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Eravacycline

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Disclosures

I am a consultant, speakers bureau member or have received research funding from:

Allergan, Bayer, Cepheid, Merck,

Melinta, Pfizer, Wockhardt, Shionogi, Tetraphase

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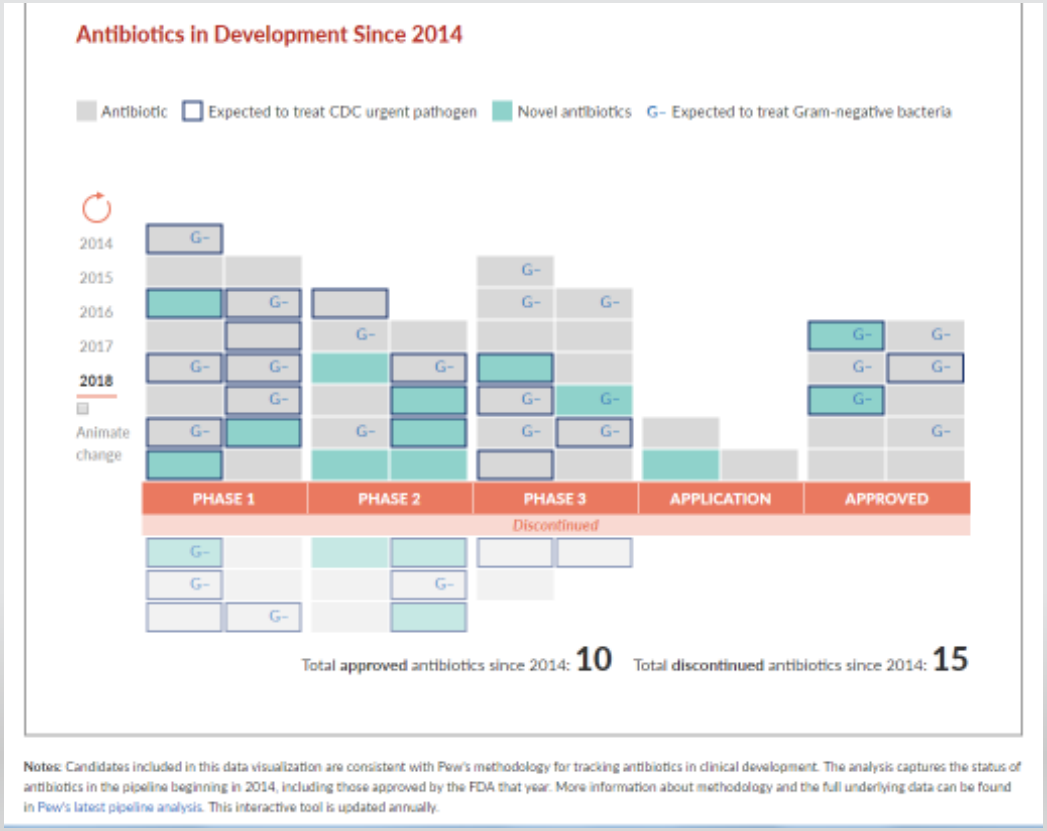
Pew Charitable Trust: Antibiotics in Development



2014-2018:

- 10 new antibiotics approved
- 6 were for Gram-negatives
  - Ceftazidime/avibactam
  - Ceftolozane/tazobactam
  - Meropenem/vaborbactam
  - Plazomicin
  - **Eravacycline [2018]**
  - Omadacycline

Accessed at: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2019/five-year-analysis-shows-continued-deficiencies-in-antibiotic-development

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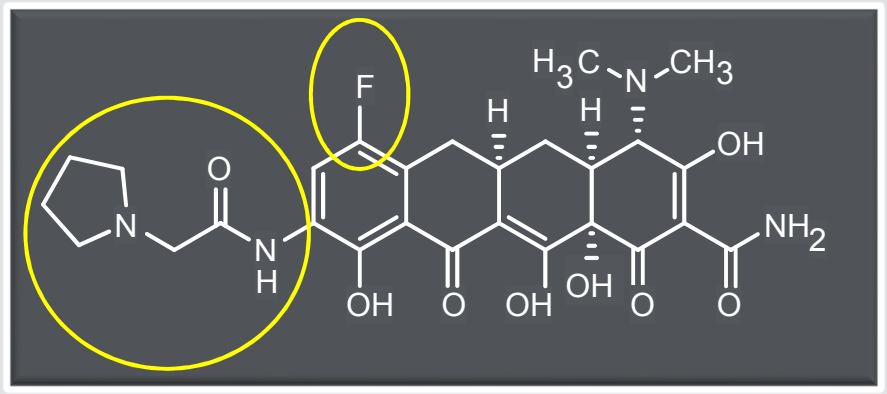
Eravacycline: Mechanism of Action

- Novel, fully-synthetic fluorocycline antibacterial[1]
- Two structural modifications to the tetracycline core: fluorine at C_7 and pyrrolidinoacetamido group at C_9[1-3]
  - Retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection)
- Binds to the 30S ribosomal subunit, disrupting bacterial protein synthesis[3]



1. XERAVA™ (eravacycline) [package insert]. Watertown, MA: Tetraphase Pharmaceuticals; 2018; 2. Xiao, et al. *J Med Chem*. 2012; 55(2): 597-605; 3. Grossman, et al. *Antimicrob Agents Chemother*. 2012; 56(5): 2559-2564

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Global Surveillance: Gram-negative Pathogens

- *In-vitro* activity of eravacycline and comparators against global Gram-negative clinical isolates (2013-2016)

Organism	N	ERV $MIC_{50/90}$	TGC $MIC_{50/90}$	MEM* $MIC_{50/90}$	AMK* $MIC_{50/90}$	PTZ $MIC_{50/90}$	FEP $MIC_{50/90}$
Acinetobacter baumannii	1600	0.5/1	2/4	32/>64	32/>64	>64/>128	>16/>64
Citrobacter spp.	1275	0.25/0.5	0.5/1	0.03/0.06	1/2	2/64	≤0.25/1
Enterobacter spp.	1416	0.5/1	0.5/1	0.06/0.12	1/2	4/64	≤0.25/4
Escherichia coli	1499	0.12/0.25	0.25/0.5	0.03/0.03	2/4	2/16	0.12/>16
Klebsiella spp.	3698	0.25/0.5	0.5/2	0.03/0.06	1/2	2/64	≤0.25/4
Proteus mirabilis	984	2/2	4/8	0.06/0.12	2/4	≤0.5/1	≤0.25/1
Serratia marcescens	902	1/2	2/2	0.06/0.12	2/4	2/16	≤0.25/0.5

In-vitro activity does not imply clinical efficacy

AMK=amikacin; ERV=eravacycline; FEP=cefepime; MEM=meropenem; MIC=minimum inhibitory concentration; N=number of isolates; PTZ=piperacillin/tazobactam; TGC=tigecycline; $MIC_{50/90}$ units are in µg/mL; * =was not tested during all years

IHMA Global Surveillance Studies 2013-2016. Compiled data from posters presented at ID congresses

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Global Surveillance: ESBL-producing Organisms

- *In-vitro* activity of eravacycline and comparators against selected Gram-negative clinical isolates in (2013-2016)

Organism	N	ERV $MIC_{50/90}$	TGC $MIC_{50/90}$	ETP* $MIC_{50/90}$	PTZ $MIC_{50/90}$	FEP $MIC_{50/90}$
E. coli	1499	0.12/0.25	0.25/0.5	0.008/0.06	2/16	0.12/>16
E. coli, ESBL-producing	159	0.12/0.5	0.25/1	0.03/0.25	4/32	>16/>16
K. oxytoca	1200	0.25/0.5	0.5/1	0.008/0.015	2/16	0.12/0.25
K. oxytoca, ESBL-producing	40	0.25/0.5	0.5/1	0.03/0.25	64/>128	>2/>16
K. pneumoniae	1496	0.25/1	1/2	0.015/0.5	4/>64	≤0.25/>16
K. pneumoniae, ESBL-producing	195	0.5/2	1/2	0.12/2	32/>128	>16/>16

In-vitro activity does not imply clinical efficacy

ERV=eravacycline; ESBL=extended-spectrum β-lactamase; ETP=ertapenem; FEP=cefepime; MIC=minimum inhibitory concentration; N=number of isolates; PTZ=piperacillin/tazobactam; TGC=tigecycline; $MIC_{50/90}$ units are in µg/mL; * = was not tested during all years of surveillance

IHMA Global Surveillance Studies 2013-2016. Compiled data from posters presented at ID congresses

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Global Surveillance: Gram-positive Pathogens

- *In-vitro* activity of eravacycline and comparators against global Gram-positive clinical isolates (2013-2016)

Organism	N	ERV $MIC_{50/90}$	TGC $MIC_{50/90}$	LIN $MIC_{50/90}$	VAN* $MIC_{50/90}$	AMP* $MIC_{50/90}$
Enterococcus faecalis	1177	0.06/0.06	0.12/0.25	2/2	1/2	1/2
VRE *faecalis*	35	0.06/0.12	0.12/0.25	2/2	>32/>32	1/2
Enterococcus faecium	852	0.03/0.06	0.12/0.25	2/2	1/>32	>8/>8
VRE *faecium*	310	0.06/0.06	0.12/0.25	2/2	>32/>32	>8/>8
Staphylococcus aureus	2024	0.06/0.12	0.12/0.25	2/2	1/1	NT
MRSA	1012	0.06/0.12	0.25/0.25	2/2	1/1	NT
Streptococcus anginosis group	196	0.015/0.06	NT	NT	NT	NT

In-vitro activity does not imply clinical efficacy

AMP=ampicillin; ERV=eravacycline; LIN=Linezolid; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S. aureus;* N=number of isolates; NT=not tested; TGC=tigecycline; VAN=vancomycin; VRE=vancomycin-resistant enterococci; $MIC_{50/90}$ units are in µg/mL; * =was not tested during all years

IHMA Global Surveillance Studies 2013-2016. Compiled data from posters presented at ID congresses

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In-Vitro Studies: Anaerobic Pathogens

- Studies investigating the *in-vitro* activity of eravacycline and comparators against anaerobic clinical isolates collected in US and EU (2012-2016)[1-3]

Organism	N	ERV $MIC_{50/90}$	TGC $MIC_{50/90}$	CLI $MIC_{50/90}$	MTZ $MIC_{50/90}$
Bacteroides fragilis	333	0.25/1	0.5/8	1/>32	0.5/1
Bacteroides caccae	28	0.5/2	1/8	8/128	1/2
Bacteroides thetaiotamicron	157	0.5/2	1/8	8/>128	<1/1
Clostridium difficile	193	0.03/0.06	<0.06/0.25	4/16	0.25/0.5
Clostridium perfringens	91	0.12/0.5	0.5/2	1/>8	<1/2
Prevotella spp.	208	0.12/0.5	0.12/0.5	<0.25/>8	<1/2

In-vitro activity does not imply clinical efficacy

ERV=eravacycline; CLI=clindamycin; MIC=minimum inhibitory concentration; MTZ=metronidazole; N=number of isolates; TGC=tigecycline; $MIC_{50/90}$ units are in µg/mL

1. Snydman D et al. *Antimicrob Agents Chemother* 2018;62(5):e02206-17; 2. Goldstein EC et al. *Anaerobe.* 2018;4:122-4; 3. Morrissey I et al. Presented at ID Week 2015, San Diego CA

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Eravacycline Antimicrobial Activity Against Pathogens in Complicated Intra-abdominal Infection (cIAI)

- Demonstrated activity both *in-vitro* and clinically against the following pathogens

Aerobic		Anaerobic	
Gram-positive	**Gram-negative**	**Gram-positive**	**Gram-negative**
Enterococcus faecalis	*Citrobacter freundii*	*Clostridium perfringens*	*Bacteroides* spp
Enterococcus faecium	*Enterobacter cloacae*		*Parabacteroides distasonis*
Staphylococcus aureus	*Escherichia coli*		
Streptococcus anginosus group	*Klebsiella oxytoca*		
	Klebsiella pneumoniae		

- *In-vitro* data are available for *Streptococcus salivarius* group, *Citrobacter koseri*, and *Enterobacter aerogenes* indicating that at least 90% of isolates are susceptible to eravacycline, but the clinical significance is unknown

XERAVA™ (eravacycline) [package insert]. Watertown, MA: Tetraphase Pharmaceuticals; 2018

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PK/PD Overview

Pharmacodynamics

- AUC/MIC of eravacycline has been shown to be the best predictor of activity

Absorption

- C_{max} and AUC increased approximately dose-proportionally over single-dose IV administration from 1 mg/kg to 3 mg/kg

Mean (%CV) Plasma Exposure of Eravacycline 1 mg/kg After Single and Multiple IV Doses in Healthy Adults

	C_{max} (ng/mL)	AUC_{0-12} (ng*h/mL)
DAY 1	2,125 (15)	4,305 (14)
DAY 10	1,825 (16)	6,309 (15)

Distribution

- Protein binding increases with increasing plasma concentrations
  - 79% to 90% bound at plasma concentrations, ranging from 100 to 10,000 ng/mL
- V_{ss}=321L

Elimination

- Mean $t_{1/2}$ is 20 hours
- Metabolized primarily by CYP3A4- and FMO-mediated oxidation
- Biliary elimination is the major route of elimination of eravacycline as assessed in healthy volunteers

AUC=area under the curve; C_{max}=maximum concentration; CYP=cytochrome P450; FMO=flavin monooxygenase; MIC=minimum inhibitory concentration; $t_{1/2}$,=half-life; V_{ss},=volume of distribution at steady state

XERAVA™ (eravacycline) [package insert]. Watertown, MA: Tetraphase Pharmaceuticals; 2018

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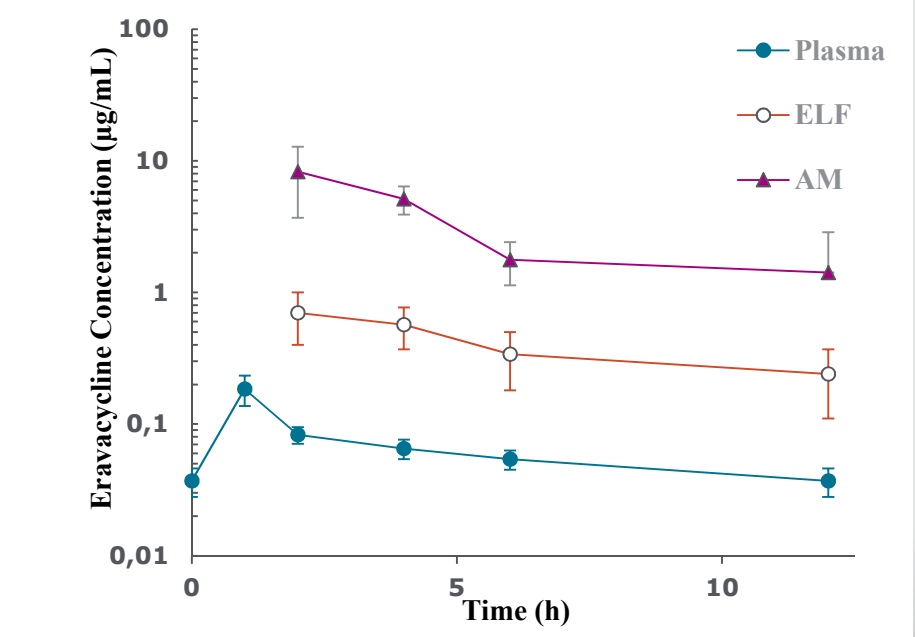
Bronchopulmonary Penetration

- Phase 1 study in healthy subjects investigating eravacycline bronchopulmonary penetration
- AUC_{0-12} for ELF and AM were 4.93 and 39.53 µg*h/mL, respectively
- Comparison of the ELF and AM AUC_{0-12} to the *f*AUC_{0-12} in plasma showed penetration ratios of 6 and 52, respectively



AM=alveolar macrophages; AUC=area under the curve; ELF=epithelial lining fluid; *f*AUC=free drug area under the curve

Connors KP et al. *Antimicrob Agents Chemother*. 2014;58(4):2113-18

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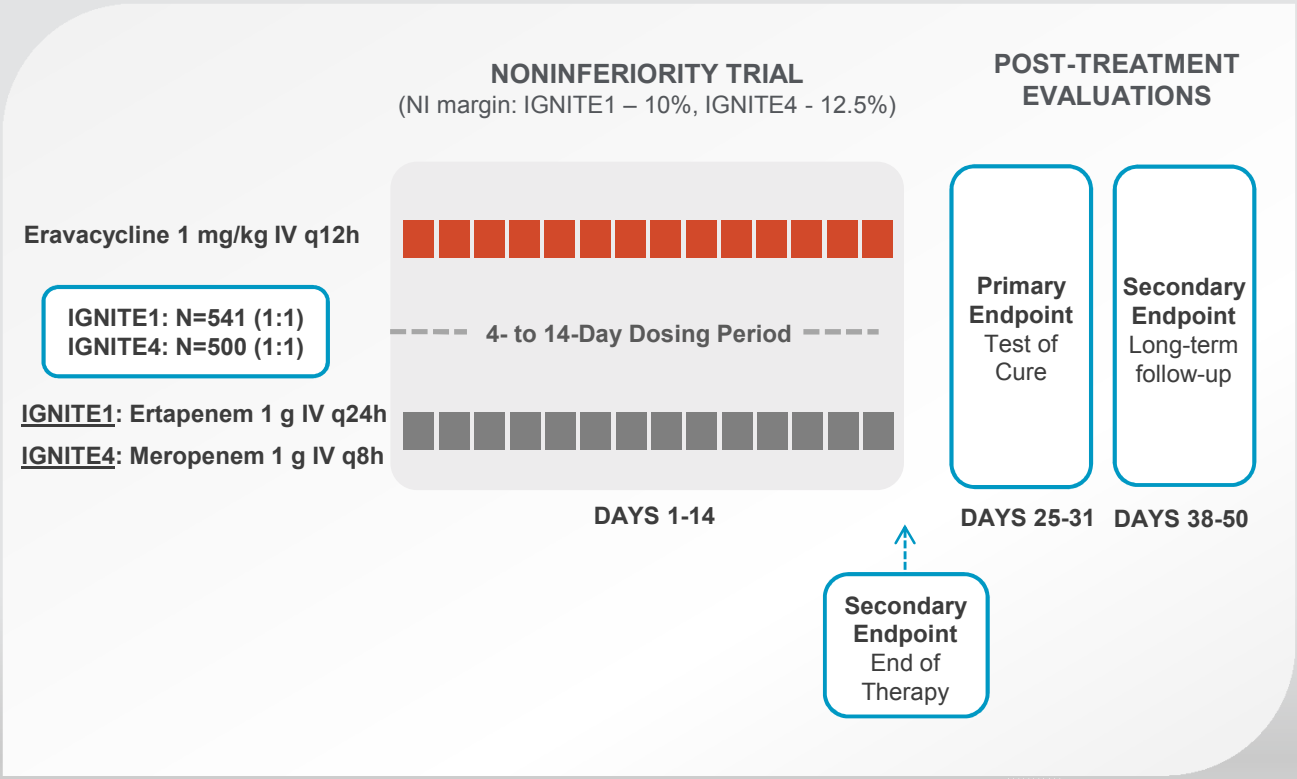
IGNITE1 and IGNITE4: Study Design



The design of both studies adhered to both the FDA and EMA development guidances

1. Solomkin et al. *JAMA Surg*. 2017;152(3):224-232; 2. Solomkin et al. *Clin Infect Dis*. 2019;69(6)921-9

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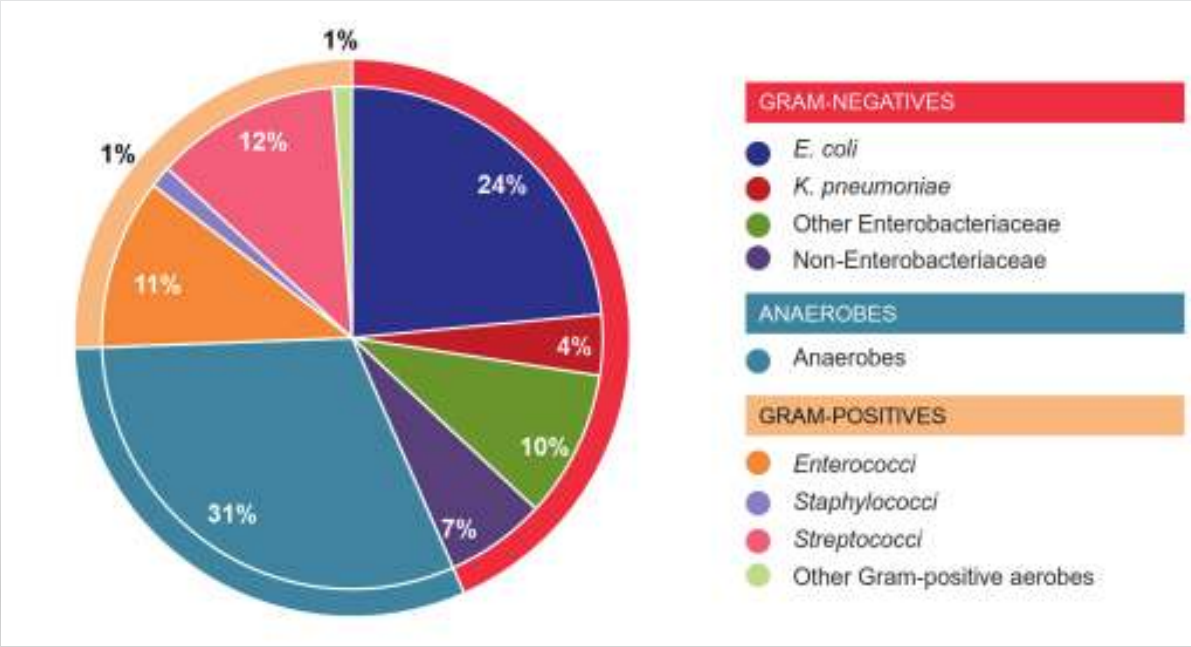
IGNITE1/4 Baseline Pathogen Distribution
micro-ITT Population

- 2,717 total baseline isolates



micro-ITT=microbiological intent-to-treat

Newman, et al. Presented at IDWeek 2018, San Francisco CA

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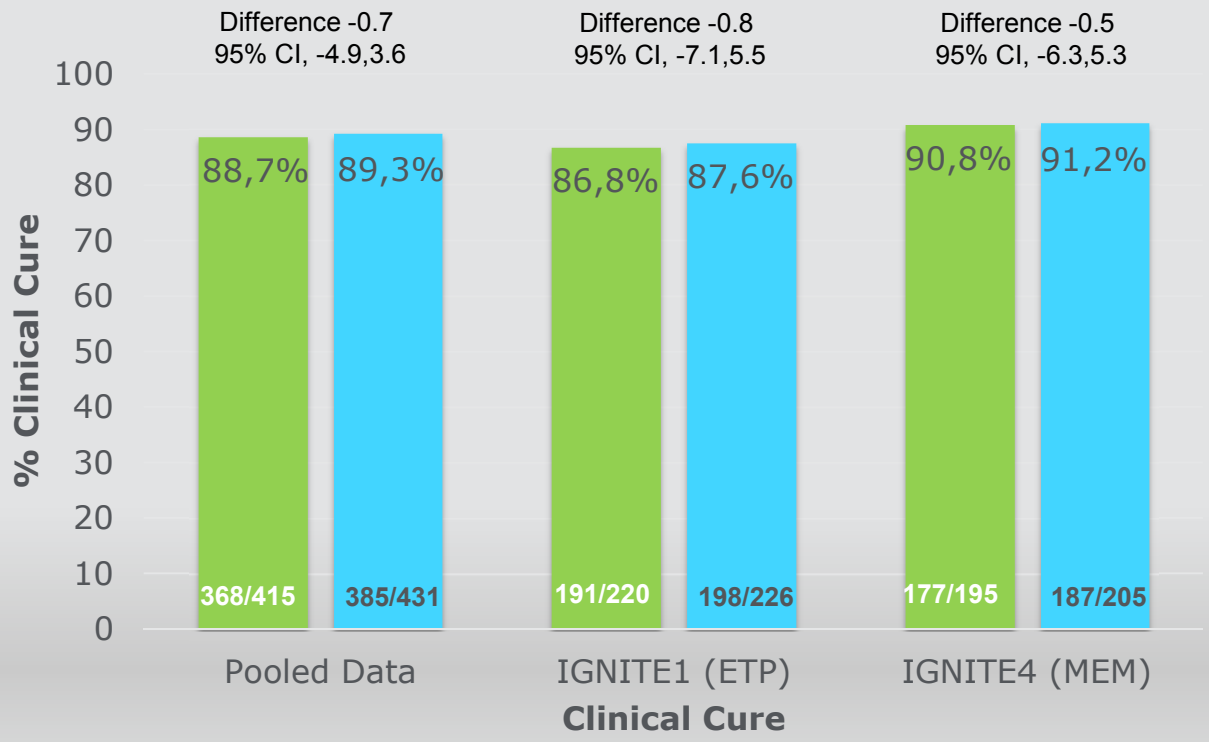
IGNITE1/4: Primary Efficacy Endpoint (FDA) Clinical Response at TOC micro-ITT Population



ERV 1 mg/kg q12h

Comparator(s)

Eravacycline demonstrated non-inferiority to ertapenem and meropenem in the FDA primary analyses

ERV=eravacycline; ETP=ertapenem; MEM=meropenem; micro-ITT=microbiological intent-to-treat; TOC=test of cure

1. Solomkin et al. *JAMA Surg*. 2017;152(3):224-232; 2. Solomkin et al. *Clin Infect Dis*. 2019;69(6)921-9

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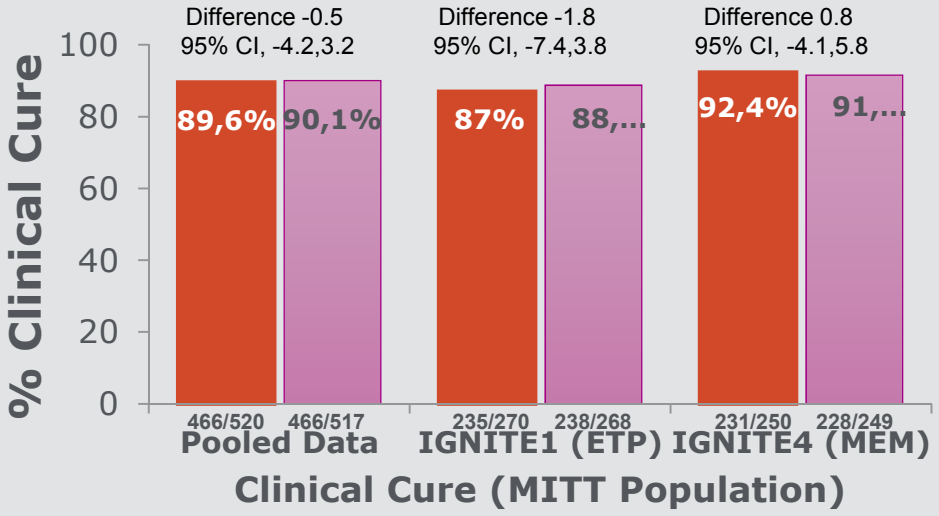
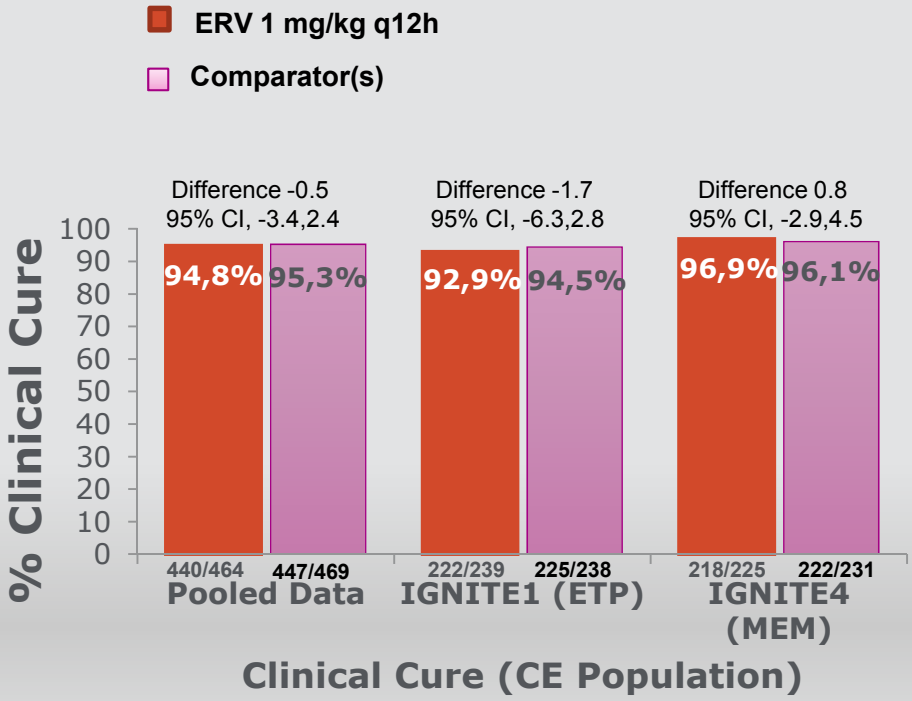
IGNITE1/4: Primary Efficacy Endpoint (EMA) Clinical Response at TOC MITT and CE Population



Eravacycline demonstrated non-inferiority to ertapenem and meropenem in the EMA primary analyses



ERV=eravacycline; ETP=ertapenem; MEM=meropenem; MITT=modified intent-to-treat; CE=clinically evaluable; TOC=test of cure

1. Solomkin et al. *JAMA Surg*. 2017;152(3):224-232; 2. Solomkin et al. *Clin Infect Dis*. 2019;69(6)921-9

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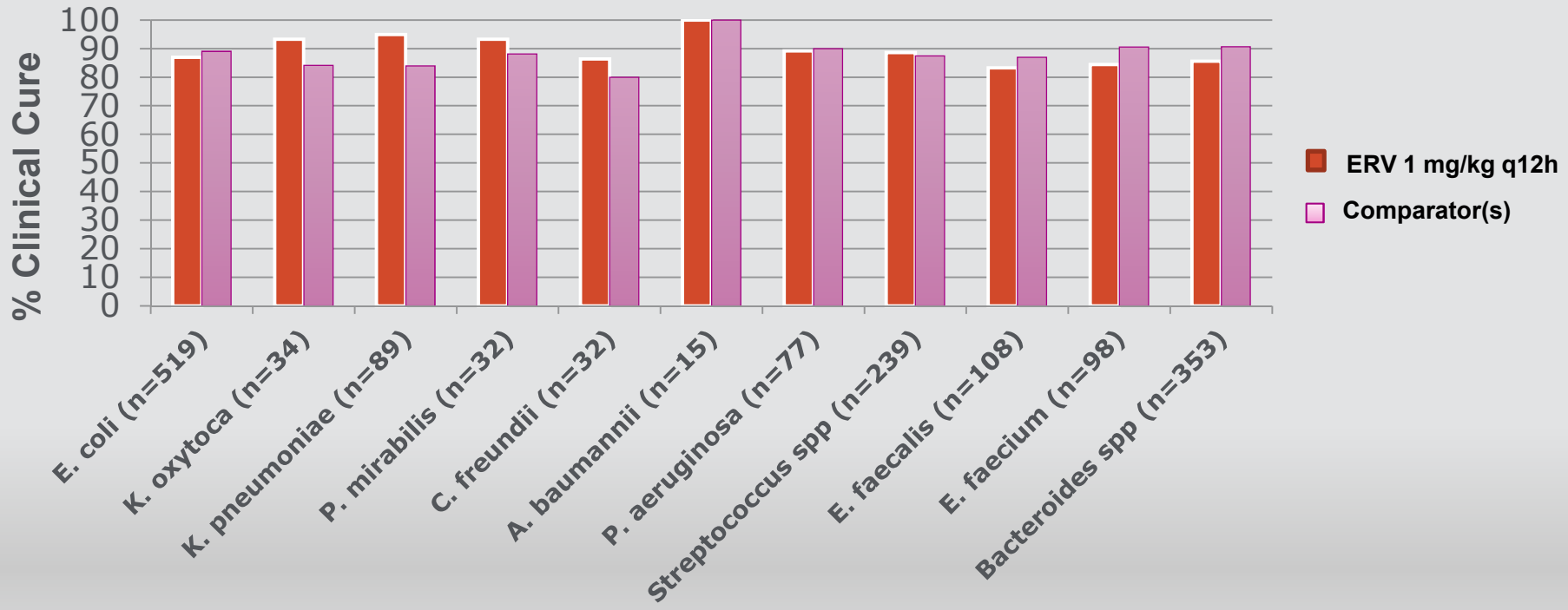
IGNITE1/4: Per Pathogen Clinical Response at TOC
micro-ITT Population



ERV=eravacycline; micro-ITT=microbiological intent-to-treat; n=number of subjects with the specified baseline pathogen; TOC=test of Cure

1. Solomkin et al. *JAMA Surg*. 2017;152(3):224-232; 2. Solomkin et al. *Clin Infect Dis*. 2019;69(6)921-9; 3. Data on File. Tetraphase Pharmaceuticals. Watertown, MA

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Clinical and Microbiological Outcomes at TOC in the micro-ITT Population for Subjects with Gram-Negative Bacilli Pathogens

Baseline Pathogen	Pooled ERV Microbiological cure n/N1 (%)	Pooled Comparator Microbiological cure n/N1 (%)	Pooled ERV Clinical cure n/N1 (%)	Pool Comparator Clinical cure n/N1 (%)
Enterobacteriaceae[*]	277/314 (88.2)	296/325 (91.1)	271/314 (86.3)	289/325 (88.9)
CEPH-R[&]	41/48 (85.4)	40/45 (88.9)	43/48 (89.6)	40/45 (88.9)
ESBL confirmed	32/36 (88.9)	26/29 (89.7)	32/36 (88.9)	25/29 (86.2)
MDR[%]	39/46 (84.7)	29/32 (90.6)	40/46 (87)	29/32 (90.6)
Acinetobacter baumannii	13/13 (100)	7/7 (100)	13/13 (100)	7/7 (100)
CEPH-R[&]	13/13 (100)	5/5 (100)	13/13 (100)	5/5 (100)
ESBL confirmed	5/5 (100)	1/1 (100)	5/5 (100)	1/1 (100)
MDR[%]	12/12 (100)	5/5 (100)	12/12 (100)	5/5 (100)

CEPH-R=cephalosporin-resistant; ERV=eravacycline; ESBL=extended-spectrum β-lactamase; MDR=multi-drug resistant; micro-ITT=microbiological intent-to-treat; n=number of subjects with clinical cure; N1=number of subjects within a specific category; TOC=test of cure

[*] = includes *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae,* and *Morganella morganii*

[&] = 3rd/4th generation cephalosporin-resistant; [%] = resistant to at least one member of ≥3 antibiotic classes

IGNITE1/4: Selected Adverse Reactions in ≥1% of Patients

Adverse Reactions	Eravacycline N=520 n (%)	Comparators N=517 n (%)
Infusion site reactions	40 (7.7)	10 (1.9)
Nausea	34 (6.5)	3 (0.6)
Vomiting	19 (3.7)	13 (2.5)
Diarrhea	12 (2.3)	8 (1.5)
Hypotension	7 (1.3)	2 (0.4)
Wound dehiscence	7 (1.3)	1 (0.2)

Comparators: ertapenem 1 g IV q24h and meropenem 1 g IV q8h
N=number of subjects; n=number of subjects with adverse reaction

Infusion site reactions include: catheter/vessel puncture site pain, infusion site extravasation, infusion site hypoaesthesia, infusion/injection site phlebitis, infusion site thrombosis, injection site/vessel puncture site erythema, phlebitis, phlebitis superficial, thrombophlebitis, and vessel puncture site swelling

XERAVA™ (eravacycline) [package insert]. Watertown, MA: Tetraphase Pharmaceuticals; 2018

Summary: Eravacycline Role in Clinical Practice

- **Twice-daily monotherapy for cIAI → *limited use for approved indication***
  - Active against ESBLs; "Carbapenem-Sparing"; limited collateral damage
- **Not indicated urinary tract infections → failed in 2 clinical trials**
- **Off-label uses:**
  - Vancomycin-Resistant Enterococci; *Acinetobacter baumannii*
  - Carbapenem-Producing Enterobacteriaceae; Achromobacter
  - Non-Tuberculosis Mycobacterium (NTM)
- **1 mg/kg [ACTUAL Body weight] q12 dosing, NO upper limit on dose**
- **No dosage adjustments for renal function**
- **Generally well tolerated → GI related AEs**

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