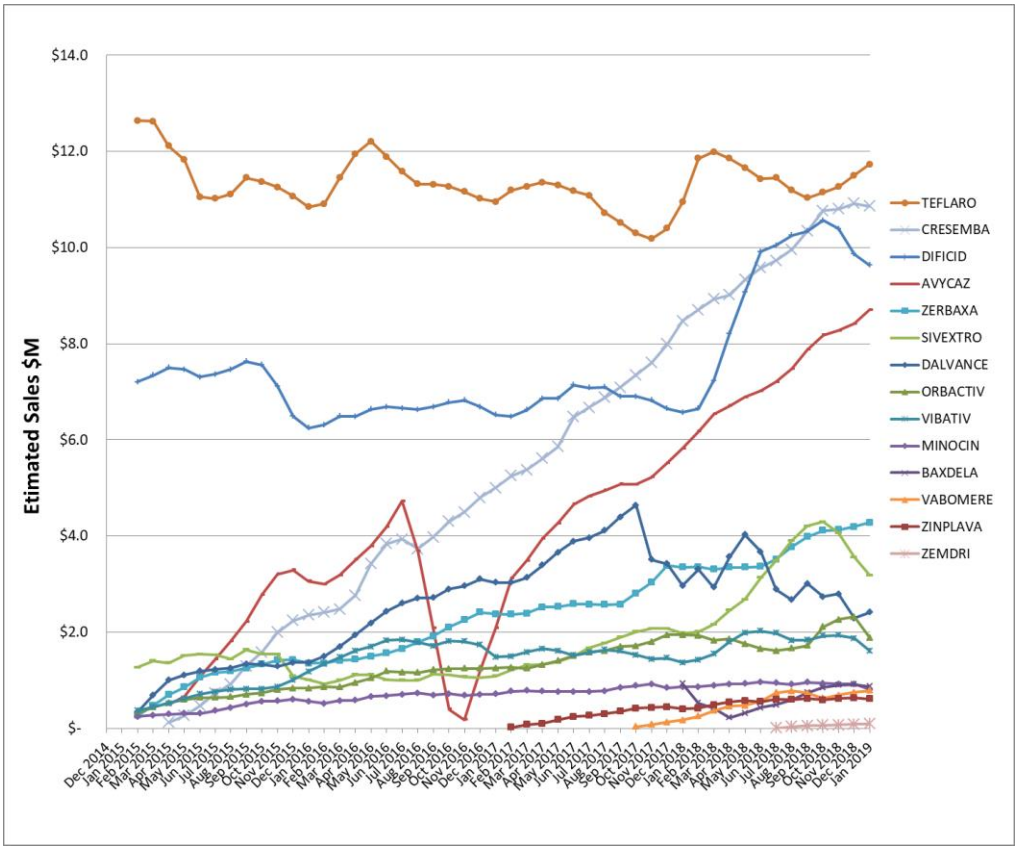


Table 2 Monthly Branded Antibiotic Sales ($M; IQVIA Data; Actual sales reported by company may differ—see Table 1)

Month	AVY	BAX	DAL	DIF	MIN	ORB	SIV	TEF	VAB	VIB	ZEM	ZER	ZIN
Jan 2016	2.6	-	1.1	6.0	0.5	0.7	0.7	9.7	-	1.2		1.2	-
Feb 2016	3.1	-	1.6	6.0	0.4	0.9	1.0	10.2	-	1.4		1.3	-
Mar 2016	3.9	-	2.5	7.4	0.9	1.0	1.3	14.5	-	1.8		1.7	-
Apr 2016	3.5	-	1.8	6.0	0.5	1.0	1.0	11.2	-	1.6		1.4	-
May 2016	3.9	-	2.3	6.3	0.6	1.2	1.0	11.0	-	1.7		1.5	-
Jun 2016	5.1	-	3.2	7.6	0.9	1.4	1.0	13.5	-	2.2		1.9	-
Jul 2016	5.1	-	2.3	6.0	0.6	0.9	1.0	10.3	-	1.6		1.5	-
Aug 2016	0.8	-	2.6	6.3	0.7	1.2	1.0	10.2	-	1.5		1.9	-
Sep 2016	0.3	-	3.4	7.8	0.8	1.6	1.4	13.5	-	2.0		2.3	-
Oct 2016	0.1	-	2.8	6.2	0.7	1.0	1.0	10.1	-	2.0		2.1	-
Nov 2016	0.1	-	2.8	6.5	0.6	1.2	0.9	9.9	-	1.5		2.4	-
Dec 2016	3.4	-	3.6	7.4	0.9	1.5	1.3	13.0	-	1.8		2.8	-
Jan 2017	2.7	-	2.6	5.9	0.7	1.0	1.1	9.9	-	1.2		2.0	-
Feb 2017	3.2	-	2.8	6.7	0.7	1.2	1.3	10.6	-	1.5		2.4	0.0
Mar 2017	4.5	-	4.0	8.3	0.9	1.5	1.6	13.3	-	2.0		2.8	0.1
Apr 2017	4.1	-	3.4	6.7	0.7	1.2	1.1	10.2	-	1.4		2.4	0.1
May 2017	4.2	-	3.6	6.4	0.7	1.5	1.5	10.4	-	1.4		2.4	0.3
Jun 2017	5.7	-	4.7	8.6	0.9	1.8	2.0	12.9	-	1.7		3.0	0.3
Jul 2017	4.6	-	3.6	6.3	0.7	1.4	1.6	9.9	-	1.6		2.4	0.2
Aug 2017	4.5	-	4.1	6.4	0.8	1.6	1.8	9.3	-	1.6		2.4	0.4
Sep 2017	6.1	-	5.5	8.1	1.1	2.1	2.4	12.3	-	1.6		3.0	0.5
Oct 2017	4.6	-	4.3	6.2	0.8	1.5	1.9	9.3	0.0	1.4		3.0	0.4
Nov 2017	5.0	-	0.7	6.2	0.9	1.8	2.0	9.0	0.1	1.3		3.0	0.4
Dec 2017	7.0	-	5.2	7.5	0.9	2.5	2.4	12.9	0.2	1.7		4.1	0.5
Jan 2018	5.5	0.9	3.0	6.0	0.9	1.5	1.6	10.9	0.2	1.1		2.9	0.3
Feb 2018	6.1	0.1	1.7	6.4	0.9	1.8	2.0	11.7	0.4	1.5		3.0	0.5
Mar 2018	8.1	0.2	4.1	9.3	1.0	2.2	2.8	13.4	0.6	2.1		3.9	0.7
Apr 2018	6.0	0.3	4.9	8.9	0.9	1.6	2.5	10.5	0.4	1.8		3.1	0.5
May 2018	6.6	0.4	3.1	9.0	0.9	1.5	2.7	11.1	0.4	2.1		3.0	0.6
Jun 2018	8.4	0.6	3.1	11.8	1.1	1.9	4.2	12.7	0.8	2.2		4.0	0.6
Jul 2018	6.6	0.5	2.5	9.3	0.9	1.5	3.6	10.6	1.0	1.7	0.0	3.5	0.6
Aug 2018	7.4	0.7	2.4	9.6	0.8	1.6	4.0	10.4	0.5	1.6	0.1	3.8	0.5
Sept 2018	9.6	1.0	4.1	12.1	1.2	2.1	5.1	12.2	0.7	2.2	0.1	4.6	0.7
Oct 2018	7.5	0.8	1.7	10.0	0.8	2.6	3.8	10.9	0.7	2.0	0.0	3.9	0.6
Nov 2018	7.7	0.8	2.6	9.1	0.8	2.1	3.3	10.7	0.7	1.7	0.1	3.9	0.6
Dec 2018	10.1	1.1	2.6	10.5	1.2	2.2	3.6	12.9	0.9	2.0	0.1	4.8	0.7
Jan 2018	8.3	0.7	2.1	9.3	0.5	1.3	2.7	11.6	0.8	1.2	0.1	4.2	0.5
Last 12 Months	92.4	7.3	34.8	115.4	10.8	22.4	40.3	138.5	7.8	21.9	NA	45.8	7.0
(y/y% growth)	57%	N/A	-22%	40%	10%	14%	92%	6%	N/A	19%		36%	99%

*Source: IMS data; *Allergan reported API shortage from August 2015 to resolution in February 2017; AVY Avycaz; BAX Baxdela; DAL Dalvance; DIF Dificid; Min Minocin; ORB Orbactiv; SIV Sivextro; TEF Teflaro; VAB Vabomere VIB Vibativ; ZEM Zemdri; ZER Zerbaxa; ZIN Zinforo*

Astellas provides sales guidance for FY2018

- Ambisome: Americas $114M (+11.4% y/y)
- Cresemba: Americas $117M (+35% y/y)
- Mycamine: Americas $94M (-15% y/y) EMEA €86 (-14% y/y) Global ¥34.3B (-16.3%)

Melinta issued sales guidance for CY2019

- All products: $65M (+40% y/y)

LATE-STAGE DEVELOPMENT LANDSCAPE

Table 3: Antibiotics in Phase 3 Development, Under Regulatory Review, or Recently Launched

Drug Company	cUTI	cIAI	ABSSSI	HABP/VABP	CABP	Gonorrhea	Other Phase 3
AAI101 Allecra	Phase 3 NCT03687255						
Avibactam Aztreonam Pfizer							Gram Negative Phase 3 NCT03329092 NCT03580044
Arikayce Insmed							NTM Market US
Cefiderocol S-649266 Shionogi	Phase 2 Completed NCT02321800	-	-	Phase 3 NCT03032380	-		Carbapenem R Phase 3 NCT02714595
Ceftobiprole Basilea	-	-	Phase 3 NCT03137173	Market (exUS)	Market (exUS)	-	Bacteremia Phase 3 NCT03138733
Delafloxacin Baxdela Melinta	-	-	Market US Review EU	-	Phase 3 Completed NCT02679573	Phase 3 Failed NCT02015637	-
Eravacycline Tetraphase	Phase 3 Failed NCT01978938 NCT03032510	Market US EU	-	-	-	-	-
ETX2514SUL Entasis	-	-	-	-	-	-	CRAB Phase 3 Planned
Fosfomycin Contepo Nabriva	FDA Review	-	-	-	-	-	-
Iclaprim Motif	-	-	FDA CRL	-	-	-	-
Lefamulin Nabriva	-	-	-	-	FDA Review	-	-
Murepavadin Polyphor				Phase 3 NCT03582007 NCT03409679			
Omadacycline Paratek	Phase 2 NCT03425396 NCT03757234	-	Market US EMA Review	-	Market US	-	-
Plazomicin Achaogen	Market US	-	-	-	-	-	BSI/ CRE Completed NCT01970371
Relebactam Merck	FDA Review EMA Review	FDA Review EMA Review	-	Phase 3 NCT02493764 NCT03583333	-	-	Imipenem-R Completed NCT02452047
Vaborbactam Melinta	Market US EU	-	-	-	-	-	CRE Completed NCT02168946
Zerbaxa Merck	Market	Market	-	FDA Review EMA Review	-	-	-

Source: Company reports; Needham & Company, LLC; clinicaltrials.gov; Ceftobiprole approved for HABP, but not VABP

ANTIMICROBIAL COMPANY VALUATIONS

TICKER	PRICE	52 HI	52 LO	YTD RETURN	2018 RETURN	MKT CAP	EV	CASH	LTM OPEX	DEBT	2019 REV EST	2020 REV EST	2019 EV/Sales	2020 EV/Sales	Development Status
AKAO	0.46	15.00	0.45	(62.6%)	(88.5%)	29.1	(26.9)	56.0	188.0	-	20.0	43.0	(1.3)	(0.6)	Market
BSLN-SWX	46.10	73.95	38.60	15.4%	(47.4%)	547.6	523.5	223.9	156.6	199.8	132.3	154.5	4.0	3.4	Market
CDTX	2.49	6.35	1.94	6.0%	(65.4%)	68.9	(5.6)	74.6	63.3	-	-	-	N/A	N/A	Phase 3 Underway
CFRX	0.40	2.93	0.36	(73.8%)	51.5%	31.8	1.4	30.5	31.1	-	-	-	N/A	N/A	Phase 2 Completed
ETTX	6.64	13.70	3.97	63.1%		87.0	(7.1)	94.0	N/A	-	10.9	2.5	(0.6)	(2.8)	Phase 3 Planned
INSM	28.12	31.58	11.31	114.3%	(57.9%)	2,180.4	2,001.9	495.1	317.2	316.6	89.2	198.9	22.5	10.1	Market
ITRM	8.11	13.00	4.70	61.8%		116.5	45.0	84.6	N/A	13.1	0.5	6.7	91.8	6.7	Phase 3 Underway
MCRB	6.96	9.75	4.42	54.0%	(55.4%)	285.7	199.9	85.8	128.6	-	42.4	41.4	4.7	4.8	Phase 2/3 Underway
MLNT	3.44	46.00	3.22	(13.2%)	(95.0%)	38.6	67.3	81.8	217.2	110.5	72.8	113.7	0.9	0.6	Market
MTFB	1.88	11.50	1.54	(71.5%)	(39.0%)	28.0	22.4	19.8	20.9	14.3	19.6	34.3	1.1	0.7	FDA Review
MTNB	1.13	1.50	0.32	89.9%	(48.7%)	157.8	151.3	6.6	15.3	0.1	0.2	N/A	756.5	N/A	Phase 2 Planned
NBRV	2.39	6.05	1.12	63.7%	(75.6%)	166.6	88.1	102.2	92.0	23.7	12.8	39.5	6.9	2.2	FDA Review
POLN-SWX	20.55	45.00	16.28	15.2%		227.0	73.9	155.6	N/A	2.5	12.1	16.6	6.1	4.5	Phase 3 Underway
PRTK	5.39	14.15	4.50	5.1%	(71.3%)	174.7	153.1	250.6	121.2	229.0	18.4	54.0	8.3	2.8	Market
SCYX	1.42	2.15	0.35	194.8%	(79.2%)	71.2	42.1	44.2	30.2	15.1	0.2	3.6	170.7	11.7	Phase 3 Underway
SMMT	1.82	14.29	1.10	58.3%	(89.6%)	58.4	23.1	35.3	68.7	-	18.0	21.8	1.3	1.1	Phase 3 Underway
SPRO	12.07	19.00	5.52	96.3%	(47.7%)	207.8	92.4	115.4	46.8	-	11.8	10.7	7.8	8.6	Phase 3 Underway
SYN	0.69	12.95	0.51	23.2%	(96.9%)	10.7	(18.2)	28.9	17.6	-	-	-	N/A	N/A	Phase 3 Planned
TTPH	1.20	4.49	1.01	6.2%	(82.1%)	64.5	(15.0)	107.8	92.2	28.3	15.8	35.5	(1.0)	(0.4)	Market
NBI	3439.07	3865.88	2801.14	13.0%	(9.3%)										
MAX				194.8%	51.5%	2,180.4	2,001.9	495.1	317.2						
MEAN				34.0%	(61.8%)	239.6	179.6	110.1	100.4						
MIN				(73.8%)	(96.9%)	10.7	(26.9)	6.6	15.3						

GRAM-NEGATIVE INFECTIONS

The need for new antibiotics is most acute in the area of Gram-negative pathogens, which include *Pseudomonas aeruginosa, Acinetobacter baumannii*, *Escherichia coli* and *Klebsiella pneumoniae.* The latter two are in the family *Enterobacteriaceae*.

A: Key Areas of Unmet Need

We believe there are two specific areas of unmet need in the Gram-negative space:

1. **Oral Antibiotics for Urinary Tract Infections**: A new potent antibiotic with an attractive safety profile and IV/ oral flexibility is needed. Fluoroquinolone efficacy in the treatment of cUTI has diminished to such a degree that the class is no longer appropriate as a comparator in certain clinical trials. All other marketed drugs with reliable and adequate efficacy can only be administered IV.

Because there are only two oral antibiotics for Urinary Tract Infections in Phase 3 testing (Iterum and Spero), we believe it is appropriate for investors to focus on this particular unmet need. The commercial opportunity reaches into the community setting and we estimate peak U.S. sales for an antibiotic ranges from $500M to $1B each.

2. **CRE, CRAB, and Multi-/Extreme-Drug Resistant (MDR/XDR *Pseudomonas*)**: A new antibiotic with activity against particularly challenging pathogens, such as Carbapenem Resistant *Enterobacteriaceae* (CRE), Carbapenem Resistant *Acinetobacter baumannii* (CRAB), and/or XDR/MDR *P. aeruginosa* is needed. Safety and IV/ oral flexibility are not as critical given severity of infection.

There are several IV antibiotics in development against CRE, CRAB, and/or MDR/XDR *Pseudomonas*. We believe investors should exercise caution in this area. Given the risk of crowding, peak WW sales for even the most differentiated IV antibiotic in the hospital Gram-negative space may be well under $500M WW. Reimbursement policy changes are needed, at a minimum, to make the space more attractive.

B: Recent Approvals in the Gram-Negative Space

- **Achaogen: Zemdri (plazomicin; FDA approval 6/25/18; EMA Review)**

  Zemdri was approved by the FDA and subsequently launched in the U.S. by Achaogen. The drug is still under review by the EMA.

  Achaogen had sought a U.S. label directed to cUTI based on the EPIC trial as well as to Bloodstream CRE infections based on the CARE trial. The FDA, however, followed advice of a May 2018 FDA Advisory Committee and included only cUTI in the label.

  Although we believe Zemdri has the potential to be an important option for CRE infections based on strength of Phase 3 CARES data, Achaogen does not have adequate resources to operate the company beyond 2Q19. Zemdri generated $0.5M in 4Q18 sales. A review of strategic options for the company is underway.

- **Allergan/ Pfizer: Avycaz (ceftazidime/avibactam; FDA approval 2/2015; EMA approval 6/2016)**

  Avycaz is used primarily for infections caused by CRE. Treatment failures have been a concern and we expected the drug to be displaced by two more recent entrants, Vabomere and Zemdri. This has not occurred, however, and Avycaz continues to have the most overall impressive sales trajectory of all branded antibiotics. The FDA label now includes cIAI, cUTI, and HABP/VABP.

- **Melinta: Vabomere (vaborbactam/ meropenem; FDA approval 8/2017; EMA approval11/2018)**

  Melinta acquired the Medicines Company antibiotic assets in late 2017. The launch into the CRE market has been unimpressive, possibly due to resource constraints at Melinta. Vabomere was approved by the FDA in 2017 for cUTI and by the EMA in 2018 for cIAI, cUTI, HAP/VAP, Bacteremia, and infections due to aerobic Gram-negative organisms where treatment options are limited.

- **Merck: Zerbaxa (ceftolozane/tazobactam; FDA approval 12/2014; EMA approval 9/2015)**

  Zerbaxa is directed toward Gram-negative infections, particularly *P. aeruginosa*. The drug is typically used off-label for HABP/VABP. A Phase 3 trial in this indication has been completed and Merck announced submission of applications to the EMA and FDA in February 2019. The PDFUA date is 7/16/19. U.S. sales and growth are still modest. The drug has already been approved for cIAI and cUTI.

- **Tetraphase: Xerava (eravacycline; FDA approval 8/27/18; EMA approval 9/20/18)**

  Tetraphase launched Xerava in the U.S. in October 2018, but has postponed plans to launch the drug independently in Europe. The company is positioning the drug as empiric monotherapy for high-risk patients and as an option for patients failing first line treatment. We have concerns over peak sales potential given only the IV formulation was successfully developed.

  The company reported $0.2M in 4Q18 sales. Xerava is on formulary at 100 hospitals as of 12/31/18 and is expected to reach 400 hospitals by mid-2019. Use is split evenly between empiric (high resistance rates at facility) and confirmed resistance or otherwise refractory/ intolerant cases. Current use is approximately 75% inpatient 25% outpatient.

  Xerava was approved last year for cIAI. Phase 3 trials in cUTI were not successful.

Table 4: Gram-Negative Antibiotic Development Programs (Preclinical and Clinical)

Profile Indication/ Pathogen/Route	Drug Class	Development Status	Company	Comments
ESBL Urinary Tract Infections Oral	Ceftibuten Tazobactam BL/BLI	Phase 1	Achaogen	Phase 1 reinitiation planned
	Tebipenem SPR994 Carbapenem	Phase 1 Market JP	Spero	Phase 3 initiation 1Q19 Phase 3 results 2020E
ESBL Urinary Tract Infections Oral/ IV	Sulopenem Carbapenem	Phase 3	Iterum	Phase 3 results 2H19E
	Omadacycline Tetracycline	Phase 2	Paratek	Phase 2 results 2H19E
ESBL IV	AAI101 Cefepime BL/BLI	Phase 3	Allecra	Phase 3 results 4Q19E
CRE IV	Avibactam Ceftazidime BL/BLI	Market	Allergan Pfizer	FDA Approval 2/15 EMA Approval 6/16
	Vaborbactam Meropenem BL/BLI	Market US Market EU	Melinta	FDA Approval 8/17 EMA Approval 11/18
	Zemdri Aminoglycoside	Market US EMA Review	Achaogen	FDA Approval 6/25/18 MAA submission 4Q18
	Contempo Fosfomycin	FDA Review	Zavante	PDUFA date 4/30/19 Zavante acquisition by Nabriva
	Avibactam Aztreonam Monobactam/BLI	Phase 3	Pfizer	Phase 3 results 2H21E Suspension due to drug availability
	BOS-228/ LYS228 Monobactam	Phase 2	Boston	Phase 2 results 2019E License from Novartis
	Nacubactam Meropenem BL/BLI	Phase 1	Nacugen	Phase 3 planned Rights retuned by Roche
	SPR-741 Polymyxin/ Potentiator	Phase 1	Spero	Phase 1b results May 2018
	NOSO-502 Odilorhabdin	Preclinical	Nosopharm	IND submission 2020E
	TBA BL/BLI	Preclinical	Antabio	IND submission 2019E
CRE IV/Oral	FG-LpxC UTI LPXC Inhibitor	Preclinical	Forge	IND submission 1Q20E
CRE Oral	ARX-1796 BL/BLI	Preclinical	Arixa	Phase 1 initiation 2019E
	ETX0282 Cefpodoxime BL/BLI	Phase 1	Entasis	Phase 1 initiated 2018 Phase 3 intiiation 2019/2020E
	VNRX-7145 BL/BLI	Preclinical	Venatorx	Phase 1 initiation 2Q19E
MDR XDR *P. aeruginosa* IV	Murepavadin Cyclic peptide	Phase 3	Polyphor	Phase 3 EMA trial initiated 1Q18 Phase 3 EMA trial results 2020E Phase 3 FDA trial initiation 4Q18 Phase 3 FDA trial results 2021E
	Aerucin Monocolonal Antibody	Phase 2	Aridis	Phase 2 results 1H19E
	MEDI3902 Monocolonal Antibody	Phase 2	AstraZeneca	Phase 2 results 1H20E
CRAB IV	ETX2514 Sulbactam BL/BLI	Phase 2	Entasis	Phase 3 CRAB initiation 2019E
CRE CRAB IV	TP-6076 Tetracycline	Phase 1	Tetraphase	Phase 1 results 4Q18
CRE *P. Aeruginosa* IV	Relebactam Imipenem BL/BLI	FDA Review EMA Review	Merck	PDUFA date 6/3/19
CRE CRAB *P. Aeruginosa* IV	Cefiderocol Siderophore Cephalosporin	Phase 3	Shionogi	NDA and MAA submission 2019E
	VNRX-5133 Cefepime BL/BLI	Phase 1	Venatorx	Phase 3 initiation 2Q19E
	GT1/GT55 Siderophore BL/BLI	Preclinical	Geom	Phase 1 initiation 2019E
	MRX-8 Polymyxin	Preclinical	MicuRx	IND submission 2019E
	POL7306 Cyclic peptide	Preclinical	Polyphor	IND submission 2020E
	RX-04 Pyrrolocytosine	Preclinical	Melinta	Develpoment Suspended/ Resources
	SPR-206 Polymyxin	Phase 1	Spero	Phase 1 results 2H19E
Intra-Abdominal Infections/CRE IV	Eravacycline Tetracycline	Market	Tetraphase	FDA Approval 8/27/18 EMA Approval 9/20/18

Source: Company reports; Needham & Company, LLC; clinicaltrials.gov

Key Area of Unmet Need #1: Oral Antibiotics for Urinary Tract Infections

Fluoroquinolones have been an attractive option for the treatment of Urinary Tract Infections due to coverage of Gram-negative pathogens and flexibility of both IV and oral administration. Data from Phase 3 cUTI trials, however, confirm that this class is no longer a reliable option. All other approved antibiotics with reliable activity against cUTI pathogens can only be administered IV.

Iterum and Spero currently have the most attractive assets in the oral UTI space. Iterum is expected to announce results of Phase 3 trials of an IV and oral carbapenem in 2H19. Spero recently initiated Phase 3 testing of an oral-only carbapenem and we believe results will be available in 2020.

Both Iterum and Spero are developing carbapenems with oral formulations. We believe these differentiated assets are likely to be helpful tools for urinary tract infections. Iterum initiated a Phase 3 program in 2018 and Spero in early 2019.

Paratek is testing oral omadacycline (Nuzyra) for UTI in two Phase 2 trials. We await more insight into efficacy in relation to safety and tolerability.

There are a few programs in preclinical or Phase 1 testing geared towards development of an oral UTI drug with CRE coverage (Achaogen, Arixa, Entasis, Forge, and Venatorx). A few novel fluoroquinolones have been tested in Phase 1 and 2 trials and may be useful for cUTI, although most have somewhat modest Gram-negative activity and none are in active development.

More advanced programs in the UTI space include the following:

- **Achaogen: Ceftibuten and Clavulanate (Phase 3 Initiation 2019E)**

  Achaogen announced in March 2017 plans to develop C-Scape (oral beta-lactam ceftibuten and oral beta-lactamase inhibitor clavulanate) for cUTI. Both drugs have separately been approved by the FDA. The company reported progress towards formulation optimization and is ready to resume Phase 1 testing, subject to funding.

- **Entasis; ETX0282 (Phase 3 Initiation 2019/2020E)**

  Entasis is testing ETX0282, a novel BLI with class A and C CRE coverage, in combination with cefpodoxime in Phase 1 trials. Results are expected to be available in 1H19.

- **Iterum: Sulopenem (Phase 3 Results 2H19E)**

  Iterum in-licensed sulopenem, a novel IV/ oral carbapenem, from Pfizer in 2015. Phase 3 trials in uUTI, cUTI and cIAI were initiated in late 2018. We believe NDA submission is possible YE19.

- **Paratek: Omadacycline**

  Paratek has initiated both planned Phase 2 trials of omadacycline in UTI. A trial in uUTI against nitrofurantoin was initiated in December 2017, followed by a trial against levofloxacin in cUTI in 2H18. Results from both trials are expected in 2H19. We question whether omadacycline is sufficiently potent against Gram-negative pathogens to be effective and well-tolerated for UTI. The antibiotic is geared toward Gram-positive pathogens rather than Gram-negative pathogens.

- **Spero: Tebipenem (Phase 3 Initiation 1Q19)**

  Spero is planning to develop tebipenem (SPR994), an oral-only carbapenem, for Urinary Tract Infections. A Phase 3 trial in cUTI is now being initiated in cUTI. The drug was in-licensed from Meiji-Seika, which in turn in-licensed from Wyeth.

Key Area of Unmet Need #2: CRE, CRAB, and MDR/XDR *Pseudomonas* Hospital Infections

A) Carbapenem-Resistant Enterobacteriaceae (CRE)

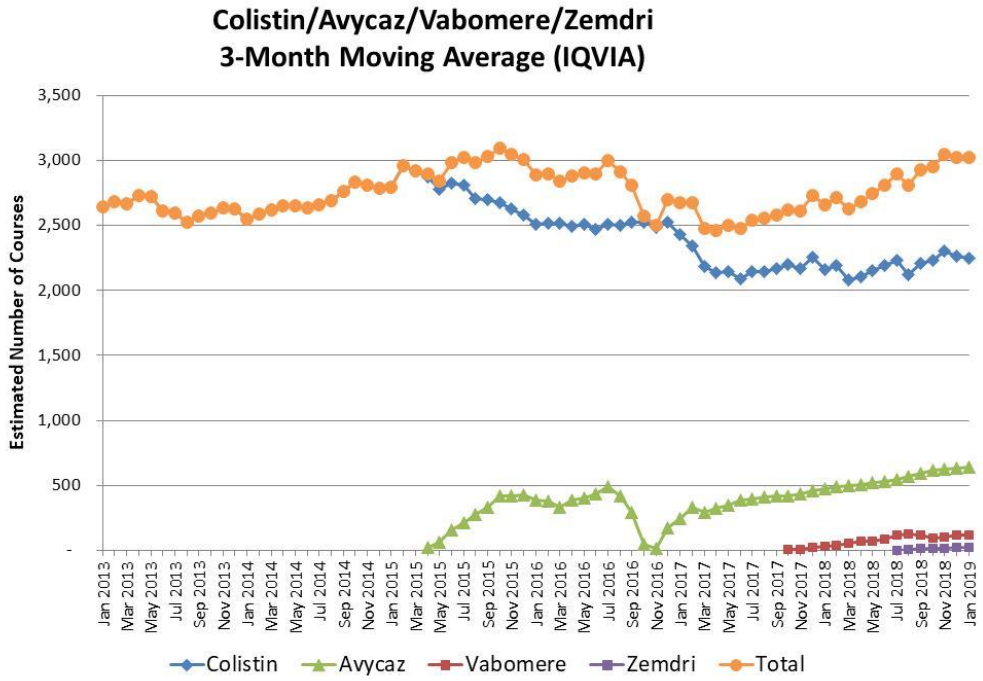
Challenging infections caused by CRE have typically been treated with colistin (polymyxin E), polymyxin (polymyxin B), tigecycline, aminoglycosides, high dose carbapenems, or combinations thereof. Avycaz was approved in the U.S. in 2015 and in Europe in 2016. The antibiotic has made a detectable penetration into the space. Vabomere was approved by the FDA in 2017 and in Europe in 2018. The drug has not yet had a meaningful impact in the treatment of CRE, potentially due to Melinta resource constraints. Zemdri was approved in late 2018 and sales have been negligible. The drug is still under formulary review at many institutions. Furthermore, Achaogen does not have adequate resources to promote the drug.

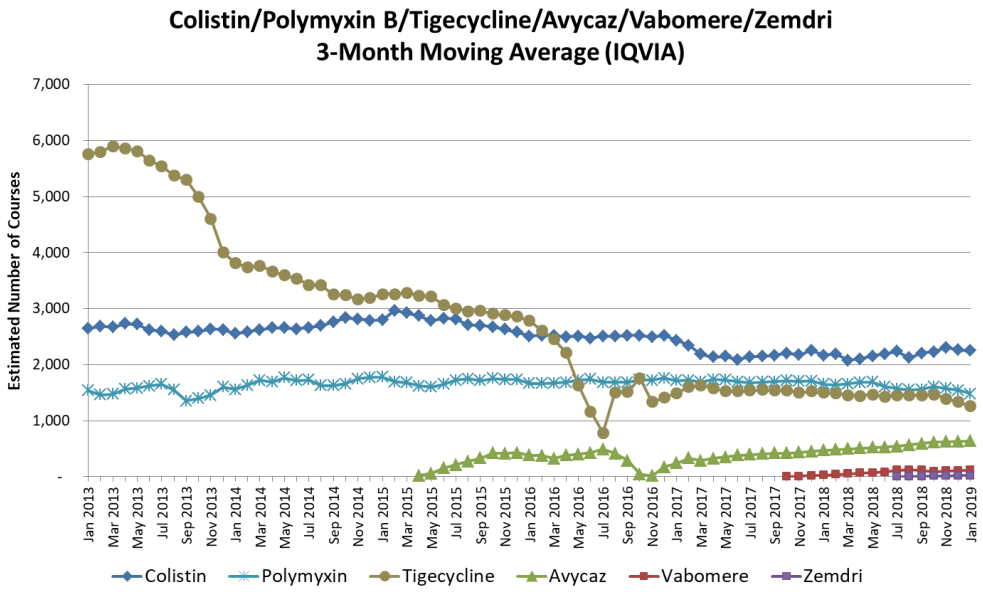
In addition to the above marketed drugs, other potential entrants over the next 18 months to the CRE market include Contepo (IV fosfomycin; Nabriva), relebactam (Merck), and possibly cefiderocol (Shionogi).

We believe there are no obvious attractive opportunities for investors in CRE. First, the hospital environment is not structured to reward innovation. Second, although the total addressable U.S. market opportunity appears to be up to around $1B in 2030, we believe the growing number of antibiotics on the market and in development for CRE may limit the peak sales opportunity for a given drug.

We have attempted to model the CRE market. Challenges include the fact that a number of antibiotics are used in various combinations and that these antibiotics are also used for other indications. We note that although both colistin and polymyxin B are used for CRE infections, only colistin scripts were visibly impacted by the introduction of Avycaz. There is no obvious impact on scripts written for other antibiotics, with the exception of tigecycline, which increased during the Avycaz supply shortage in 2016.

In consideration of these factors, we follow the space with two graphs. The first includes colistin, Avycaz, Vabomere, and Zemdri estimated courses of treatment based on Iqvia vial data. We note, however, that through the first several months of launch, Zemdri has not been used for CRE. Rather, the drug has instead been used primarily in the outpatient setting for challenging UTI infections. Our second graph includes colistin, polymyxin B, tigecycline, Avycaz, Vabomere, and Zemdri estimated courses of treatment.





We believe the total commercial opportunity in the U.S. for CRE infections is around $1B in 2030. We acknowledge the market would be larger if branded agents are used in combination.

We base our market size estimates on Avycaz, Vabomere, Zemdri and colistin IMS sales and vial data. If colistin were a branded agent today ($13,000 per course), we believe total U.S. CRE market sales would be approximately $450M. We assume CRE infection annual growth rate of 2% and annual price increases of 5% to arrive at our $1B estimate in 2030.

If one were to add polymyxin B vials sold to those of Avycaz, Vabomere, Zemdri and colistin, total current market sales would be around $700M and 2030 sales would be around $1.6B. This figure may be an appropriate estimate of the combined CRE and CRAB (dual carbapenem aminoglycoside-resistant *Acinetobacter*) markets as well as part of the MDR/XDR *Pseudomonas* U.S. market. The addition of Zerbaxa captures more of the MDR/XDR *Pseudomonas* U.S. market.

Table 5 Market Opportunity Estimates

	2018 Estimated Courses Acutal Iqvia Vial Data	2018 Total Market Estimate $13,000 Course	2030 Estimated Courses +2% y/y Growth	2030 Total Market Estimate $23,300 Course (+5% y/y)
Colistin Avycaz Vabomere Zemdri	34,200	$445M	43,400	$1.0B
Colistin Polymyxin Avycaz Vabomere Zemdri	53,300	$695M	67,600	$1.6B
Colistin Polymyxin Avycaz Vabomere Zemdri Zerbaxa	58,339	$760M	72,600	$1.7B

Source: Needham & Company, LLC estimates; Estimated courses of treatment based on Iqvia eaches vial data, 14-day treatment duration, and dose according to label or guidelines; Zerbaxa estimated coursed assume only off-label use for Pneumonia (3g q8h)

Europe

We believe it may be a challenge for a company to capture significant CRE revenue in Europe, given that countries most affected have limited financial resources.

The latest Antimicrobial Resistance Surveillance in Europe report (2017) indicates that less than 1% of *E. coli* isolates are resistant to carbapenems in most countries, the exception being Greece (1-5% resistant; Romania improved to <1% from 2015 report).

Substantially more *K. pneumoniae* isolates are resistant to carbapenems and there have been a number of shifts since the 2015 report. Most countries still report <1% resistance rates. However, some have worsened from the <1% to the 1-5% range, including Belgium, Austria, and Slovakia. Croatia and Slovenia improved from the 1-5% range to <1%. Other notable countries:

- Greece: >50% (unch)
- Italy: 25-50% (unch)
- Romania: 10-25% (unch)
- Bulgaria: 10-25% (worsened from 1-5%)
- Poland: 5-10% (worsened from <1%)
- Portugal: 5-10% (worsened from 1-5%)
- Spain: 1-5% (unch)

Companies with notable programs directed against CRE in late-stage development or on the market

- **Achaogen** launched Zemdri in July 2018. Benefits over colistin were established in a Phase 3 trial (CARES), although data from this trial were not included in the label. Regardless, given its mechanism of action, we believe Zemdri represents a differentiated option from the two recently approved BL/BLI combinations (Vabomere and Avycaz).
- **Melinta** acquired Vabomere (vaborbactam/ meropenem) from Medicines Company. The drug had been approved by the FDA in August 2017. Vaborbactam is a novel beta-lactamase inhibitor with coverage of the following: KPC, SME, TEM, SHV, CTX-M, CMY, and ACT beta-lactamases. The drug is not active against pathogens with metallo beta-lactamases and oxacillinases.
- **Merck** announced NDA and MAA filings for relebactam in cUTI and cIAI in early 2019. The applications are based on data from the RESTORE-IMI 1 trial of relebactam and imipenem against colistin in CRE infections. These data were presented in April 2018 at the ECCMID meeting.

  A Phase 3 trial against piperacillin/tazobactam in 536 patients with HABP/VABP in China is still ongoing, with results expected in 2019 (RESTORE-IMI 2). A smaller Phase 3 trial in 270 HABP/VABP patients was initiated in 2018, with results expected in 2021. Both trials have mortality endpoints. A PK trial in pediatric patients with Gram-negative infections continues to enroll patients, with results expected in 2020. A Phase 3 trial in cUTI in Japan was completed last year.
- **Nabriva** submitted a 505(b)(2) NDA for Contepo (IV formulation of fosfomycin) in 2018 and the PDUFA date is 4/30/19. An oral formulation is already approved for uncomplicated UTI. Nabriva acquired Zavante and its sole asset Contepo in late 2019.

  The company plans to position Contepo for use in seriously ill patients with suspected MDR infections, potentially in combination with a carbapenem or aminoglycoside. IV fosfomycin is used in combination with other agents for challenging Gram-negative infections in Europe, where it has a broad label

(Osteomyelitis, cUTI, Nosocomial Respiratory Tract Infections, Meningitis, Bacteremia). The drug has broad coverage (High susceptible: MRSA and E. coli; Moderate: *K. pneumoniae* and *P. aeruginosa*). The safety profile is generally clean, although serum electrolytes require monitoring. Tissue penetration into bone, lung, and CSF is high.

The FOREST trial (Spanish Network for Research in Infection Disease) may have an impact on uptake of Contepo in the U.S. The trial is evaluating IV fosfomycin against meropenem in patients with ESBL bloodstream-cUTI infections. Non-inferiority to meropenem would strengthen its position as a carbapenem-sparing agent. Results are expected in 2019 according to clinicaltrials.gov.

- **Pfizer** initiated a Phase 3 trial of avibactam in combination with aztreonam in patients with serious Gram-negative infections in 2018. Enrollment has been suspended, however, due to drug supply issues. Results are expected in 2021 (was 2020). A second smaller trial in patients with infections due to metallo beta lactamase producing Gram-negative pathogens is planned (NCT03580044).

  Target profile is an antibiotic with coverage of CRE with either serine or metallo beta lactamases.

- **Shionogi** is developing cefiderocol, a novel siderophore cephalosporin, for the treatment of MDR Gram-negative infections, including CRE. An NDA is reportedly in preparation.

  The company presented data from a cUTI trial (APEKS-cUTI) in 2017. Two additional trials are ongoing, including a 150-patient Phase 3 trial in patients with Gram-negative carbapenem-resistant infections (Initiated August 2016; NCT02714595) and a Phase 3 trial in HABP/ VABP opened to enrollment in July 2017. (NCT03032380). Results from these trials are expected in 2019.

  There are concerns around development of resistance through the siderophore iron uptake mechanism of cefiderocol. We are therefore cautious regarding commercial potential of the drug. We acknowledge, however, impressive *in vitro* clinical isolate data.

- Xerava, marketed by **Tetraphase**, is effective against CRE clinical isolates *in vitro*. There are no immediate plans to evaluate the drug in patients.

B) MDR/XDR *P. aeruginosa*

Zerbaxa, a novel cephalosporin launched in the U.S. in early 2015, is positioned as a solution for MDR *P. aeruginosa*. More potent antibiotics are needed, however. There is a growing collection of potent broad spectrum antibiotics with *P. aeruginosa* coverage as well as a few antibiotics or antibodies directed specifically to *P. aeruginosa.*

We have concerns around feasibility of development of a narrow-spectrum antibiotic for MDR/ XDR *P. aeruginosa*. The infections are uncommon and we believe it may be difficult to enroll and complete a registration trial. Importantly, narrow-spectrum antibiotics designed to specifically target *P. aeruginosa* cannot leverage the same pathway to market through cUTI registration trials because these drugs are not active against *E. coli*.

Trial feasibility is an important consideration against *P. aeruginosa.* Any antibiotic with efficacy against both *Enterobacteriaceae* and *P. aeruginosa* can be developed through a standard and straightforward cUTI trial. A narrow spectrum antibiotic, however, must be tested in patients with confirmed *P. aeruginosa* infections (HABP/ VABP) to satisfy FDA requirements. We are skeptical that a trial can be completed in a reasonable period of time. The EMA is substantially more flexible (see Polyphor below).

Narrow MDR/XDR *P. aeruginosa* Programs

- **Polyphor** is conducting two Phase 3 trials of IV murepavadin. The antibiotic (cyclic peptide) is only active against *P. aeruginosa*. The EMA has requested a

150-patient (confirmed Pseudomonas VABP) observational trial comparing a 2-drug standard of care regimen to murepavadin in combination with a standard of care drug (1:2; NCT03409679). The FDA has requested a 250-patient (confirmed *Pseudomonas* HABP/ VABP) trial comparing meropenem or pip-tazo to murepavadin in combination with ertapenem. All-cause 28-day mortality is the primary endpoint (1:1; NCT03582007).

- **AstraZeneca** initiated a Phase 2 trial of MEDI3902 in March 2016 in mechanically ventilated patients. MEDI3902 is a bispecific anti-PcrV/Psl monoclonal antibody. Efficacy endpoints in the Phase 2 trial include incidence of *P. aeruginosa* nosocomial pneumonia. Target enrollment was reduced to 286 patients from 429 patients in March 2017 and then to 195 in December 2018. Results are expected in early 2020.
- **Aridis** is conducting a 108-patient Phase 2 trial of Aerucin in patients with *P. aeruginosa* pneumonia. Aerucin is an anti-alginate *P. aeruginosa* IgG1 mAb. Results are expected to be available in 2019 (was 2H18).

Broader Spectrum Gram-Negative Programs with MDR/XDR *P. aeruginosa* Coverage

- **Merck:** Relebactam/ Imipenem (FDA and EMA Review)
- **Shionogi:** Cefiderocol (Phase 3)
- **Venatorx:** VNRX-5133 (Phase 1; Phase 3 start 2Q19E)
- **Geom:** GT1/GT55 (Preclinical; Phase 1 2019E)
- **MicuRx:** MRX-8 (Preclinical; IND 2Q19E)
- **Polyphor:** POL7306 (Preclinical)
- **Spero:** SPR-206 (Phase 1)

C) Carbapenem Resistant *Acinetobacter baumannii* (CRAB)

There are no satisfactory treatment options for drug-resistant *A. baumannii,* particularly dual carbapenem-aminoglycoside resistant. The infection is uncommon in the U.S., but resistance rates are over 50%. We have the same trial feasibility concerns around development of a narrow spectrum antibiotic for CRAB as we do for *P. aeruginosa.*

We have concerns around feasibility of development of a narrow-spectrum antibiotic for CRAB. The infections are rare and we believe it may be difficult to enroll and complete a registration trial. Importantly, narrow-spectrum antibiotics designed to specifically target CRAB cannot leverage the same pathway to market through cUTI registration trials because these drugs are not active against *E. coli*.

Entasis is developing ETX2514, a beta-lactamase inhibitor (class A, C, and D), in combination with sulbactam for MDR *A. baumannii*. The drug combination is not particularly active against *Enterobacteriaceae*, precluding a registration path in the U.S. through a cUTI trial.

The company announced in February 2019 that an End of Phase 2 meeting had been held with the FDA and guided for initiation of a Phase 3 trial in 1Q19. This trial is designed to enroll approximately 130 patients at 85 sites WW with confirmed carbapenem resistant *A. baumannii* infection, randomized to either ETX2514 and imipenem or colistin and imipenem. The primary endpoint will be all cause mortality at day 28 (19% Non-Inferiority margin). The company believes 220 patients will need to be enrolled in order to enroll the target 130 patients with resistant infections. Design is generally consistent with a proposal presented by the company at an FDA workshop and Advisory Committee meeting (118 patients with confirmed HABP/VABP or Bloodstream MDR *A. baumannii* infection; 28-day mortality endpoint with 20% NI margin; 80% power with two-sided 95% CI, assuming 40% mortality in comparator arm and 35% in ETX2514/sulbactam arms).

Tetraphase is considering development of TP-6076 for CRAB. Phase 1 development was completed in 2018 and discussions are underway with the FDA around registration requirements.

Other Broader Spectrum Gram-negative candidates that may have activity against CRAB include cefiderocol (Shionogi; Phase 3), VNRX-5133 (Venatorx; Phase 1), GT1/GT55 (Geom; Preclinical), MRX-8 (Micurx; Preclinical), POL7306 (Polyphor; Preclinical), RX-04 (Melinta; Preclinical), and SPR-206 (Spero; Phase 1).

COMMUNITY ACQUIRED BACTERIAL PNEUMONIA (CABP)

Although there are a number of generic antibiotics available for CABP, vulnerabilities are emerging with the most important options. We believe lefamulin from Nabriva is the strongest among a small number of antibiotics in development for this indication.

CABP is treated in the hospital inpatient, hospital outpatient, and community settings. The inpatient opportunity is fairly modest in our opinion. However, an antibiotic with IV and oral formulations as well as an exceptionally clean safety and tolerability profile may gain traction in the large outpatient/ community setting. Peak sales for the ideal antibiotic in this indication could reach or possibly exceed $1B in the U.S.

Epidemiology of Community Pneumonia and Limitations of Current Treatment Options

- **In the Outpatient/ Community setting**, azithromycin (e.g. Z-Pak) is the standard tool for CABP. However, emergence of widespread *S. pneumoniae* resistance to both beta-lactam antibiotics and macrolide antibiotics has prompted a broad shift in the U.S. to fluoroquinolones, particularly in the case of moderate to severe infections.

  Although fluoroquinolones are generally safe and well tolerated, the class is associated with *C. difficile* infection, tendinitis and tendon rupture, QT prolongation and hepatotoxicity. The FDA approved class label changes in July 2016 to enhance warnings around these safety concerns and to limit use in patients with less serious infections (e.g. Chronic Bronchitis, uUTI, and Acute Bacterial Sinusitis). The FDA required additional safety labeling changes in July 2018 to strengthen warnings around mental health adverse events and hypoglycemia.

- **In the Inpatient setting**, treatment guidelines call for use of a fluoroquinolone (often levofloxacin) or a macrolide in combination with a beta-lactam (often ceftriaxone and azithromycin). Ceftriaxone, however, is only available IV. Physicians must therefore switch antibiotics upon discharge from the hospital, which is not considered optimal.

How a New Antibiotic Can Succeed in CABP

We believe a new antibiotic with flexibility of IV and oral administration, a strong safety and tolerability profile, and the right spectrum of activity will draw physician interest.

- **Enhanced safety and tolerability profile relative to fluoroquinolones**. The FDA held an Advisory Committee meeting in November 2015 to discuss safety concerns with fluoroquinolones and then followed with labeling changes in 2016 and 2018 to enhance warnings about the drug class.

- **Activity spectrum focused on respiratory pathogens**. Antibiotics with coverage restricted to respiratory pathogens, as opposed to broad-spectrum antibiotics, may have safety/ tolerability advantages, including potentially lower risk of *C. difficile* infection. Use of an antibiotic with a more limited and appropriate spectrum is consistent with antimicrobial stewardship. Key target pathogens are Multi-Drug Resistant *S. pneumonia* as well as atypical pathogens.

- **IV and Oral Administration**. This would present advantages over IV-only ceftriaxone upon hospital discharge to step-down oral therapy. Oral administration is a prerequisite for use in the outpatient/ community setting.

- **Novel mechanism of action**. A new antibiotic with a new mechanism of action may present advantages around susceptibility to resistance to existing classes.

- **Pediatric Indication**. Safety and efficacy in pediatric patients may expand the market opportunity substantially.

Companies with Late-Stage Antibiotics in Development for CABP

- **Melinta** completed a Phase 3 trial testing **Baxdela** in CABP and announced results in October 2018. The trial met primary endpoints of non-inferiority to moxifloxacin. The company has guided for sNDA submission in 2Q19. Baxdela was approved in 2017 by the FDA for the treatment of ABSSSI. Initial sales have been modest and we note trends against use of fluoroquinolones.
- **Nabriva** is developing **lefamulin** specifically for CABP. Top-line results from the Phase 3 trials were announced in September 2017 and May 2018. Both trials met non-inferiority endpoints against comparator moxifloxacin. However, adverse event rate and adverse events leading to discontinuations were somewhat higher for lefamulin than moxifloxacin, driven in part by GI tolerability. The overall profile nevertheless still appears to be suitable for the outpatient/ community setting. The company submitted an NDA in December 2018 and the PDUFA date is 8/19/19.
- **Paratek** announced results from Phase 3 trials of **Nuzyra** in both ABSSSI and CABP in 2016 and 2017. The drug was approved in October 2018 and subsequently launched in the U.S. in February 2019. Nuzyra may be administered for ABSSSI initially as an IV or oral. For CABP, the drug is to be administered IV on day 1 and then maintenance IV or oral.

We view lefamulin as the overall most attractive new antibiotic for CABP. All of the above antibiotics are expected to be available in IV and oral formulations, but we believe lefamulin has the most appropriate spectrum, safety and tolerability profile for the outpatient/ community setting. We are not aware of any other antibiotics in development directed toward the outpatient/ community setting.

Table 6: Selected Antibiotics on the Market and Under Development for CABP

Drug	Company	Status	Class	Dosing	Comments
Amoxicillin/ Clavulanate Augmentin	Generic	Market	Beta-lactam/ Beta-lactamase inhibitor	BID IV/Oral	Mild-Moderate *S. pneumoniae* resistance; Poor atypical coverage; Penicillin allergy
Azithromycin Zithromax/Z-Pak	Pfizer Generic	Market	Macrolide	QD IV/Oral	High *S. pneumoniae* resistance
3rd Generation Cephalosporin	Generic	Market	Cephalosporin	BID IV/Oral	Mild-Moderate *S. pneumoniae* resistance; Poor atypical coverage Penicillin allergy
Teflaro Ceftaroline	Allergan	Market	Cephalosporin	BID IV	Penicillin allergy
Clarithromycin Biaxin	Abbvie Generic	Market	Macrolide	QD Oral	High *S. pneumoniae* resistance Drug-drug interactions QT prolongation
Delafloxacin Baxdela	Melinta	Market ABSSSI	Fluoroquinolone	BID IV/Oral	FDA ABSSSI approval 6/2017 CABP Phase 3 results 10/2018 Fluoroquinolone AEs; MRSA coverage
Doxycycline Vibramycin	Pfizer Generic	Market	Tetracycline	BID IV/Oral	Moderate-High *S. pneumoniae* resistance; No pediatric use; Drug-drug interactions; *C. difficile*
Lefamulin	Nabriva	FDA Review	Pleuromutilin	BID IV/Oral	Phase 3 results 9/2017 and 5/2018 PDFUA date 8/19/19 GI AE; QT interval; MRSA coverage
Levofloxacin Levaquin	J&J Generic	Market	Fluoroquinolone	QD IV/Oral	Low *S. pneumoniae* resistance; Drug-drug interactions; Tendinitis; C. difficile Cardiac AE (QTc; Arrhythmia)
Moxifloxacin Avelox	Bayer Generic	Market	Fluoroquinolone	QD IV/Oral	Low *S. pneumoniae* resistance; Drug-drug interactions; Tendinitis; C. difficile Cardiac AE (QTc; Arrhythmia)
Omadacycline Nuzyra	Paratek	US Market EMA Review	Tetracycline	QD IV/Oral	FDA approval 10/2/18 No pediatric use (<8 yrs); MRSA coverage

Source: Company reports; Needham & Company, LLC

Melinta: Delafloxacin (Baxdela): FDA Approved ABSSSI 2017 and Label Expansion to CABP YE19E

Melinta announced results of a Phase 3 trial of Baxdela in CABP in October 2018. Baxdela is a broad-spectrum IV/oral fluoroquinolone with MRSA activity. Two Phase 3 trials had already been completed in skin infections, both of which demonstrated non-inferiority to comparator vancomycin.

Patients in the Phase 3 CABP trial were randomized to receive either Baxdela or moxifloxacin. All primary (FDA and EMA) and secondary endpoints were reportedly met (FDA primary ECR 88.9% Baxdela vs. 89.0% Moxifloxacin [95% CI -4.4%; +4.1%]. Adverse event rates were reportedly similar across arms.

Nabriva: Lefamulin: Launch CABP 2H19E

Nabriva is seeking to position lefamulin as first-line option for CABP, highlighting a respiratory-focused spectrum, activity against MRSA, and safety profile. Lefamulin, a pleuromutilin, also has a unique structure and novel mechanism of action relative to other systemic antibiotics on the market and in development. Nabriva will need to convey value over levofloxacin (safety profile) and ceftriaxone (no need to switch antibiotics for oral formulation and better atypical coverage). With adequate resources behind a larger commercial organization, lefamulin may find a role in the outpatient CABP setting.

Nabriva has conducted two Phase 3 trials of lefamulin against comparator moxifloxacin in CABP. Results were announced from the first trial (IV and oral) in September 2017 and results from the second trial (oral only) in May 2018. The drug is under regulatory review.

Paratek: Omadacycline (Nuzyra): Launch CABP and ABSSSI 1Q19

Nuzyra is a broad-spectrum IV/oral tetracycline antibiotic with MRSA coverage. Paratek announced results from a Phase 3 trial in CABP (IV/oral) in 2017. Patients were randomized 1:1 to IV/oral omadacycline or IV/oral moxifloxacin. Results from Phase 3 trials in ABSSSI against comparator linezolid were announced in June 2016 and in July 2017. All trials met non-inferiority endpoints and the drug was launched in February 2019.

Table 7: Phase 3 CABP Trial Results: Lefamulin and Omadacycline

	LEAP 1		LEAP 2		OPTIC			
	Lefamulin IV ORAL (n=273)	Moxifloxacin (±) Linezolid (n=273)	Lefamulin ORAL (n=370)	Moxifloxacin (n=368)	Omadacycline (n=386)	Moxifloxacin (n=388)	Delafloxacin	Moxifloxacin
ECR	87.3%	90.2%	90.8%	90.8%	81.1%	82.7%	88.9%	89.0%
IACR CE-TOC	86.9%	89.4%	87.5%	89.1%	92.9%	90.4%	90.5%	89.7%
IACR mITT	81.7%	84.2%	89.7%	93.6%	87.6%	85.1%		
TEAE	104 (38.1%)	103 (37.7%)	120 (32.6%)	92 (25.0%)	157 (41.1%)	188 (48.5%)		
All SAE	19 (7.0%)	13 (4.8%)	17 (4.6%)	18 (4.9%)	23 (6.0%)	26 (6.7%)		
Related SAE	3 (1.1%)	1 (0.4%)	0 (0)%	1 (0.3%)	2 (0.5%)	2 (0.5%)		
AE/ Discontinue	5 (1.8%)	11 (4.0%)	5 (1.4%)	5 (1.4%)	7 (1.8%)	9 (2.3%)		
Deaths	6 (2.2%)	5 (1.8%)	3 (0.8%)	3 (0.8%)	8 (2.1%)	4 (1.0%)		
Nausea	8 (2.9%)	6 (2.2%)	19 (5.2%)	7 (1.9%)	9 (2.4%)	21 (5.4%)		
Insomnia	8 (2.9%)	5 (1.8%)	0.0%	4 (1.1%)	10 (2.6%)	8 (2.1%)		
Hypertension	2 (0.7%)	6 (2.2%)	5 (1.4%)	5 (1.4%)	13 (3.4%)	11 (2.8%)		
Diarrhea	2 (0.7%)	21 (7.7%)	45 (12.2%)	4 (1.1%)	4 (1.0%)	31 (8.0%)		
Vomiting			12 (3.3%)	3 (0.8%)	10 (2.6%)	6 (1.5%)		
C. difficile	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0)%	0 (0.0%)	8 (2.1%)		
ALT >3xULN	19(7.1%)	17 (6.4%)	15 (4.2%)	17 (4.7%)	7/281 (2.5%)	11/295 (3.7%)		
ALT >5xULN	6 (2.2%)	5 (1.9%)	7 (2.0%)	3 (0.8%)	2/281 (0.7%)	11/295 (3.7%)		
ALT >10xULN	1 (0.4%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	2/281 (0.7%)	0 (0.0%)		
AST >3xULN	11 (4.1%)	7 (2.6%)	12 (3.4%)	8 (2.2%)	5/323 (1.5%)	5/328 (1.5%)		
AST >5xULN	2 (0.7%)	2 (0.7%)	6 (1.7%)	5 (1.4%)	3/323 (0.9%)	1/328 (0.3%)		
AST >10xULN	1 (0.4%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1/323 (0.3%)	0 (0.0%)		
Bili >1.5xULN	3 (1.1%)	3 (1.1%)	3 (0.8%)	3 (0.8%)	1/333 (0.3%)	6/343 (1.7%)		
Bili >2xULN	0 (0.0%)	2 (0.7%)	2 (0.6%)	0 (0.0%)	1/333 (0.3%)	4/343 (1.2%)		
QT 30-60 msec	12 (4.6%)	14 (5.4%)	56 (15.4%)	68 (18.5%)	26 (8.2%)	42 (13.2%)		
QT > 60 msec	0 (0.0%)	1 (0.4%)	4 (1.1%)	7 (1.9%)	1 (0.3%)	4 (1.3%)		
Any > 500 msec	1 (0.4%)	1 (0.4%)	1 (0.3%)	2 (0.5%)	3 (0.9%)	3 (0.9%)		
Baseline Pathogen	ECR (%) n=159	ECR (%) n=159	ECR (%) n=205	ECR (%) n=186	Clinical success (%) n=204	Clinical success (%) n=182		
S. pneumoniae	82/93 (88%)	91/97 (94%)	110/123 (89%)	115/126 (91%)	37/43 (86%)	31/34 (91%)		
Penicillin S	17/21 (81%)	16/18 (89%)	19/25 (76%)	36/38 (95%)	23/26 (88%)	21/22 (95%)		
Macrolide-R	6/6 (100%)	5/6 (83%)	8/9 (89%)	9/11 (82%)	10/10 (100%)	5/5 (100%)		
S. aureus	10/10 (100%)	5/6 (100%)	13/13 (100%)	6/6 (100%)	8/11 (73%)	9/11 (82%)		
H. influenzae	47/51 (92%)	54/57 (95%)	50/56 (89%)	44/48 (92%)	26/32 (81%)	16/16 (100%)		
M. pneumoniae	16/19 (84%)	18/20 (90%)	20/20 (100%)	14/14 (100%)	66/70 (94%)	50/57 (88%)		
L. pneumophila	16/18 (89%)	12/14 (86%)	13/16 (81%	16/17 (94%)	35/37 (95%)	36/37 (97%)		
C. pneumoniae	10/11 (91%)	18/19 (95%)	15/16 (94%)	12/12 (100%)	25/28 (89%)	25/28 (89%)		

Source: Company reports; Needham & Company, LLC

CLOSTRIDIUM DIFFICILE

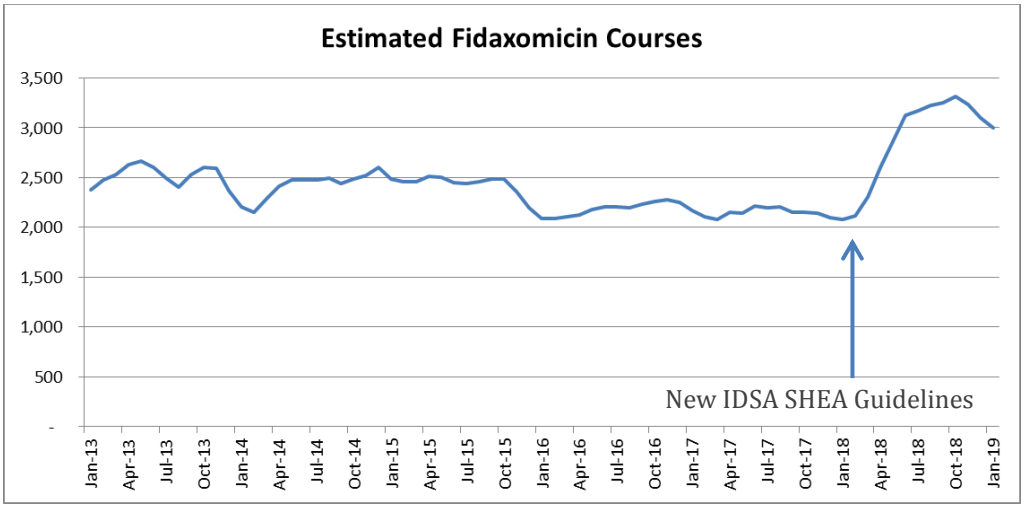
C. difficile is an ongoing problem in healthcare facilities and in the community setting. Prevalence is believed to be around 500,000 cases per year.

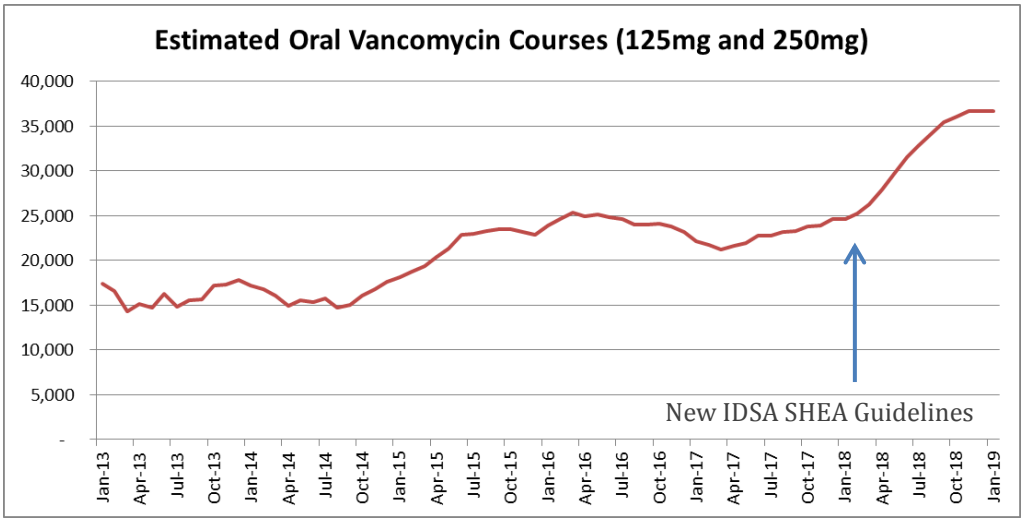
Treatment Guidelines Update

IDSA/SHEA published new treatment guidelines in February 2018, replacing guidelines last published in May 2010. Under the old guidelines, metronidazole was the drug of choice for mild to moderate infections (500mg TID 10-14 days) and vancomycin was the drug of choice for an initial severe infection (125mg QID 10-14 days). New treatment guidelines recommend either vancomycin (125mg QID 10 days) or fidaxomicin (200mg BID 10 days) for an initial infection. Fulminant (severe or complicated) infections are to be treated with vancomycin (500mg QID). First recurrence of infection is to be treated with vancomycin (tapered and pulsed regimen) or a 10 day course of fidaxomicin.

Commercial Update

The new treatment guidelines have had a meaningful impact on prescription patterns in the space. Dificid was launched in 2011 and generated modest sales with no growth over an extended period until March 2018 (+30-40%). Vancomycin scripts increased significantly in March 2018 as well. Zinplava, an antibody directed against Toxin B, was approved in October 2016 and has generated very little in sales. Dificid cost per course is $3865 (WAC) and Zinplava $3800 (WAC).





Development Updates

Summit initiated a Phase 3 program in early 2019. Valneva and Synthetic Biologics are seeking collaborators and/ or funding to support Phase 3 trial initiations. Seres is deprioritizing early stage research after a corporate restructure in early 2019. Vedanta initiated a Phase 2 trial of a microbial therapeutic.

Table 8: *C. difficile* Commercial and Clinical Development Landscape

Drug	Company	Development Status	Comments
Vancocin Vancomycin	ANI/Generic	Market	Antibiotic Generic oral formulations approved March 2012 IV formulation (generic) used off-label and taken PO
Flagyl Metronidazole	Pfizer/Generic	Market	Antibiotic Not FDA approved for C. difficile (used off label) First line option for mild/moderate cases
Dificid Fidaxomicin	Merck	Market	Antibiotic Launch U.S. July 2011; EU June 2012; CA July 2012
Zinplava Bezlotoxumab MK 6072	Merck	Market	mAb Toxin B Results 2015; Approval U.S. Oct 2016
PF-06425090	Pfizer	Phase 3	Vaccine Phase 3 initiated Mar 2017 (NCT03090191)
RBX2660	Ferring (Rebiotix acquired)	Phase 3	Microbial therapeutic Phase 3 initiated Jul 2017 (NCT03244644)
SER-109	Seres	Phase 3	Microbial therapeutic Phase 3 initiated Jun 2017 (NCT03183141 NCT03183128)
Ridinilazole SMT19969	Summit	Phase 3	Antibiotic BARDA funding Phase 3 initiation Feb 2019 NCT03595553 NCT03595566
IC84 VLA84	Valneva	Phase 2	Vaccine Phase 2 results 2015 (NCT02316470) Phase 3 planned: Seeking partner/ funding
Ribaxamase SYN-004	Synthetic Biologics	Phase 2	Beta-lactamase; In-licensed from IPSAT Phase 2 results Jan 2017 Phase 3 planned: Seeking partner/ funding
VE303	Vedanta	Phase 2	Microbial therapeutic (NCT03788434)
SER-262	Seres	Phase 1b	Microbial therapeutic Phase 1b initiated 3Q16 (NCT02830542)
ACX-362E	Acurx	Phase 1	Phase 1 results 2019E (No NCT)
CRS3123	Crestone	Phase 1	No active clinical trials
DS-2969 DS11960558	Daiichi Sankyo	Phase 1	Seeking Partner
RBX7455	Ferring (Rebiotix acquired)	Phase 1	Microbial therapeutic No active clinical trials
MGB-BP-3	MGB	Phase 2	Phase 1 completed December 2015 Phase 2 initiation 1Q19
IMM-529	Immuron	Phase 1	Polyclonal antibodies (Toxin B)
OraCAb	Micropharm	Preclinical	Ovine polyclonal antibodies (Toxins A/B)

Source: Company reports, Needham & Company, LLC

- **Ferring** announced plans to acquire Rebiotix in April 2018. A Phase 3 trial of RBX2660 for the prevention of recurrent *C. difficile* infection is underway (PUNCHCD3) and results may be available in mid-2019 (was early 2019). The primary endpoint is proportion of patients with recurrent *C. difficile* infection over eight weeks. RBX2660 has been granted Breakthrough Therapy designation.
- **Pfizer** initiated a Phase 3 trial of PF-06425090, a *C. difficile* vaccine, in March 2017. Approximately 15,000 individuals (ages 50 and older) at risk of developing *C. difficile* infection are being randomized either to three doses of PF-06425090 vaccine or placebo. The primary efficacy endpoint is time to first

case of CDI (up to 3 years after 3rd dose). Enrollment is ongoing and, according to clinicaltrial.gov, results are expected in 2H20.

- **Seres** initiated a 320-patient Phase 3 trial of SER-109 in patients with multiply recurrent *C. difficile* infection (ECOSPOR-III) in June 2017. We believe results will be available in 2019, although enrollment has reportedly been a challenge. The primary endpoint is recurrence rate at up to 8 weeks after administration.

  Seres had announced negative results in July 2016 from an 89-patient Phase 2 trial of SER-109. Management believes trial execution may have played a role in the failure, driven in part by misdiagnosis of *C. difficile* infection at baseline (reliance on PCR rather than cytotoxin assay). In the ECOSPOR-III trial, diagnosis at entry is confirmed by cytotoxin assay and patients are receiving SER-109 at a dose 10x higher than the Phase 2 trial. SER-109 has been granted Orphan Drug and Breakthrough Therapy status by the FDA. SER-109 is derived from healthy human donors.

  SER-262 development has been suspended to conserve resources. A corporate restructure was announced in February 2019.

- **Summit** initiated two identical 680-patient Phase 3 trials of ridinilazole against placebo in 1Q19. Enrollment criteria include confirmation of a positive CDI toxin test. Patients are randomized to either 200mg BID ridinilazole or 125mg qid vancomycin for 10 days. The primary endpoint is superiority in sustained clinical response at day 30. Results are expected to be available in 2H21. Development is supported by funding from BARDA.

- **Synthetic Biologics** announced in November 2018 that the company has made progress in discussions with the FDA around Phase 3 trial design for ribaxamase. The trial is expected to have a primary efficacy endpoint of reduction in incidence of C. difficile infection at one month and a primary safety endpoint of non-inferiority in mortality at 3 months. The company is seeking additional funding and/or a collaborator to support Phase 3 trial initiation.

  Ribaxamase is an enteric-coated oral formulation of a proprietary beta-lactamase for the prevention of *C. difficile* infection. The drug is intended to block antibiotic activity in the GI tract in order to preserve a balance between normal glut flora and *C. difficile*.

  The drug was granted Breakthrough designation by the FDA in May 2017, but this was subsequently withdrawn in April 2018 due in part to an imbalance in deaths observed in Phase 2 testing.

- **Vedanta** initiated a Phase 2 trial of VE303 for the prevention of recurrent *C. difficile* infection in December 2018. The trial is expected to enroll 146 patients, randomized to high or low dose VE303 or placebo. Results may be available in late 2019.

  VE303 is a microbial therapeutic comprised of a consortium of clonal bacterial cell lines. Results of a Phase 1 trial in healthy volunteers were announced in October 2018. VE303 was safe and well-tolerated Colonization was observed through at least 12 weeks at all doses tested. Microbiota recovery after vancomycin administration was observed in a dose-dependent manner.

ANTIBODIES AND BIOLOGICS FOR BACTERIAL INFECTIONS

A number of companies are exploring development of antibodies or biologics for the prevention or treatment of bacterial infections. A few candidates have reached Phase 2 testing.

Clinical proof of concept with an antibody has not yet been established. Arsanis announced in 2018 that a Phase 2 trial of ASN100 for the prevention of *S. aureus* pneumonia was discontinued after an interim analysis indicated the trial was unlikely to meet the primary endpoint. Aridis is expected to announce results of a Phase 2 trial of AR-015 in VABP caused by *P. aeruginosa* in 1H19. Enrollment was completed in late 2018 in the Phase 2 SAATELLITE trial of MEDI4893 in MRSA HAPB, but results have not yet been disclosed.

Contrafect announced results from a Phase 2 trial of exebacase in *S. aureus* Bacteremia in 2018. There is evidence of a benefit over standard of care, although the trial missed the primary endpoint. A Phase 3 trial is planned.

- **Aridis:** Antibody candidates in development as adjunctive therapies to standard of care include AR-301 (HABP caused by *S. aureus)* and AR-105 (VABP caused by *P. aeruginosa*.) A 240-patient Phase 3 trial of the former was initiated in March 2019 and a Phase 2 trial of the latter was initiated in 2017.
- **Arsanis:** Development of ASN100 was discontinued in 2018 and Arsanis subsequently completed a reverse merger with X4 Pharma. ASN100, comprised of two antibodies directed against six *S. aureus* virulence factors (Hla, HlgAB, HlgCB, LukED, LukSF, and LukGH), was under development for the prevention of *S. aureus* pneumonia,
- **AstraZeneca:** MEDI4893 is in Phase 2 testing for MRSA HABP and MEDI3902 in Phase 2 testing for *P. aeruginosa*. Results may be available from the former in 2019 and from the latter in 2020.
- **Cidara:** Research programs directed to discovery and development of antibody-drug conjugates and bispecific antibacterial immunotherapies for multidrug-resistant Gram-negative infections have been suspended. The company is now directing the Cloudbreak platform to viral pathogens.
- **Contrafect:** Results from a Phase 2 trial of exebacase (CF-301) in *S. aureus* Bacteremia were announced in January 2019. Exebacase is a recombinant lysin. The trial enrolled 116 patients, randomized to standard of care or standard of care with exebacase. There were differences in baseline characteristics. Fewer patients in the exebacase arm had Bacteremia (77.5% vs. 86.7). Approximately 38.8% of patients in the exebacase arm had a MRSA infection, compared to 35.5% in the placebo arm. More patients in the exebacase arm had left-sided endocarditis than in the placebo arm (15.5% vs. 6.7%).

  A trend toward greater efficacy was observed in the primary analysis patient population at day 14 (70.4% vs. 60.0%; p=0.314; n=116). Statistically significant differences were reported in the MRSA subset (74.1% vs. 31.3%; p=0.01) and in the Bacteremia subset (81.8% vs. 61.5%; p=0.035), but not in the MSSA subset (68.2% vs. 73.3%). The AE and serious AE rates were similar, however, there was a greater number of deaths in the exebacase arm (n=14 19.4% vs. n=7 14.9%). No serious AEs were attributed to drug.

  A Phase 3 trial is planned, potentially with a focus on patients with Bacteremia and Right-Sided Endocarditis. The company has guided for discussions around trial design with the FDA around mid-2019.
- **InhibRx:** INBRX-111, a multi-specific and multi-epitopic anti-virulence/ opsonizing biologic, is in development for *Pseudomonas.*

- **Roivant:** A Phase 2 trial of SAL200, a bacteriophage endolysin directed to *S. aureus*, is expected to be initiated in 2019. Roivant obtained rights to the drug from Intron through a November 2018 license agreement.
- **Locus:** A CRISPR-Cas3/Phage-based antibacterial drug is in development in collaboration with J&J. The company is guiding for initiation of clinical development in 1H19.
- **Otsuka:** VIS705, an antibody drug conjugate, had been in development by Visterra for *P. aeruginosa.* Visterra was acquired by Otsuka in 2018.
- **Roche Genentech:** DSTA4637/RG7861, a drug antibody conjugate is in Phase 1/2 testing. Patients with *S. aureus* bacteremia are administered standard of care with or without DSTA4637/RG7861. Results from the trial, which was initiated in 2017, are expected in 2019.
- **Shionogi:** COT-143, a humanized antibody targeting PcrV protein, is in preclinical development for *P. aeruginosa*. The company presented mouse model data in 2018.
- **Trellis:** TRL1068, a human antibody targeting biofilm, is in preclinical development.
- **XBiotech**: Results from a Phase 1/2 trial evaluating 514G3, a human-derived antibody, in 52 patients with *S. aureus* bloodstream infections were announced in 2017. A relative risk reduction in overall incidence of SAEs and in *S. aureus*-related SAEs was observed in patients receiving 514G3 (p=NS). A trend toward reduction in average length of hospitalization was also observed.

PUBLIC POLICY AND REGULATORY UPDATE

Regulatory Environment and Recent FDA and EMA Actions

U.S. Regulatory Environment

The U.S. regulatory environment for antibiotics is generally favorable, with the FDA demonstrating flexibility around statistics and number of trials needed for approval. Statutory exclusivity periods were extended by five years under the GAIN Act (2012).

Trial feasibility is still a significant hurdle for companies addressing certain uncommon challenging infections

Trial feasibility is a challenge for companies addressing certain pathogens and outcome of the plazomicin FDA Advisory Committee meeting in 2018 raises questions about the relevance of the Limited Population Antibacterial Drugs (LPAD) development pathway, which was established by the 21st Century Cures Act in 2016.

We do not believe it is feasible to conduct a non-inferiority or superiority trial against CRE, MDR/XDR *P. aeruginosa* or CRAB. The only path to registration is through a traditional indication Phase 3 trial (i.e. cUTI or cIAI). The drug would then be used off-label for the intended indication. This is a straightforward process for an antibiotic with activity against *E. coli* because this pathogen is prevalent in cUTI. However, this is not an option for antibiotics with a narrow spectrum of activity against *P. aeruginosa* or CRAB,

Expected 2019 Regulatory Agency Actions

There were four FDA approvals in 2018 and three more approvals are possible in 2019

Two drugs from Nabriva and one drug from Merck are under FDA review. We expect both Contepo and lefamulin from Nabriva to be approved and assume relebactam will be approved. This follows approval of four drugs by the FDA last year (Zemdri/ Achaogen; Arikayce/ Insmed; Xerava/ Tetraphase; and Nuzyra/ Paratek).

The EMA approved Vabomere and Xerava in 2018. We expect review decisions for Baxdela (Melinta), Zemdri (Achaogen), and Nuzyra (Paratek) in 2019. All of these antibiotics are already approved in the U.S.

Table 9: Antibiotics in Regulatory Review or Recently Approved (U.S. and Europe)

Company	Drug	Development Status	Comments
Achaogen	Zemdri Plazomicin	US Approval 6/25/18 EMA Review	FDA cUTI Approval; Bloodstream Infections CRL
Aradigm	Apulmiq (Linhaliq) Ciprofloxacin Non-CF Bronchiectasis	FDA Review EMA Review	FDA Complete Response 1/26/18
Insmed	Arikayce Amikacin	US Approval 9/28/18	Nontuberculous Mycobacterial Lung Disease Approval
Melinta	Vabomere Vaborbactam	US Approval 8/29/17 EMA Approval 11/27/18	cUTI Approval
	Baxdela	US Approval 6/19/17 EU Review	ABSSSI Approval Collaborator Menarini submitted MAA 3/2018 sNDA CABP Submission 2Q19E
Merck	Zerbaxa	FDA Review (Expansion) EMA Review (Expansion)	HABP/VABP Label Expansion PDUFA date 7/16/19
	Relebactam	FDA and EMA Review	PDUFA date 6/3/19
Motif	Iclaprim	FDA Review	Complete Response 2/14/19
Nabriva	Contepo	FDA Review	PDUFA date 4/30/19
	Lefamulin	FDA Review	PDUFA date 8/19/19; EMA Submission 1H19E
Paratek	Nuzyra Omadacycline	US Approval 10/2/18 EMA Review	ABSSSI and CABP Approval
Tetraphase	Xerava Eravacycline	US Approval 8/27/18 EU Approval 9/20/18	cIAI Approval

Source: Company reports; Needham & Company, LLC estimates

- **Achaogen:** Zemdri MAA was submitted in 4Q18 and a review decision is expected in 4Q19.
- **Aradigm** FDA issued an Apulmiq/ Linhaliq Complete Response Letter in January 2018. The company submitted an MAA in the same indication in March 2018.
- **Melinta**: Collaborator **Menarini** submitted an MAA in March 2018 for delafloxacin. Melinta is guiding for sNDA submission for CABP in 2Q19.
- **Merck:** NDA and MAA submissions were announced in February 2019 for relebactam in cUTI and cIAI patients with limited or no alternative therapies available. An sNDA was also submitted for Zerbaxa in HABP/ VABP.
- **Motif**: An Iclaprim NDA was submitted in June 2018. A Complete Response Letter was issued in February 2019 due to concerns around liver toxicity.
- **Nabriva**: A Lefamulin NDA was submitted in late December 2018 and we expect a review decision by the 8/19/19 PDUFA date. An MAA submission is expected soon. The Contepo PDUFA date is 4/30/19.
- **Paratek**: A Nuzyra MAA accepted in October 2018 and a review decision is expected in 2H19.

FDA Advisory Committee Meetings

An FDA Advisory Committee meeting pertaining to use of intramuscular injection bacitracin for infants with pneumonia and empyema caused by Staphylococci is scheduled for April 2019. The agency is reportedly not planning to hold meetings for Contepo nor lefamulin. Recent meetings are summarized below.

An FDA public workshop focused on Nontuberculous Mycobacterial Disease is scheduled for 4/8/19.

Table 10: Recent and Planned FDA Antimicrobial Drugs Advisory Committee Meetings (AMDAC)

Date	Drug/ Topic	Company	Indications	Vote Outcome		FDA Action
4/26/19	IM Bacitracin		Infants with Pneumonia and Empyema			
8/8/18	Nuzyra Omadacycline	Paratek	Community Pneumonia	CABP	14 Yes 4 No	Approved 10/2/18
			Skin Infections	ABSSSI	17 Yes 1 No	
8/7/18	Arikayce	Insmed	NTM *Mycobacterium avium* complex	Overall Risk Benefit	12 Yes 2 No	Approved 9/28/18
5/2/18	Zemdri Plazomicin	Achaogen	Urinary Tract Bloodstream	Urinary Tract	15 Yes 0 No	Approved 6/25/18
				Bloodstream	4 Yes 11 No	Complete Response 6/25/18
1/11/18	Ciprofloxacin Inhalation Linhaliq	Aradigm	Non-CF Bronchiectasis	Overall Risk Benefit	3 Yes 12 No 1 Abstain	Complete Response 1/29/18
11/16/17	Ciprofloxacin Inhalation	Bayer	Non-CF Bronchiectasis	14 Day Regimen	6 Yes 9 No	Complete Response 12/17
				28 Day Regimen	1 Yes 14 No	

Source: Company Reports; Needham & Company, LLC

Policies to Support Antibiotic Development

Momentum is building in the U.S. for a Pull incentive, but we do not have sufficient evidence to believe that a new mechanism will be implemented in 2019.

A sense of urgency within the U.S. government, foundations, the academic and medical community, as well as industry is evident. We detect a greater degree of collaboration among the various stakeholders, but we do not yet have conviction that anything meaningful will be implemented in 2019.

PULL: Unconventional strategy revolving around alternative payment mechanisms after approval

Potential mechanisms include tax incentives, market entry reward in lieu of or in addition to revenues from commercial sales, and changes to reimbursement, such as a Medicare add-on payment (DRG exclusion or carve-out).

- **The Margolis Center for Health Policy** proposed the Priority Antimicrobial Value and Entry (PAVE) Award in August 2017. The proposal recommends implementation of a market entry award upon regulatory approval spread over 5-6 years, with the largest in year 1. Additional revenue would be derived from value-based contracts with payers.
- The European Innovative Medicines Initiative (**IMI**) established the **DRIVE-AB** project, a private-public consortium comprised of 23 entities across Europe. A final report was published in January 2018. Among key recommendations 1) the G20 Global R&D Collaboration Hub on Antimicrobial Resistance acting as a central coordinator for push and pull mechanisms and 2) $1B market entry reward should be implemented.
- Senators Orrin Hatch and Bob Casey introduced a bill in December 2018 (115th Congress) that would have allowed Medicare to offer an add-on payment for certain antibiotics. (Table 11; **DISARM**; S. 3787). It appears likely that similar legislation will be introduced in the 116th Congress.

Push: Conventional funding mechanisms to support development as well as increased regulatory flexibility

There are a variety of programs put in place by a wide range of entities designed to provide funding for antibiotic discovery and development. They include BARDA, CARB-X, the IMI, the European Investment Bank, WHO, and Drugs for Neglected Diseases initiative, among others.

- **BARDA** posted earlier this year a Request for Information for DRIVe Ventures. This RFI intends to research the use of the corporate venture capital community to invest in a range of efforts, which could include antibiotic development.

A 5-year **United Kingdom** national action plan was published in January 2019. Three general goals are outlined: 1) reducing the need for antimicrobials; 2) optimizing use of antimicrobials, and 3) investment in innovation, supply, and access. Among several proposals is a de-linkage of the price paid for antimicrobials from the volume sold. Current plans are to test this on a national level as a subscription model with 2-3 antibiotics (Set fee for unlimited access to the drugs). An antibiotic investment charge on the pharmaceutical sector in which each company may either pay the charge or invest in antimicrobial drug development is under consideration.

U.S. Legislative Update

A variety of bills have been introduced (some repeatedly over the years) to address a range of matters in the antibiotic space. Only a BARDA reauthorization bill has been introduced in the 116th congress.

Table 11: U.S. Proposed Legislation

Bill	Sponsor	Date Last Introduced	Comments
116th Congress			
Pandemic and All-Hazards Preparedness and Advancing Innovation (H.R.269)	Eshoo	1/2019	Passed House 1/8/19
115th Congress			
Preservation of Antibiotics for Medical Treatment Act (PAMTA; H.R. 1587)	Slaughter	3/2017	Limit antimicrobial use in agriculture Introduced in 2007, 2009, 2011, 2013, 2015
Improving Access to Affordable Prescription Drugs Act (H.R. 1776)	Schakowsky	3/2017	Establish antibiotics prize fund ($2B total)
Reinvigorating Antibiotic and Diagnostic Innovation Act of 2017 (H.R. 1840)	Paulsen	3/2017	Tax credits for 50% of clinical development costs for new antibiotics or antifungal agents direct to qualifying pathogens and certain new diagnostic devices; Credit is transferrable
Medical Innovation Prize Fund Act (S. 495)	Sanders	3/2017	Establish prizes for new drugs
Preventing Antibiotic Resistance (S. 629)	Feinstein	3/2017	Limit antimicrobial use in agriculture Introduced in 2013, 2015
Strategies to Address Antibiotic Resistance Act (STAAR; S.2469)	Brown	2/2018	Establish Task Force and Advisory Council to address antibiotic resistance; Surveillance of antibiotic use and resistance; Clinical trial network
Strengthening Antibiotic Oversight (S. 3099)	Warren	6/2018	Require review of durations of use of approved indications of medically-important antibiotics labeled for use in animals
Re-Valuing Anti-Microbial Products (REVAMP H.R. 6294)	Shimkus	6/2018	Award of a transferable exclusivity extension period
Pathogen Reduction and Testing Reform (H.R. 7336)	DeLauro	12/2018	Grant authority to USDA to issue a recall of meat, poultry, and egg products that contain microbial pathogens associated with serious illness or death or are resistant to two or more antibiotics critically important for human medicine.
Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM; S. 3787)	Hatch	12/2018	Additional payment under Medicare

Source: Needham & Company, LLC estimates; congress.gov

PHARMA INTEREST IN ANTIBIOTICS

Allergan continues to seek a buyer for its antibiotic assets and Novartis ended its internal research effort in the space in 2018. Both J&J and Boehringer Ingelheim entered into collaboration agreements with smaller biotech companies.

Transactions 2H18-2019

- Locus and J&J (Jan 2019) entered into an agreement for the development and commercialization of a CRISPR-Cas3-based bacteriophage product.
- Roche (Jan 2019) returned nacubactam rights to Fedora and Meiji Seika. A joint venture was formed by Fedora and Meiji Seika (Nacugen) to continue development. Roche had in-licensed the drug in January 2015.
- Novartis out-licensed three candidates to Boston Pharmaceuticals (Oct 2018).
- Boehringer Ingelheim and Bioharmony (Jan 2019) announced a collaboration for the development of lysins for *A. baumannii* infections.
- Roivant and Intron (Nov 2018) entered into an agreement for the development of SAL200, a lysin directed against S. aureus. Roivant also obtained an option to earlier stage lysin programs directed against other pathogens.

Table 12: Pharma Activity in Antibiotic Space

Company	Branded Antibiotics*	Development Efforts	Interest in Acquiring Antibiotics	Transactions Comments
AbbVie	-	No	No	
Allergan	Teflaro Dalvance Avycaz	Clinical Development	No Sale Planned	Durata acquisition (2014) Quinsair out-licence (2015)
Amgen	-	No	No	
Astellas	Dificlir (EU/JP)	Clinical Development	Possible	
AstraZeneca	-	Biologics in Clinical Development	No	R&D spin-out Entasis (2015); Small molecule assets sold to Pfizer (2016)
Bayer	-	No	No	Tedizolid (Trius 2011; Terminated 2018); Non-CF Bronchiectasis (Discontinued)
BMS	-	No	No	
Boehringer Ingelheim	-	No	Possible	Bioharmony (2019)
Eli Lilly	-	No	No	
Gilead	Cayston	No	No	
GSK	-	Discovery; Clinical Development	Possible	
J&J	Sirturo	Limited	Possible	Locus (2019)
Merck	Invanz Dificid Sivextro Zerbaxa Zinplava	Discovery; Clinical Development	Possible	Cubist Acquisition (2014) Out-license to Prokaryotics (2018)
Novartis	Tobi Podhaler	No	No	TB assets out-licensed to TB Alliance (2014); Vaccines divested to GSK (2014); All research terminated (2018); Boston out-license (2018)
Pfizer	Zinforo (ex-US) Avycaz (ex-US)	Discovery; Clinical Development	Possible	Bacterial vaccines; Acquired AZ small molecule antibiotic assets (2016)
Roche Genentech	-	Discovery; Clinical Development	Yes	Polyphor (2013); RQX (2013; Later acquired); Discuva (2014); Spero (2014; terminated 2016); Fedora/Meiji (2014; terminated 2019); Warp Drive/Revolution
Sanofi	-	No Clinical Development	Possible	R&D Collaboration: Fraunhofer (2014) Evotec (2018)
Shionogi	Doribax	Clinical Development	Possible	Hsiri (2018)
Takeda	-	No	No	

** Source: Company reports; Needham & Company, LLC estimates, company communications*

R&D UPDATE AT SELECTED COMPANIES

Achaogen (AKAO; HOLD)

- Zemdri (Plazomicin)

  Lead antibiotic Zemdri, an internally-discovered aminoglycoside derivative, was approved by the FDA in 2018. An MAA is under review.

- C-Scape (Ceftibuten-Clavulanate)

  Achaogen disclosed in 2017 a new oral program, C-Scape, directed to cUTI. The components are ceftibuten and clavulanate. Formulation work has been completed to optimize PK/PD and a Phase 1 trial is planned.

Allecra Therapeutics (Private, Weil am Reim, Germany)

Allecra was established in 2013 around a novel beta-lactamase inhibitor program from Orchid. Lead asset AAI101 is an extended-spectrum beta-lactamase inhibitor. The company initiated a global 1000-patient Phase 3 cUTI trial in 2018. The comparator is piperacillin-tazobactam. Top-line results may be available late this year.

Allergan (AGN; NR)

Allergan announced plans to divest its infectious disease unit in May 2018 and continues to seek a buyer. The company markets Teflaro and Avycaz, which were acquired by Forest through transactions in 2006 and 2009, respectively. Durata, which developed Dalvance, was acquired by Actavis in 2015.

Antabio (Private; Labege France)

Antabio completed a €12.5M Series A financing in July 2018. The company is seeking to develop a metallo beta-lactamase inhibitor as well as a *Pseudomonas* Elastase inhibitor for Cystic Fibrosis infections. The company is planning to select a candidate from the metallo beta-lactamase inhibitor program and begin Phase 1 testing in 2019.

Arixa (Private: Palo Alto)

Arixa announced an $8M seed financing in May 2018 to support development of ARX-1796, an oral prodrug of avibactam. The company has guided for initiation of Phase 1 testing in 2019.

Arrevus (Private; Raleigh NC)

Arrevus is seeking to develop fusidic acid (Taksta) for refractory bone and joint infections. Cempra had previously conducted clinical development with this drug, which is commercially available outside the U.S.

Arrevus acquired the asset from Melinta, which had completed a reverse merger into Cempra.

AstraZeneca (AZN; NR)

AstraZeneca spun out its early stage small molecule antibiotic research and development business into a separate company, Entasis, in 2015. The company subsequently sold its commercial small molecule antibiotic assets to Pfizer in August 2016.

Two programs, MEDI4893 and MEDI3902, are in Phase 2 testing for MRSA and *P. aeruginosa* infections, respectively, in conjunction with COMBACTE.

- MEDI4893

  The SAATELLITE trial enrolled approximately 200 ventilated ICU patients at risk of *S. aureus* pneumonia. The trial was completed in 2018, but results have not been disclosed.

- MEDI3902

  The EVADE trial is evaluating MEDI3902, a bispecific monoclonal antibody directed against two *P. aeruginosa* targets, for the prevention of ventilator-associated pneumonia in adult ICU patients. Results are expected to be available in 2020 (was 2021) according to clinicaltrials.gov.

Basilea (BSLN-SWX; NR)

Basilea initiated a Phase 3 trial of ceftobiprole in ABSSSI in February 2018 and a Phase 3 trial in patients with *S. aureus* Bacteremia in mid-2018. Results from the former are expected to be available late in 2019 and from the latter in 2021. Both trials are under an SPA announced in April 2017. A Phase 3 trial in pediatric patients with CABP/HABP was also initiated in February 2018 and may be completed by YE19. Basilea has been awarded up to $108M in contracts from BARDA for ceftobiprole Phase 3 development.

Ceftobiprole is marketed for CABP and HABP in many regions worldwide, with the exception of the U.S.

Boston Pharmaceuticals (Private; Cambridge MA)

Boston in-licensed three assets from Novartis in 2018, including an IV monobactam (BOS-338), an IV beta-lactamase inhibitor (BOS-572), and an oral LpxC inhibitor. Novartis had initiated Phase 2 testing of BOS-338 (LYS228), which was engineered to add coverage of serine beta-lactamases to that of metallo beta-lactamases. The other two programs are still in preclinical development.

Centauri (Private; Kent UK)

Centauri is leveraging an immunotherapy platform to develop drugs for both oncology and infectious diseases. A candidate directed against Gram-negative pathogens is in lead optimization. The company was founded in 2010

Combioxin (Geneva Switzerland)

Lead asset CAL02 is comprised of empty liposomes designed to neutralize bacterial toxins. A Phase 1 trial has been completed.

Contrafect (CFRX; NR)

Contrafect is developing CF-301, a bacteriophage lysin directed against *S. aureus*, for the treatment of bacteremia. Results of a Phase 2 trial in patients with *S. aureus* bloodstream infections were announced in January 2019. The company plans to meet with the FDA to discuss registration trial design. A Phase 3 trial with a focus on patients with Bacteremia and Right-Sided Endocarditis is under consideration.

Contrafect is also conducting early stage development of a lysin directed against *P. aeruginosa*, with support from CARB-X.

Entasis Therapeutics (ETTX; Waltham, MA)

AstraZeneca spun out its small molecule antibiotic research and development business into Entasis in 2015. The company completed an IPO in September 2018.

Entasis is developing ETX2514, an IV beta-lactamase inhibitor (Class A, C, and D), and ETX0282, an oral beta-lactamase inhibitor (Class A and C). Zolidoflacin is in development with Global Antibiotic Research and Development Partnership (GARDP). The company is also seeking to develop a non-beta-lactam penicillin-binding protein antibiotic.

- EXT2514 (IV) is in development in combination with sulbactam for *A. baumannii* infections. A Phase 3 trial in *MDR A. baumannii* is expected to be initiated in early 2019.

- ETX0282 (Oral) is being developed in combination with cefpodoxime for cUTI. Phase 1 testing in healthy volunteers is underway, with results likely available in 2019. An IV formulation will not be developed.
- Zoliflodacin (ETX0914), a novel benzisoxazole DNA gyrase inhibitor, is in development for the treatment of gonorrhea. Entasis entered into an agreement in July 2017 with GARDP for Phase 3 development. A 179-patient Phase 2 trial was initiated in 4Q14 and top-line results were announced in September 2016. The trial met its primary endpoint (100% response 3g ETX0914 and 98% response 2g arm). Phase 1 PK, food effect, and QT trials were completed in 2018 and 2019.

Evotec (EVT; Hamburg Germany)

Evotec conducts development in collaboration with several entities across a wide range of disease areas. The company has more recently announced a number of deals around early stage antibiotic assets and research programs. These include agreements with Forge (2016), Sanofi (2018), Spero, GARDP (2019), as well as several academic institutions.

Forge Therapeutics (Private; San Diego, CA)

Forge is leveraging a novel selective non-hydroxamic acid metal-binding chemistry to discover and develop drugs across a wide range of indications, including bacterial infections. A number of antibiotic programs are underway.

- FG-LpxC UTI: IV and oral LpxC inhibitor for UTI with coverage of drug-resistant pathogens, including ESBL and CRE. Forge has guided for IND submission in 1Q20. This program is supported by CARB-X
- FG-LpxC LUNG: IV LpxC inhibitors for respiratory infections caused by Gram-negative bacteria, including *P. aeruginosa*. This program is supported by CARB-X and is in lead optimization.

Other programs directed toward discovery and development of a DXR inhibitor, IsPF inhibitor, and a bacterial RNA polymerase inhibitor are in research stage.

GSK (GSK; NR)

Only one antibiotic is listed in the GSK pipeline, gepotidacin (GSK2140944), an IV/oral broad-spectrum topoisomerase inhibitor. The drug has been evaluated in a series of Phase 1 and 2 trials, including in ABSSSI and gonorrhea. There are no active trials listed in clinicaltrials.gov.

GSK and Shionogi had collaborated in the development of GSK3342830 and cefiderocol (S-649266; GSK2696266) until an agreement was reached in November 2016 in which GSK3342830 was assigned to GSK and cefiderocol was assigned to Shionogi.

Insmed (INSM; NR)

Insmed launched Arikayce, an inhaled once-daily formulation of liposomal amikacin in late 2018. The drug was approved by the FDA for the treatment of Mycobacterium avium complex lung disease. Insmed reported $9.8M in 4Q18 sales. Over 500 patients have reportedly initiated treatment.

The company plans to initiate a Phase 3 trial in front-line Mycobacterium avium complex lung disease in 2019 and seek regulatory approval in Europe and Japan.

Iterum Therapeutics (ITRM; BUY)

Iterum was founded in 2015 and completed an IPO in May 2018. The company in-licensed sulopenem, an IV/ oral carbapenem antibiotic, from Pfizer. Phase 3 trials in cUTI, uUTI, and cIAI were initiated in late 2018 and results are expected to be available in late 2019. We expect an NDA submission around YE19.

Locus (Private; Morrisville NC)

Locus is exploring development of a bacteriophage product containing a CRISPR-Cas3 system (crPhage). The company entered into a collaboration agreement with J&J in 2019.

Macrolide Pharmaceuticals (Private; Boston)

Macrolide is focused on the discovery and development of fully synthetic macrolide derivatives for antimicrobial applications as well as non-infection indications.

Target profile for the antibiotic program is a macrolide with Gram-negative activity. The company is also seeking to develop a drug for Nontuberculous Mycobacteria.

Matinas BioPharma (MTNB; NR)

Matinas is focused on the development of novel lipid-crystal nanoparticle formulations of existing antimicrobials. The lead clinical asset is MAT2203, an oral formulation of amphotericin B. Earlier stage MAT2501 is an oral formulation of amikacin.

Matinas announced completion of a Phase 1 SAD trial of MAT2501 in May 2017. Development has been suspended in order to focus on other programs.

Melinta Therapeutics (MLNT; NR)

Melinta became a public company through a reverse merger with Cempra in November 2017. The company subsequently acquired the clinical development and commercial-stage antibacterial assets of Medicines Company through a transaction that closed in January 2018.

- Baxdela (Delafloxacin), a broad spectrum IV/oral fluoroquinolone with MRSA coverage, was approved by the FDA in June 2019 for ABSSSI. A Phase 3 trial in CABP was completed in 2018 (IV/oral; moxifloxacin/ linezolid comparator; NCT02679573). This drug has less risk of phototoxicity and QT prolongation than other fluoroquinolones.
- Vabomere, a combination of serine beta-lactamase inhibitor vaborbactam (RPX7009) and meropenem, was approved by the FDA in August 2017 and the EMA in November 2018.
- Minocin, a new IV formulation of minocycline, was approved by the FDA in 2015.
- RX-04 Program

  Melinta had sought to discover and develop a novel Gram-negative drug, but has suspended the program due to resource constraints.

Merck (MRK; NR)

- Zinplava (bezlotoxumab) was approved by the FDA in October 2016. Merck in-licensed the fully human monoclonal antibody targeting *C. difficile* toxin B from Medarex in April 2009.
- Relebactam (MK-7655), a beta-lactamase inhibitor, is being developed in combination with imipenem/cilastatin (Primaxin) for the treatment of Gram-negative infections. Relebactam is active against Class A and C serine enzymes in CRE and carbapenem-resistant *Pseudomonas aeruginosa*, but is not active in *Acinetobacter baumannii*.

  An NDA and MAA were filed in early 2019 based on data from the Phase 3 RESTORE-IMI 1 trial, which evaluated relebactam and imipenem/cilastatin against colistin and imipenem in 47 patients with imipenem-non-susceptible infections. Additional Phase 3 trials in HABP/VABP comparing relebactam and imipenem/cilastatin to piperacillin/ tazobactam are underway.

- Merck is developing V114, a conjugate vaccine for pneumococcal disease. Two Phase 3 trials were initiated in late 2018 and early 2019. FDA Breakthrough designation was granted in 2019 based in part on data from a 1050-subject Phase 2 trial.

Motif Bio (MTFB; NR)

Motif is developing iclaprim, a DHFR inhibitor, for ABSSI and HABP/VABP. The company is positioning the drug as a targeted-spectrum (MRSA) option for empiric therapy in high-risk patients with renal impairment in the hospital setting.

An NDA was submitted in ABSSSI in June 2018. A Complete Response letter was issued in February 2019, reportedly due to concerns over liver toxicity.

The company conducted two identical Phase 3 trials in ABSSSI (REVIVE-1 and REVIVE-2). Top-line results from REVIVE-1 were announced in April 2017. Both early and TOC endpoints were met against comparator vancomycin. Positive REVIVE-2 top-line results were announced in October 2017.

Iclaprim was acquired from Arpida by Acino and then Nuprim. Motif acquired Nuprim in 2015. Arpida had previously conducted two Phase 3 cSSSI trials with linezolid as a comparator. Although both trials met pre-specified endpoints, the FDA changed regulatory requirements by the time the drug was under review and issued a Complete Response letter.

Nabriva (NBRV; BUY)

Nabriva was founded in 2005 as a spin-off from Sandoz. The company acquired Zavante and its sole asset IV fosfomycin in 2018.

- Lead drug lefamulin is in development for the treatment of Community Acquired Bacterial Pneumonia (CABP). Lefamulin is a novel semisynthetic pleuromutilin antibiotic. No other pleuromutilin antibiotics have been approved for the treatment of systemic infections in man.

  An NDA was submitted in 2018 and the PDUFA date is 8/19/19.

  Phase 3 trials were initiated in October 2015 and April 2016. Positive top-line results from the IV-to-oral lefamulin Phase 3 LEAP1 trial and the oral lefamulin Phase 3 LEAP2 trial were announced in September 2017 and May 2018. All EMA (IACR EC) and FDA (NI Early Clinical Response ITT) primary endpoints were met in both trials.

- Zavante, founded in 2014, developed an IV formulation of fosfomycin for the U.S. market (Contempo [was Zolyd]; ZTI-01). Only the oral formulation is currently available in the U.S. Both formulations are on the market in Europe. The IV formulation is approved for osteomyelitis, cUTI, nosocomial respiratory infections, and bacterial meningitis in Europe.

  Nabriva submitted a 505(b)(2) NDA in 2018 and the PDUFA date is 4/30/19.

  The drug will be positioned as first-line therapy as a single agent for cUTI patients with suspected MDR pathogens and as second-line therapy in combination with other agents for patients with documented ESBL, CRE, MDR *P. aeruginosa*, VRE, or MRSA.

  A Phase 3 trial (ZEUS) was completed in 2017.

Nosopharm (Private; Lyon France)

Nosopharm is seeking to develop novel antimicrobial agents derived from *Xenorhabdus* and *Photorhabdus* natural products. Target pathogens are *Enterobacteriaceae*, *P. aeruginosa* and *Candida spp*. The most advanced program is in candidate selection.

Paratek (PRTK; NR)

Nuzyra (Omadacycline; PTK796) is a novel IV/ oral semi-synthetic tetracycline derivative. The drug was approved by the FDA in October 2019 for CABP and ABSSSI. The drug is under review by the EMA.

Paratek is also evaluating omadacycline in Urinary Tract Infections in two Phase 2 trials.

Pfizer (PFE; NR)

Pfizer acquired rights to several antibiotics in a transaction with AstraZeneca in August 2016. The deal included Zinforo (Rights outside North America and Japan), Zavicefta (Rights outside North America), Aztreonam/ Avibactam (ATM-AVI; Rights outside North America), Ceftaroline/ Avibactam (CXL; Rights outside North America), and meropenem (Available as a generic). Allergan retained North American rights to Zinforo (Teflaro), Zavicefta (Avycaz), ATM-AVI, and CXL.

Pfizer initiated a 300-patient Phase 3 trial evaluating ATM-AVI against meropenem in combination with colistin for Gram-negative infections in cIAI and HABP/VABP (REVISIT) in 2018. Avibactam adds coverage of CRE with serine beta-lactamases to that of metallo beta-lactamases by aztreonam.

There are several vaccines in development at Pfizer, including PF-06760805 (Phase 1 Invasive Group B Streptococcus infection), PF-06842433 (Phase 2 Pneumococcal infection), PF-06482077 (Phase 3 Pneumococcal infection), and PF-06425090 (Phase 3 *C. difficile*).

Polyphor (POLN-SWX; NR)

Polyphor is seeking to develop murepavadin for the treatment of *P. aeruginosa* nosocomial pneumonia. The antibiotic, a cyclic peptide, is only active against *Pseudomonas*. The company initiated Phase 3 development in 2018.

Polyphor has also made progress towards the discovery and development of a novel broad-spectrum Gram-negative antibiotic. Candidates have low MIC values against challenging CRE, *Acinetobacter*, and *Pseudomonas* isolates. The lead compound is POL7306 and the company has guided for Phase 1 initiation in 2020.

Procarta (Private, Stevenage UK)

Procarta is seeking to develop novel antimicrobials with its oligonucleotide transcription factor decoy platform technology. Lead asset PRO-202 is in preclinical development for cUTI and cIAI.

Prokaryotics (Private, Union NJ)

Prokaryotic was founded in 2017 around a series of preclinical programs in-licensed from Merck. Terms of the deal have not been disclosed. Target pathogens include both Gram-positive and Gram-negative bacteria. A variety of compounds directed against a range of drug targets are in early development.

Qpex Biopharma (Private; San Diego CA)

Qpex raised $33M through a Series A financing in late 2018. The company was founded by the management team from Rempex with assets from the Medicines Company.

Lead assets include IV/ oral broad spectrum beta-lactamase inhibitors. The company is also developing a series of compounds directed against an undisclosed target for Gram-negative pathogens. Management has guided for presentation of data at the ASM Microbe meeting later this year and plans to advance candidates from both programs into the clinical in 2020.

Qpex has a contract with BARDA worth up to $132M.

Revolution (Private; Redwood CA)

Warp Drive was acquired by Revolution Medicines in October 2018. The collaboration announced in October 2017 with Roche will continue.

Roche (NR)

Roche initiated clinical development of RG7861 (DSTA4637S), an antibody-antibiotic conjugate directed against *S. aureus* in 2015. A second trial was initiated in July 2017 in patients with *S. aureus* bacteremia. The program is partnered with Seattle Genetics and Symphogen.

Roche obtained rights to RG6080 (Nacubactam; OP0595, FPI-1459), a diazabicyclooctane beta-lactamase inhibitor under a license agreement with Fedora and Meiji Seika in January 2015. This license was terminated in January 2019.

Roche entered into a license agreement with Discuva in February 2014 for the discovery and development of antibiotics directed against MDR Gram-negative infections. Discuva received a $16M upfront fee and is eligible to receive up to $175M in milestone payments per product. Summit acquired Discuva in late 2017.

Savara (SVRA; NR)

Savara acquired assets from Cardeas in July 2018, including an amikacin/ fosfomycin inhalation solution for Ventilator Associated Bacterial Pneumonia (VABP).

Savara is conducting a Phase 3 trial of inhalation vancomycin (AeroVanc) in Cystic Fibrosis patients with MRSA infections. Enrollment in the AVAIL trial is expected to be completed in 2019.

Seres (MCRB; NR)

Seres is focused on the development of microbial therapeutics for various indications. The company announced a corporate restructure in February 2019 as well as a strategic prioritization of a Phase 2b program in Ulcerative Colitis, the Phase 3 program in *C. difficile*, and an early stage immuno-oncology program.

Setlance (Siena Italy)

Setlance is seeking to develop antimicrobial peptide SET-M33 for Gram-negative pathogens, including *Enterobacteriaceae*, *A. baumannii*, and *P. aeruginosa*.

SNIPR Biome (Private; Copenhagen Denmark)

Snipr Biome raised $50M in a series A finding in March 2019. The company is developing a CRISPR-based technology to target bacterial pathogens.

Spero (SPRO; NR)

Spero Therapeutics was founded in 2013 based on research by L. Rahme at Harvard University around MvfR as a target for *P. aeruginosa* infections. Since then, the company has been active in in-licensing several early stage programs for further evaluation and clinical development. The company completed an IPO in November 2017.

- SPR994

  Spero in-licensed tebipenem (SPR994), an oral-only carbapenem, from Meiji Seiki in 2017. The company has initiated a Phase 3 trial in cUTI.

- SPR741

  SPR741, an IV potentiator polymyxin derivative, has been evaluated in Phase 1 trials as monotherapy and in combination with several different antibiotics, including azithromycin, pip-tazo, ceftazidime, and aztreonam. SPR741 does not have antibacterial activity as monotherapy. The drug has been well tolerated in both SAD (up to 800mg) and MAD (up to 600mg tid qh8 14 days) trials. Data

reportedly support development of SPR741 in combination with other antibiotics. SPR741 was in-licensed from Northern Antibiotics.

- SPR206

  SPR206 is also a novel IV polymyxin derivative, but does have antimicrobial activity as a single agent, unlike SPR741. The drug reportedly has impressive activity against all key MDR/XDR Gram-negative pathogens, including carbapenem-resistant *P. Aeruginosa*, *A. baumannii* (CRAB), and *Enterobacteriaceae* (CRE). Spero announced in May 2018 that the company has completed a series of preclinical IND-enabling studies. A Phase 1 trial was initiated in December 2018.

- SPR720

  SPR720 is in Phase 1 testing for non-tuberculous mycobacterial (NTM) infections. A trial was initiated in healthy volunteers in January 2019.

Summit Therapeutics (SMMT; NR)

Summit initiated Phase 3 testing of ridinilazole for *C. difficile* infection in February 2019. The company acquired Discuva, a private company based in Cambridge UK, in December 2017.

- Ridinilazole (SMT19969)

  Summit announced top-line results from a Phase 2 trial in September 2017 and initiated two 680-patient Phase 3 trials in February 2019. The company has guided for top-line results in 2H21. BARDA previously awarded Summit a contract of up to $62M for development of ridinilazole.

- Discuva Antibiotic Drug Discovery Platform

  Discuva, which was acquired by Summit for £5.0M cash and £5.0M in stock, has a drug discovery platform directed toward both Gram-positive and Gram-negative pathogens.

  Summit announced in March 2018 that several compounds with a novel mechanism of action against Gonorrhea had been identified with the Discuva platform. The company has guided for initiation of a Phase 1 trial of SMT-571 in 2H19.

  Discuva had entered into a collaboration with Roche in 2014 for the development of novel Gram-negative agents. In connection with the Summit-Discuva acquisition, Summit agreed to pay Discuva shareholders 50% of the development and clinical milestones received from Roche related to the platform.

Tetraphase (TTPH; HOLD)

Tetraphase leverages an internal tetracycline chemistry platform to discover and develop novel antibiotics. The company recently disclosed a tetracycline derivative oncology program.

- Xerava (Eravacycline) is an internally discovered broad-spectrum tetracycline derivative approved by the EMA and FDA for cIAI. Two Phase 3 trials of an IV formulation were successfully completed by the company (IGNITE1 and IGNITE4).

  The company announced negative results from Phase 3 trials in cUTI evaluating IV and oral formulations (IGNITE2) and the oral formulation alone (IGNITE3). Development of the oral formulation and development in cUTI has been suspended.

- TP-6076 was selected in early 2015 as a second-generation Gram-negative tetracycline candidate for development. Efficacy against MDR clinical isolates is encouraging. A Phase 1 trial began in August 2016. Discussions are underway with the FDA around registration strategy in CRAB.
- TP-271 is a broad spectrum antibiotic under development for biodefense applications. This development effort is supported by funding from the NIAID. An IND was submitted in 3Q15 and a Phase 1 trial was initiated in January 2016.

Venatorx (Private; Malvern, PA)

Venatorx was founded in 2010 by members of the Protez management team.

- VNRX-5133, a novel IV beta-lactamase inhibitor with activity against both serine and metallo beta-lactamase inhibitors in *Enterobacteriaceae* and *P. aeruginosa*, has completed Phase 1 testing. A Phase 3 trial in combination with cefepime in cUTI is expected to begin in 2Q19. Another trial in CRE infections will be run in parallel. Results may be available in 2020 or 2021.
- VNRX-7145 is a novel IV/oral beta-lactamase inhibitor in preclinical development. Phase 1 testing appears likely to begin in 2019.
- A next generation Penicillin Binding Protein inhibitor is in preclinical development.

Table 13: Selected Antibiotics under Development

Company	Product	Potential Indications	Route of Admin.	Development Status	Class/MOA	Comments
Achaogen	Zemdri Plazomicin ACHN-490	CRE	QD IV	US Market EMA Review	Aminoglycoside	Unpartnered
	C-Scape Ceftibuten Clavulanate	cUTI	Oral	Phase 1	B-Lactamase Inhibitor B-lactam	Unpartnered
Acurx	ACX-362E	*C. difficile*	Oral	Phase 1	DNA polymerase Inhibitor	From GLSynthesis
Adenium	Arenicin AA139	Gram-Negative	IV	Preclinical	Antimicrobial peptide	Unpartnered No recent update
	AP138	MRSA		Preclinical	Plectasin derivative	
Aicuris	AIC499	Gram-Negative	IV	Phase 1	B-Lactam	IMI
Allecra	AAI101	Gram-Negative	IV	Phase 3	B-Lactamase Inhibitor B-lactam	Unpartnered
Allergan	Seysara Sarecycline	Acne	QD Oral	Market	Tetracycline	From Paratek
Ampliphi	AB-PA01	*P. aeruginosa*	IV/ Inhale	Phase 1/2	Bacteriophage	Unpartnered
	AB-SA01	*S. aureus*	IV	Phase 1/2	Bacteriophage	Unpartnered
Aridis	AR-101 KBPA-101 Aerumab	*P. aeruginosa* Pneumonia	IV	Phase 2	PA Serotype O11 mAb	From Kenta
	AR-301 Salvecin KBSA301	MRSA Pneumonia	IV	Phase 3	Anti-Alpha Toxin mAb	From Kenta
	AR-105 Aerucin	*P. aeruginosa* Pneumonia	IV	Phase 2	Anti-alginate mAb	Unpartnered
	AR-501 Gallium Citrate	Cystic Fibrosis	Inhale	Phase 1/2	Gallium Citrate	Unpartnered
Arixa	ARX-1796	Gram-Negative	Oral	Preclinical	B-Lactamase Inhibitor Avibactam prodrug	Unpartnered
Arrevus	Taksta	Gram-Positive	Oral	Phase 2	Fusidic Acid	From Cempra
AstraZeneca	MEDI4893	MRSA	IV	Phase 2	Anti-Alpha Toxin mAb	COMBACTE
	MEDI3902	*P. aeruginosa*	IV	Phase 2	Bispecific mAb	COMBACTE
Basilea	Zevtera Ceftobiprole	Broad Spectrum CABP HABP	IV	EU Market FDA CRL/Phase 3	Cephalosporin	Quintiles (EU) BARDA
Biocidium	BCM-0184	Broad Spectrum	IV/Oral/ Topical	Phase 1		Unpartnered
Bioharmony	BH01	Burn Infections	Topical	Preclinical	Lysin	
Boston	BOS228 LYS228	Gram-Negative	IV	Phase 2	Monobactam	From Novartis
	IID572	Gram-Negative	IV	Preclinical	B-Lactamase Inhibitor	From Novartis
	MAK181	*P. aeruginosa*	Oral	Preclinical	LpxC Inhibitor	From Novartis
Cantab	NVB333	Gram-Positive		Preclinical	Semisynthetic Derivative Lantibiotic Deoxyactagardine B	Seeking Partner From Novacta
Combioxin	CAL02				Liposomes	
Contrafect	CF-301	*Staphylococcus* Bacteremia Endocarditis	IV	Phase 2	Bacteriophage Lysin	Unpartnered
Crestone	CRS3123 REP3123	*C. difficile*	Oral	Phase 1	Methionyl-tRNA synthetase inhibitor	From Replidyne
Daiichi Sankyo	DS-2969 DS11960558	*C. difficile*	IV/Oral	Phase 1	GyrB inhibitor	Seeking partner
Debiopharm	Afabicin Debio 1450	*Staphylococcus* ABSSSI	IV/Oral	Phase 2	Fatty Acid Biosynthesis Inhibitor	From Affinium
	Debio 1453	*N. gonorrhoeae*		Preclinical	Fatty Acid Biosynthesis Inhibitor	From Affinium
	Debio 1454	Enteric species		Preclinical	Fatty Acid Biosynthesis Inhibitor	From Affinium
Deinove	DNV3837 MCB3837	Gram-Positive *C. difficile*	IV	Phase 1	Oxazolidinone Fluoroquinolone	Deinove acquired Morphochem
	DNB101/102	Gram-Positive		Preclinical	Not disclosed	
Destiny	Exeporfinium XF-73	Gram-Positive	Intranasal	Phase 1/2	Porphyrin	Unpartnered
Dong-A	DA-7310			Preclinical	LpxC inhibitor	

Emergent	GC-072	Burkholderia	IV/Oral	Preclinical	Type II topoisomerase Inhibitor	From Evolva
	EBX205	Broad Spectrum	IV/Oral	Preclinical	Type II topoisomerase Inhibitor	From Evolva
Enbiotix	EBX-001 Fumarate Tobramycin	Cystic Fibrosis	Inhalation	Preclinical	Tobramycin+ Fumarate Potentiator	Unpartnered
	EBX-002 Amikacin	Nontuberculous Mycobacteria		Preclinical	Amikacin+ Undiscl Potentiator	Unpartnered
	EBX-003 ME1100 Arbekacin	HABP/VABP	Inhalation	Phase 1	Aminoglycoside	From Meiji Seika
	ColiFin	Cystic Fibrosis	Inhalation		Colistin	Market Ex-U.S.
Entasis	Zoliflodacin ETX0914 AZD0914	Gonorrhea	Oral	Phase 2	Benzisoxazole DNA Gyrase Inhibitor	GARDP NIAID
	ETX2514	*Acinetobacter*	IV	Phase 2	B-lactamase Inhibitor	Unpartnered
	ETX0282 ETX1317	Gram-negative cUTI	Oral	Phase 1	B-lactamase Inhibitor	Unpartnered
Ferring	RBX2660	*C. difficile*	Enema	Phase 3	Microbe	From Rebiotix
	RBX7455	*C. difficile*	Oral	Phase 1	Microbe	
Forge	FG-LpxC UTI	cUTI	IV/ Oral	Preclinical	LpxC inhibitor	
Geom	GT1 GT55	Gram-Negative	IV	Preclinical	B-Lactamase Inhibitor B-lactam	From Legochem
Gladius	S201			Preclinical	Cephalosporin	From Sopharmia
Grifols	Pulmaquin Linhaliq Ciprofloxacin	Non-CF Bronchiectasis	QD Inhalation	FDA CRL EMA Review	Fluoroquinolone	From Aradigm
GSK	Gepotidacin GSK2140944	Broad Spectrum	IV/Oral	Phase 2	Topo 2 isomerase inhibitor	
Helperby	Azidothymidine	Gram-Negative		Phase 1	Thymidine analog	Unpartnered
Hsiri		Nontuberculous Mycobacteria		Preclinical		Shionogi Collaboration
		Tuberculosis		Preclinical		
Inhibrx	INBRX-111	*Pseudomonas*	IV	Preclinical	Biologic	Unpartnered
Innovation	Brilacidin	Oral Mucositis ABSSSI	IV	Phase 2	Antimicrobial peptide	Polymedix Acquisition
Insmed	ALIS Amikacin	Nontuberculous Mycobacteria	Inhalation	US Market	Aminoglycoside	Unpartnered
	Rv40	Gram-Positive		Preclinical	Lipoglycopeptide	Unpartnered
Intron	SAL200 N-Rephasin	*S. aureus*	IV	Phase 2 Korea	Lysin	Seeking partner
Iterum	Sulopenem	cUTI uUTI cIAI	IV/ Oral	Phase 3	Carbapenem	Unpartnered
KBP	KBP-7072	Broad Spectrum		Phase 2	Aminomethylcycline	Unpartnered
	KBP-7909	Gram-Negative		Preclinical	LpxC inhibitor	No recent update
Kyorin	AM-1977 Lascufloxacin	Broad Spectrum	IV/ Oral	Review Japan	Fluoroquinolone	Seeking partner
Legochem	Delpazolid LCB01-0371		Oral	Phase 2 Korea	Oxazolidinone	
Matinas	MAT2501 Amikacin	Cystic Fibrosis	Oral	Phase 1	Aminoglycoside Lipid Nanocrystal	Unpartnered
Melinta	Baxdela Delafloxacin RX-3341	Broad Spectrum ABSSSI CABP cUTI	IV/Oral	US Market EU Review	Fluoroquinolone	Eurofarma Menarini Malin
	Minocin Minocycline	Gram-Negative	IV	US Market	Tetracycline	IMI Menarini
	Radezolid RX-1741	Gram-Positive	Topical IV/Oral	Phase 2 Topical	Oxazolidinone	Topical out-licensed
	Solithromycin T-4288	Broad Spectrum	IV/Oral	FDA CRL Phase 3 Japan	Macrolide	Toyama
	Vabomere Vaborbactam + Meropenem	Gram-Negative CRE cUTI	Q8H IV	US Market EMAMarket	B-lactamase Inhibitor/Carbapenem	Rempex Medicines Co Menarini
Merck	Relebactam MK-7655	Gram-Negative HABP	IV	FDA Review EMA Review	B-lactamase Inhibitor	-
Merlion	Finafloxacin	cUTI	IV/Oral	Phase 2	Fluoroquinolone	Seeking partner Novartis: Xtoro Otitis Externa
MGB Biopharma	MGB-BP-3	Gram-Positive *C. difficile*	Oral	Phase 2	DNA Minor Groove Binder	Unpartnered

Microbiotix	MBX-4191			Preclinical	Pyranopyridine RND Efflux Pump Inhibitor	
MicuRx	Contezolid MRX-I	Gram-Positive	Oral	Phase 3	Oxazolidinone	Shanghai MengKe
	Contezolid MRX-4	Gram-Positive	IV	Phase 2	Oxazolidinone	IV prodrug
	MRX-8	Gram-Negative	IV	Preclinical	Polymyxin	Unpartnered
Motif	Iclaprim	HABP/ABSSSI	IV	FDA Review CRL	DHFR Inhibitor	From Roche/ Arpida
Nabriva	Contepo Fosfomycin	cUTI	IV	FDA Review	Fosfomycin	Unpartnered
	Lefamulin	CABP	IV/Oral	FDA Review	Pleuromutilin	Unpartnered
Nacugen	RG6080 OPO595 FPI-1459 Nacubactam	Gram-Negative	IV	Phase 1	B-lactamase Inhibitor	Roche returned; Meiji/Fedora Joint Venture
Nosopharm	Noso 502	Gram-Negative	IV	Preclinical	Odilorhabdin	Unpartnered
Novabiotics	Luminaderm NP108	*S. aureus*	Topical	Preclinical	Antimicrobial peptide	Unpartnered
	Novarifyn NP432	Gram-Positive Gram-Negative		Preclinical	Antimicrobial peptide	Unpartnered
Otsuka	OPS-2071	*C. difficile*	Oral	Phase 2	Quinolone	
	VIS705	*P. aeruginosa*	IV	Preclinical	Antibody Conjugate	Visterra
Pamlico	PneumoMab	*S. pneumoniae*	-	Preclinical	Monoclonal Antibody	No recent update
Paratek	Omadacycline PTK 796	Broad Spectrum CABP ABSSSI	QD IV/Oral	US Market EU Review	Tetracycline	Unpartnered
Pfizer	Avibactam+ Aztreonam	MDR Gram-Negative	IV	Phase 3	B-Lactamase Inhibitor B-lactam	From Novexel AstraZeneca
Phico	SASPject PT1.2	*S. aureus*	IV	Phase 1	Bacteriophage	Nasal Decolonization
	SASPject PT3	*P. aeruginosa*	IV	Preclinical	Bacteriophage	
Polyphor	Murepavadin POL7080 RG7929	*P. aeruginosa*	IV	Phase 3	Peptidomimetic	Unpartnered
	POL7306	Gram-Negative	IV	Preclinical	Peptidomimetic	Unpartnered
Pylum	Avidocin	*C. difficile*		Preclinical	Bacteriocin	Fmr Avid
Roche	RG7861 DSTA4637S	*S. aureus*	IV	Phase 1	Antibody-Antibiotic Conjugate	Genentech
Savara	AeroVanc	MRSA Cystic Fibrosis	Inhalation	Phase 3	Glycopeptide	Unpartnered
Seachaid	SP2078	Gram-Positive	-	Preclinical	Glycopeptide	Unpartnered
	SP1001 Cefepime	Broad spectrum	Oral	Preclinical	Cephalosporin	Unpartnered
Sequella	SQ109	*H. pyloi* Tuberculosis	Oral	Phase 2/3	1,2-ethylene diamine	Unpartnered
	Sutezolid	Tuberculosis	Oral	Phase 2	Oxazolidinone	From Pfizer
	SQ641	*C. difficile*	Oral	Preclinical	Translocase-1 inhibitor	From Daiichi
	SQ609	Tuberculosis		Preclinical	Diperidine	Unpartnered
Seres	SER-109	*C. difficile*	Oral	Phase 3	Microbe	Unpartnered
	SER-262	*C. difficile*	Oral	Phase 1	Microbe	Unpartnered
Shionogi	Cefiderocol S-649266 GSK2696266	Gram-Negative	IV	Phase 3	Siderophore Cephalosporin	
	Cot-143	*P. aeruginosa*	IV	Preclinical	Antibody PcrV	
Spero	SPR994 Tebipenem	cUTI	Oral	Phase 3	Carbapenem	From Meiji Market (Japan)
	SPR741	Gram-Negative	IV	Phase 1	Polymyxin Potentiator	From Northern
	SPR206	Gram-Negative	IV	Phase 1	Polymyxin	From Northern
	SPR720	NTM	Oral	Phase 1	Undisclosed	From Vertex
Summit	Ridinilazole SMT19969	*C. difficile*	Oral	Phase 3	Bibenzoimidazole	BARDA
	SMT-571	*N. gonorrhoeae*	Oral	Preclinical		From Discuva
Symbiomix	Solosec secnidazole SYM-1219	Bacterial Vaginosis	Single-dose Oral	Market (US)	5-nitroimidazole	Unpartnered

Synthetic Biologics	SYN-004 Ribaxamase	*C. difficile*	Oral	Phase 2	B-lactamase	Unpartnered
	SYN-006			Preclinical	B-lactamase	Unpartnered
Taigen	Nemonoxacin Taigexyn TG873870	CAP ABSSSI Diabetic Foot	Oral	Market (Asia)	Quinolone	From P&G Zhejiang China/Taiwan
Tetraphase	Eravacycline TP-434	Broad Spectrum cIAI	BID IV	US Market EU Approval	Tetracycline	Unpartnered
	TP-271	Broad Spectrum Biothreat	IV/Oral	Phase 1	Tetracycline	Unpartnered
	TP-6076	Gram-Negative		Phase 1	Tetracycline	Unpartnered
Theravance	TD-1792	Gram-Positive	QD IV	Phase 3 (Russia)	Glycopeptide Cephalosporin Conjugate	R-Pharm
Trellis	TRL1068	Broad Spectrum	IV	Preclinical	Monoclonal Antibody	Unpartnered
Union	ATx201	Atopic Dermatitis	Topical	Phase 2		Fmr AntibioTx
Vedanta	VE303	*C. difficile*	Oral	Phase 2	Microbe	
Venatorx	VNRX-5133	Gram-Negative	IV	Phase 1	B-lactamase Inhibitor	Unpartnered
	VNRX-7145	Gram-Negative	Oral	Preclinical	B-lactamase Inhibitor	Unpartnered
Wockhardt	WCK771 Levonadifloxacin	ABSSSI	IV/ Oral	Phase 3	Fluoroquinolone	WCK2349 is prodrug of WCK771
	WCK2349					
	Nafithromycin WCK4873	CABP	Oral	Phase 2	Macrolide	Unpartnered
	WCK 5222 Cefepime-Zidebactam		IV	Phase 1	B-lactamase Inhibitor	Unpartnered
XBiotech	514G3	MRSA Bacteremia	IV	Phase 1/2	Monoclonal Antibody	Unpartnered

Source: Company reports; Needham & Company, LLC estimates

2019 ECCMID Meeting (Amsterdam)

Company	Abstract	Title
Achaogen	P1747	First performance of ETEST Plazomicin for minimum inhibitory concentration determination of Enterobacterales
	P1872	Plazomicin activity against *Enterobacteriaceae* isolates carrying genes encoding extended-spectrum beta-lactamases, carbapenemases, and/or aminoglycoside-modifying enzymes
	P1873	Antimicrobial activity of plazomicin tested against *Enterobacteriaceae*isolates from European medical centres stratified by infection type (2014-2017)
Allecra	P1170	In vitro activity of the extended-spectrum beta-lactamase inhibitor AAI101, in combination with cefepime, against 90 molecularly characterized Enterobacteriaceaeisolates expressing a variety of non-beta-lactam resistance mechanisms
Allergan Pfizer	O0285	Total reversal of carbapenemase-producing Klebsiella pneumoniaeepidemiology from blaKPC to blaVIM in an ICU after introduction of ceftazidime-avibactam
	O0288	Emergence of resistance to ceftazidime-avibactam in carbapenem-resistant Klebsiella pneumoniae isolates
	O0290	The importance of monitoring a novel antibiotic: national surveillance of ceftazidime-avibactam resistance and usage in England, 2018
	O0301	Ceftaroline fosamil in neonates and very young infants with late-onset sepsis: safety and efficacy results from a Phase II trial
	P1140	In vitro activities of ceftazidime-avibactam and comparator agents against Enterobacteriaceae from Europe stratified by region, ATLAS Global Surveillance Program 2017
	P1141	In vitro activities of ceftazidime-avibactam and comparator agents against Enterobacteriaceae from Europe stratified by infection type from the ATLAS Global Surveillance Program 2015-2017
	P1142	Susceptibility to ceftazidime/avibactam in German MDR/XDR Pseudomonas aeruginosa
	P1143	In vitro activities of ceftazidime-avibactam and comparators against Pseudomonas aeruginosafrom Europe stratified by infection type, ATLAS Global Surveillance Program 2015-2017
	P1144	In vitro activities of ceftazidime-avibactam and comparator agents against Enterobacteriaceae and Pseudomonas aeruginosa from Israel collected through the ATLAS Global Surveillance Program 2012-2017
	P1145	In vitro activities of Ceftazidime-Avibactam and comparator agents against Enterobacteriaceae and Pseudomonas aeruginosa from Turkey collected through the ATLAS Global Surveillance Program 2012-2017
	P1146	In Vitro activity of ceftazidime-avibactam and comparator agents against Enterobacteriaceae and Pseudomonas aeruginosacollected from paediatric patients as part of the ATLAS Global Surveillance Program 2012-2017
	P1147	In vitro activities of Ceftazidime-Avibactam and comparator agents against Pseudomonas aeruginosafrom Europe stratified by region, ATLAS Global Surveillance Program 2017
	P1148	In vitro activity of ceftazidime-avibactam and comparators against Gram-negative pathogens isolated from patients in Canadian hospitals in 2009-2017: CANWARD surveillance study
	P1149	In vitro activity of ceftazidime-avibactam against contemporary carbapenem-resistant/carbapenemase-producing Enterobacteriales and Pseudomonas aeruginosa clinical isolates from Argentina
	P1150	In vitro activity of ceftazidime/avibactam and ceftolozane/tazobactam against clinical isolates of Enterobacteriaceae and Pseudomonas aeruginosa: results from a multi-centre study in China, 2017
	P1152	Activity of ceftolozane/tazobactam and ceftazidime/avibactam against well characterized multidrug-resistant Gram-negative bacilli collected from clinical samples
	P1151	Potentiation of oral cephalosporins and carbapenems by the addition of avibactam
	P1153	In vitro activity of aztreonam-avibactam and comparator agents against Enterobacteriaceae from Europe collected during the ATLAS Global Surveillance Program 2015-2017
	P1154	In vitro activity of aztreonam-avibactam against MBL-producing Enterobacteriaceae and Pseudomonas aeruginosa isolates collected during the ATLAS Global Surveillance Program 2015-2017
	P1155	In vitro activities of aztreonam-avibactam and ceftazidime-avibactam against less commonly encountered Gram-negative bacteria collected during the ATLAS global surveillance program 2012-2017
	P1156	In Vitro Activities of aztreonam-avibactam and comparator agents against carbapenemase-producingEnterobacteriaceae collected during the ATLAS Global surveillance program 2015-2017
	P1158	Evaluation of aztreonam-based combination therapies for NDM-producing Enterobacteriaceae: aztreonam plus ceftazidime-avibactam vs. aztreonam plus meropenem-vaborbactam
	P1952	Population pharmacokinetic-pharmacodynamic modelling to optimise aztreonam-avibactam dose selection
	P2003	Phase II, open-label REJUVENATE study of the pharmacokinetics and safety of aztreonam-avibactam plus metronidazole in hospitalised adults with complicated intra-abdominal infections
Arixa	P1159	Oral prodrugs of avibactam, medicinal chemistry, and synthesis of ARX-1796
	P1160	Identification and characterization of novel oral prodrugs of avibactam
Arrevus	P1996	Efficacy of ARV-1502, a novel proline-rich antimicrobial peptide, in a murine model of bacteraemia caused by multidrug-resistant Acinetobacter baumannii
Basilea	P1863	*In vitro* activity of ceftobiprole against Gram-positive isolates from clinical samples from a tertiary hospital
	P1864	*In vitro* activity of ceftobiprole against isolates of common involved pathogens in nosocomial pneumonia from a tertiary hospital
	P1865	Susceptibility of ceftobiprole and other beta-lactams against Gram-negative pathogens from hospital-acquired pneumonia in the UK and Ireland since 2011
	P1866	Susceptibility of ceftobiprole and comparators against methicillin-resistant *Staphylococcus aureus*from respiratory tract infections
	P1867	Activity of ceftaroline and ceftobiprole against staphylococci and *Streptococcus pneumoniae* in the UK and Ireland
Bugworks	P1844	BWC0977, a novel dual target topoisomerase inhibitor: potency, spectrum and mechanism of action

	P1845	In vitro activity of BWC0977, a novel bacterial topoisomerase inhibitor, and comparators against recent clinical Enterobacteriaceae and non-fermentor isolates from two hospitals in Bengaluru, India
	P1846	In vitro activity of BWC0977, a novel bacterial topoisomerase inhibitor, against molecularly characterised Enterobacteriaceae and non-fermentor isolates of the CDC collection and biodefense pathogens
	P1847	In vitro activity of BWC0977 (a novel bacterial topoisomerase inhibitor) and comparators against recent clinical and molecularly characterized Enterobacteriaceae and non-fermenter isolates from the United States and Europe
Cidara	O0271	Rezafungin PK/PD in a mouse model of Pneumocystis pneumonia
	O0741	Rezafungin is more effective than micafungin in treating of FKS-mutant Candida glabrata intra-abdominal candidiasis
	O0115	EUCAST susceptibility testing of rezafungin: MIC data for contemporary Danish clinical yeast isolates
	O0818	Cloudbreak: a novel approach for the treatment and prevention of influenza virus
	P0115	Absorption, distribution and excretion of rezafungin after single-dose intravenous administration in rats and monkeys
	P1821	Novel Cloudbreak bifunctional molecule protects against Acinetobacter pneumonia
	P2161	Activity of rezafungin against common and rare Candida species in vitro
	P2174	EUCAST reference testing of rezafungin susceptibility: impact of choice of plastic plates
	P2284	Outcomes in Europe from the STRIVE clinical trial of rezafungin treatment of candidemia and/or invasive candidiasis
Contrafect	P0528	Lysin exebacase (CF-301) exhibits potent bactericidal activity in human synovial fluid against biofilm-forming *Staphylococcus epidermidis* isolates
Crestone	O0519	Mode of action, spectrum of activity, and preclinical *in vivo*efficacy of CRS0540, a PolC DNA polymerase inhibitor of resistant Gram-positive pathogens
Dong-A	P1837	In vitro antibacterial activity of DA-7310, a novel inhibitor of Gram-negative bacteria
	P1841	Antibacterial activity of DA-7310 in combination with other antibiotics
	P1842	In vivo efficacy of the LpxC inhibitor DA-7310 in murine infection model
Entasis	O0300	A double-blind, randomised, placebo-controlled study to evaluate the safety and efficacy of intravenous sulbactam-ETX2514 in the treatment of hospitalised adults with complicated urinary tract infections, including acute pyelonephritis
	O0527	Discovery of a novel series of penicillin-binding protein 3 inhibitors as monotherapy forPseudomonas aeruginosainfections: rational design of biochemical potency and bacterial permeation
	P1184	The novel beta-lactamase inhibitor ETX1317 effectively restores the activity of cefpodoxime against recent global Enterobacteriaceae isolates from urinary tract infections
	P1185	The novel beta-lactamase inhibitor ETX2514 effectively restores sulbactam activity against recent global Acinetobacter baumanniicalcoaceticus complex clinical isolates
	P1186	The susceptibility of global isolates of Acinetobacter baumannii to ETX2514SUL and comparators
	P1953	Population pharmacokinetic and pharmacokinetic-pharmacodynamic target attainment analyses of ETX2514SUL to support dosing regimens in patients with varying renal function
	P1991	Efficacy of cefpodoxime proxetil and ETX0282 in a murine UTI model with Escherichia coli and Klebsiella pneumoniae
Geom	P1187	Penicillin-binding protein activity of beta-lactamase inhibitor GT-055
GSK	P1849	In vitro activities of gepotidacin, a novel triazaacenaphthylene topoisomerase IV and DNA gyrase inhibitor, against Gram-negative bacteria and Staphylococcus saprophyticus
Helperby	O0201	*In vitro* and *in vivo* efficacy of combinations of azidothymidine and colistin against MDR strains
	P1955	Urinary and serum bactericidal activity of colistin and azidothymidine combinations against colistin-susceptible and -resistant Gram-negative pathogens
Iterum	P1705	*In vitro* activity of sulopenem against resistant *Neisseria gonorrhoeae*
	P1992	Post-antibiotic and sub-inhibitory minimum inhibitory concentration effects of sulopenem
Melinta	P1169	In vitro activity of meropenem combined with vaborbactam against KPC-producing Enterobacteriaceae in China
	P1738	Multi-centre evaluation of meropenem/vaborbactam MIC results for *Enterobacteriaceae*using MicroScan Dried Gram-negative MIC panels
	P1741	ETEST meropenem/vaborbactam for antimicrobial susceptibility testing of Enterobacterales and *Pseudomonas aeruginosa*: performance results from a multi-centre study
	P1885	Delafloxacin tentative ECOFF values for common Gram-positive and Gram-negative bacteria
	P2781	An FDA-approved study for an AST disc 510(k) submission: comparison of an oxoid AST disc to a predicate AST disc for meropenem-vaborbactam
Merck	O0283	Stability of imipenem /relebactam against Pseudomonas aeruginosabeta-lactam (including recently introduced combinations) resistance mechanism Melissa Barnes
	O0284	Imipenem /relebactam efficiently inhibits D179 variants of the KPC-2 beta-lactamase
	O0287	In vitro activity and selection of imipenem-relebactam resistance against carbapenem-resistant Enterobacteriaceae
	O0302	Clinical and microbiologic outcomes by causative pathogen in the ASPECT-NP randomised, controlled, phase III trial evaluating ceftolozane /tazobactam for treatment of ventilator-associated pneumonia
	P1161	Activity of imipenem-relebactam against KPC-positive Enterobacteriaceae isolates from Europe: SMART 2015-2017
	P1162	Activity of imipenem-relebactam and comparators against Enterobacteriaceae and Pseudomonas aeruginosa from hospitalised patients in Europe - SMART 2017
	P1163	Identification of beta-lactamases in Enterobacteriaceae with varied levels of susceptibility to imipenem/relebactam collected for the SMART surveillance programme, 2015-2017
	P1164	In vitro activity of imipenem/relebactam and comparator agents against Gram-negative isolates recovered from cancer patients

	P1165	Activity of imipenem-relebactam in clinical isolates of Enterobacteriaceae obtained from a national study in Spain
	P1167	Relebactam is efficacious against Pseudomonas aeruginosa and Klebsiella pneumoniae, with sufficient penetration into epithelial lining fluid in a neutropenic mouse model
	P2019	Imipenem-cilastatin/relebactam lowers acute kidney injury in a preclinical model of vancomycin nephrotoxicity
Microbion	P1826	Activity profile of MBN-101: a novel antimicrobial agent with broad-spectrum activity against bacteria, including ESKAPE pathogens
Micurx	P1956	Population pharmacokinetics of the new oxazolidinone prodrug contezolid acefosamil (MRX-4) and its metabolites after single and multiple ascending intravenous doses in healthy volunteers
Motif Bio	O0303	An efficacy analysis by lesion size of iclaprim versus vancomycin in patients with acute bacterial skin and skin structure infections: pooled phase III REVIVE trials
	O1162	Pharmacokinetics of iclaprim by age, weight, race and renal/hepatic function in patients with acute bacterial skin and skin structure infections: phase III REVIVE trials
	P1884	Surveillance of iclaprim activity against Gram-positive cocci, including antibiotic-resistant strains, collected from patients with skin and skin structure infections during 2017 from European and American hospitals
	P2287	Iclaprim versus vancomycin for patients with acute bacterial skin and skin structure infection complicated by *Staphylococcus aureus* or streptococcal bacteraemia: a pooled analysis of the phase III REVIVE trials
Nabriva	P1823	Antimicrobial activity of lefamulin against a large longitudinal collection of clinical bacterial isolates collected worldwide: results from the SENTRY antimicrobial surveillance program
	P1828	In vitro activity of lefamulin against isolates commonly causing community-acquired bacterial pneumonia collected during the SENTRY surveillance programme 2017 in Europe
	P1945	Population pharmacokinetic analysis for lefamulin using data from healthy volunteers and infected patients
	P1946	Pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses to support lefamulin dose justification and susceptibility breakpoint determinations for patients with community-acquired bacterial pneumonia (CABP)
	P1947	Continuous infusion of fosfomycin in healthy volunteers
Nacugen	P1168	In vitro activity of meropenem-nacubactam against carbapenem-resistant and ceftazidime-avibactam-resistant Enterobacteriaceae
Paratek	O0304	Safety and efficacy of omadacycline for treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections in patients with mild to moderate renal insufficiency
	O0306	Safety and efficacy of omadacycline by patient body mass index for the treatment of acute bacterial skin and skin structure infections
	P1876	*In vitro* activity of omadacycline and comparators against Gram-positive and -negative clinical isolates collected in 2018 from patients in European medical centres: SENTRY surveillance program results
	P1943	Omadacycline pharmacokinetics: impact of comorbidities
	P1944	Assessment of pharmacokinetics-pharmacodynamics to support omadacycline dosing regimens for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI)
	P2011	Omadacycline hepatic safety: integrated analysis of randomized controlled phase III trials
Polyphor	P1836	Activity of murepavadin against colistin-resistant Pseudomonas aeruginosa clinical isolates
	P1838	POL7306, a new outer membrane protein targeting antibiotic: the effect of testing parameter variations and body fluids on in vitro activity
	P1839	Outer membrane protein targeting antibiotics: pharmacokinetics and in vivo efficacy of POL7306
	P1840	In vitro propensity of resistance development of POL7306, a new outer membrane protein targeting antibiotic
	P1843	Antimicrobial activity of POL7306 tested against clinical isolates of Gram-negative bacteria collected worldwide
Rebiotix	O0126	Evaluation of a prototype microbiome health index for RBX7455: non-frozen, lyophilised, oral microbiota therapy for recurrent Clostridium difficileinfection
Setlance	O0521	The antimicrobial peptide SET-M33: a case of preclinical drug development
Shionogi	P1851	Cefiderocol in vitro activity against Gram-negative clinical isolates collected in Europe: result from SIDERO-CR-2014/2016
	P1852	Cefiderocol in vitro activity against Gram-negative clinical isolates collected in Europe: result from three SIDERO-WT surveillance studies between 2014-2017
	P1853	Cefiderocol susceptibility and geographical analysis against globally isolated meropenem non-susceptible Gram-negative bacteria containing serine- and metallo-carbapenemase gene
	P1854	In vitro and in vivo activity of cefiderocol against Burkholderia cepacia complex clinical isolates
	P1855	In vitro antibacterial activity of cefiderocol against an international collection of carbapenem-non-susceptible Gram-negative bacteria isolated from respiratory, blood, skin/soft tissue and urinary sources of infection: SIDERO-WT-2014-2016
	P1856	Activity of cefiderocol on a reference collection of carbapenemase-, ESBL-, and acquired class C beta-lactamases-producing Gram-negative pathogens
	P1857	Characterization of isolates showing high MICs to cefiderocol from global surveillance study SIDERO-CR-2014/2016
	P1858	In vitro activity of cefiderocol (S-649266) against clinical isolates of Burkholderia pseudomallei
	P1859	In vitro activity of cefiderocol against Gram-negative pathogens circulating in Germany
	P1860	In vitro activity of cefiderocol against extensively drug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii from the UK
	P1861	Activity of cefiderocol (S-649266), a new siderophore cephalosporin, against multidrug-resistant Enterobacteriaceae, Acinetobacter baumannii, Pseudomonas aeruginosa and Stenotrophomonas maltophilia
Spero	O0305	Single- and multiple-ascending dose study demonstrates the human pharmacokinetics and tolerability of SPR994 (tebipenem pivoxil hydrobromide), an oral carbapenem, at the predicted therapeutic dose

	P1862	Activity of tebipenem, an oral carbapenem, against multidrug-resistant urinary tract infection-causing pathogens with characterized resistance mechanisms collected in Europe and the United States in 2016
Summit	O0520	Novel small-molecule inhibitors of bacterial lipoprotein transport with potent antimicrobial activity against Enterobacteriaceae
Taxis	O0524	Indole-2-carboxamides as potent efflux pump inhibitors in Pseudomonas aeruginosa
Tetraphase	P1735	Multi-centre evaluation of eravacycline MIC results for *Escherichia coli* using MicroScan Dried Gram-negative MIC panels
	P1874	*In vitro* activity of eravacycline and comparators against Gram-positive bacteria collected from European hospitals in 2017
	P1875	Surveillance of the *in vitro* activity of eravacycline and comparators against clinical isolates from Europe during 2017
	P1994	In vivo efficacy of TP-6076 in murine thigh and lung infection models challenged with Acinetobacter baumannii
	P2012	Safety, tolerability and pharmacokinetics of multiple doses of TP-271, a novel fluorocycline, in normal healthy subjects
VenatoRx	P1175	Antimicrobial activity of cefepime in combination with VNRX-5133 against a global 2018 surveillance collection of clinical isolates
	P1176	Antimicrobial activity of cefepime in combination with VNRX-5133 against a collection of beta-lactamase-producing Enterobacteriaceae
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	P1178	VNRX-5133 maintains potent inhibitory activity in engineered NDM-1 variants with increased cefepime hydrolytic efficiency
	P1179	Evaluation of the in vitro activity of cefepime plus VNRX-5133 and comparative agents against carbapenem-resistant Enterobacteriaceae
	P1180	In vitro activity of the orally available ceftibuten/VNRX-7145 combination against a challenge set of Enterobacteriaceae pathogens carrying molecularly characterised beta-lactamase genes
	P1181	Selection of ceftibuten as the partner antibiotic for the oral beta-lactamase inhibitor VNRX-7145
	P1182	Ceftibuten/VNRX-7145, an orally bioavailable beta-lactam/beta-lactamase inhibitor combination active against serine-beta-lactamase producing Enterobacteriaceae
	P1183	Oral ceftibuten/VNRX-7145 as a step-down therapy for infections caused by multidrug-resistant Enterobacteriaceae
	P1951	Pharmacokinetics of VNRX-5133 alone and combined with cefepime when co-administered with metronidazole
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	P1172	Cefepime-zidebactam (WCK-5222) activity when tested against Gram-negative organisms isolated from patients hospitalised in Europe and the Asia-Pacific region in 2018
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	P1941	Pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses to support WCK-771 (INN: levonadifloxacin) clinical dose selection
	P1954	Population pharmacokinetics of zidebactam (WCK5107), a novel beta-lactam enhancer antibiotic, in individuals with various renal function
	P1986	In vitro intracellular activity of levonadifloxacin against Legionella pneumophila

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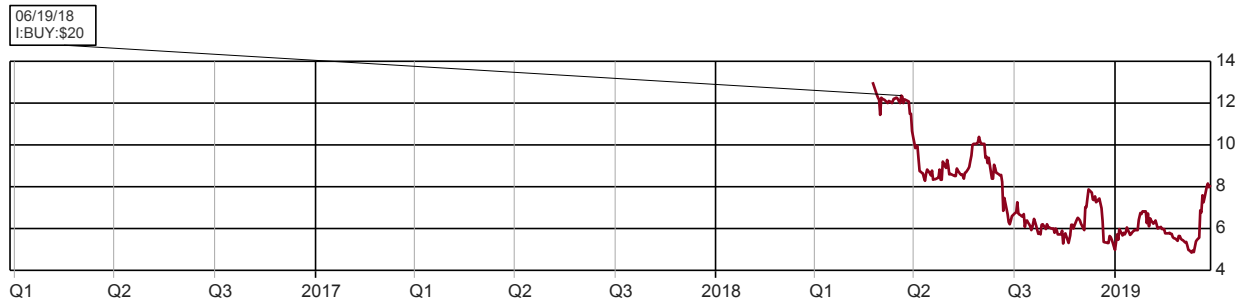

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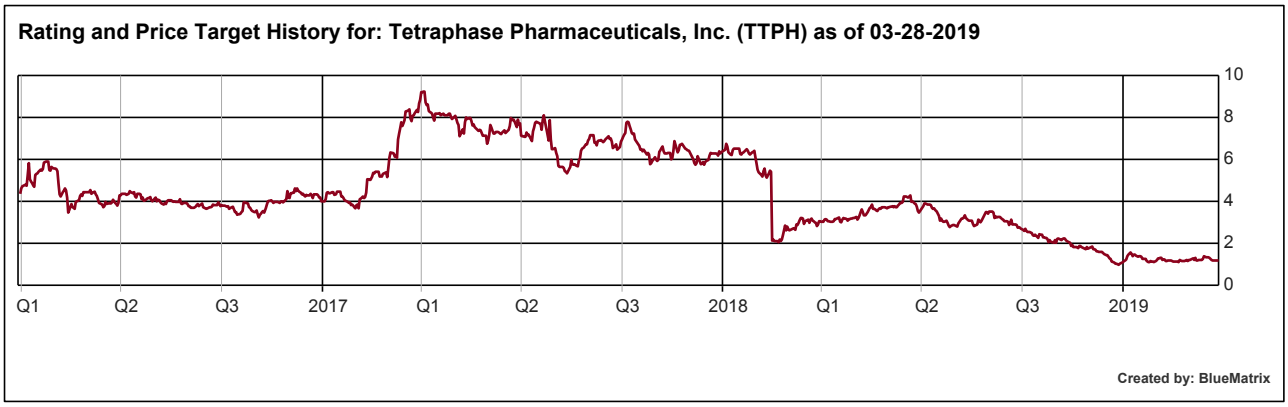

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