# Characterization of Colistin-Resistant Acinetobacter baumannii-calcoaceticus Complex (ABC) Isolates from a Recent, Global Phase 3 Trial (ATTACK)

## **EIENTASIS** THERAPEUTICS

## Abstract

**Background:** Due to a lack of effective therapies, last-resort agents such as colistin are being used to treat drug-resistant ABC infections. Consequently, colistin-resistant (COL-R) ABC is becoming more common, with some countries such as Greece reporting rates of >50%<sup>1</sup>. The efficacy and safety of sulbactam-durlobactam (SUL-DUR) was recently compared to COL, both on a background of imipenem/cilastatin, in patients with ABC infections, including multidrug-resistant strains. SUL-DUR was non-inferior to colistin with respect to 28-day all-cause mortality (19 vs. 32.3%). SUL-DUR therapy resulted in higher clinical cure rates and significantly improved safety compared to COL. Here, we describe results for COL-R ABC in ATTACK.

Methods: Antibiotic susceptibility was determined by broth microdilution according to CLSI guidelines at IHMA, Inc (Schaumburg, IL). COL-R was defined as MIC  $\geq$  4 µg/ml. Next generation sequencing was performed using Nextera® libraries on an Illumina MiSeq system (San Diego, CA) at JMI Laboratories (North Liberty, IA) and Entasis Therapeutics. Assembly and analyses were performed using CLC Genomics Workbench.

**Results:** 17% (30 of 175) baseline ABC isolates from m-MITT (microbiologically modified Intent-to-Treat) patients were COL-R. All were extensively drugresistant<sup>2</sup> and 26 were pan-drug resistant (PDR). Two additional ABC isolates became COL-R in patients with pneumonia who received COL therapy, both of whom did not survive to 28 days. Most came from 5 clinical sites: Hungary (N = 9), Russia (N = 7), Greece (N = 6), Israel (N = 3), Turkey (N = 2), Taiwan (N = 2) and Lithuania (N = 1). No COL-R ABC was found in China or the Americas. Sequencing analysis on selected isolates suggested sites in Hungary and Russia had clonal outbreaks, whereas others were non-clonal but closely related (>99%). SUL-DUR was highly active in vitro against COL-R ABC isolates, with an MIC<sub>50/90</sub> of 2/4  $\mu$ g/ml. Of the 22 patients with COL-R ABC infections treated with SUL-DUR, 17 (77%) survived to 28 days with clinical and microbiological cure at test-of-cure (TOC).

**Conclusions:** A notable number of ABC infections in ATTACK were COL-R, most of which were PDR and SUL-DUR-sensitive. If approved, SUL-DUR could be an effective treatment for patients with these types of infections.

### Introduction

Acinetobacter baumannii-calcoaceticus complex (ABC) organisms can cause serious nosocomial infections that are difficult to treat due, in part, to rising rates of antimicrobial resistance. The lack of effective therapies has resulted in the use of colistin (COL) to treat ABC infections, leading to a rise in COL-resistant ABC<sup>1</sup>.

Sulbactam-durlobactam (SUL-DUR) is a  $\beta$ -lactam/ $\beta$ -lactamase inhibitor (BL/BLI) combination currently being developed for the treatment of infections caused by ABC organisms including carbapenem-resistant and multidrug (MDR) strains. Sulbactam (SUL) is an approved BLI with antibacterial activity against Acinetobacter spp. due to its inhibition of PBP3, an enzyme required for cell wall biosynthesis<sup>3</sup>. However, degradation of sulbactam by the  $\beta$ -lactamases present in most contemporary ABC isolates limits its clinical use. Durlobactam (DUR, ETX2514) is a diazabicyclooctane  $\beta$ -lactamase inhibitor (BLI) with potent activity against class A, C and D serine  $\beta$ -lactamases<sup>4</sup>. DUR protects SUL from degradation, restoring antibacterial activity against ABC organisms.

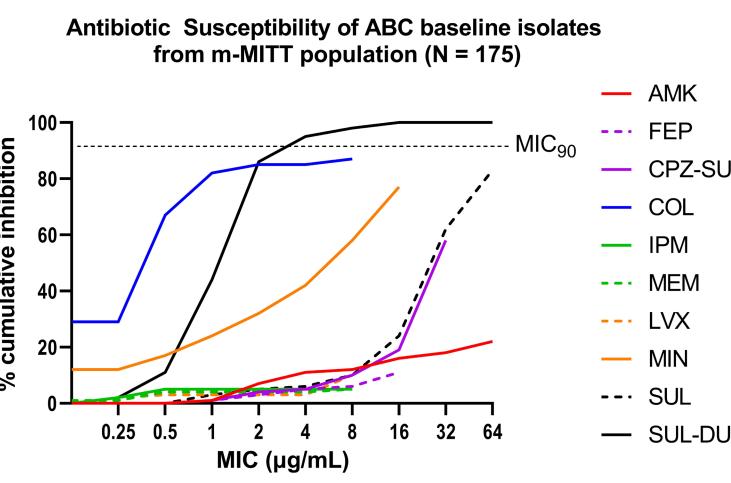
ATTACK was a Phase 3, randomized, controlled, noninferiority trial conducted to evaluate the efficacy and safety of SUL-DUR vs. COL, both in combination with imipenem/cilastatin (IMI) as background therapy, for patients with ABC infections. Treatment with SUL-DUR demonstrated lower mortality, higher clinical cure rates and greater microbiologically favorable outcomes in patients with carbapenem-resistant ABC infections. Here, the results for the COLresistant ABC in ATTACK are presented.

ATTACK was a Phase DUR versus colistin, including carbapenem

Part A Patients with document ABC infections (HABP/VABP/VP or BSI

Part B, open-label Patients with documente ABC infections not eligible for Part A (colistin-resistant or intolerant)

## SUL-DUR Maintai



Antibiotic susceptibility was deter AMK, amikacin; FEP, cefepime; ( imipenem; LVX, levofloxacin; ME sulbactam-durlobactam

## Outcomes for

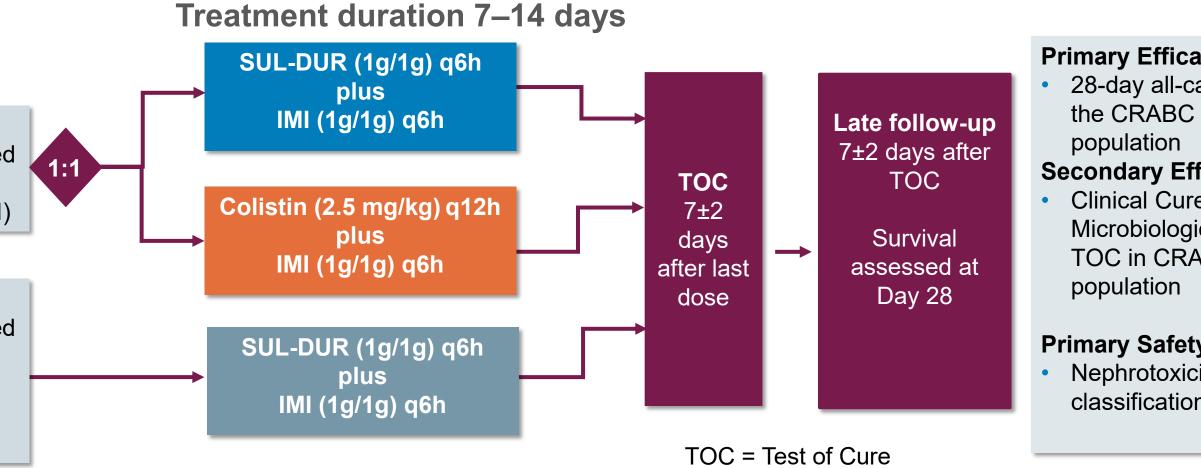
### CRABC m-MITT

28-Day All-Cause

**Clinical Cure at** 

Microbiological Fa Outcome at TOC

## Samir H. Moussa, <u>Sarah M. McLeod</u>, and Alita A. Miller Entasis Therapeutics, Waltham, MA, USA



Trial Design							Whole Genome Sequencing Results for Colistin-Resistant ABC Isolated from Patients in ATTACK																
ninferiority trial conducted to evaluate the efficacy and safety of SUL- s background therapy, for patients with serious infections due to ABC,								Country	Clinical Site ID	No. of cases		Г	β-lacta	imase genes		PmrB variants	Colist MIC (µg/ml	N	L-DUR MIC g/mL)	076-002 158-001	Country	6 <sup>0</sup> 00 <sup>2</sup>	
days Primary Efficacy Endpoints:							Hungary	348-003	9	ST <sup>Ox</sup> 195 / 3	ST <sup>Pa</sup> 2	ADC-73, TEM-1, (	OXA-23, OXA-58, C	DXA-66	T13A, I23L, P96L, V117D, V227A, Q277F N305Y, N353I, A408T		1	- 4	<sup>376.007</sup>		643002		
					-	use mortality in	Ð	Russia	643-002	7	ST <sup>Ox</sup> 195 / 3	ST <sup>Pa</sup> 2	ADC-73,	OXA-23, OXA-66		V227A	>8		2 79	792-002		643-002	
		Late follow-up 7±2 days after TOC Survival assessed at Day 28			e CRABC r	n-MITT	elin		300-002	1	ST <sup>Ox</sup> 436 / 3	ST <sup>Pa</sup> 2	ADC-73, TEN	/I-1, OXA-23, OXA-	66	A226V, V227A	>8		4	00-005		300-005	
<b>TO</b> 7±2					inical Cure	cacy Endpoints: and Favorable	) at bas	Greece	300-005	4	ST <sup>Ox</sup> 195 / ST <sup>Pa</sup> 2 ST <sup>Ox</sup> 425 / ST <sup>Pa</sup> 2		ADC-73, OXA-23, OXA-66 ADC-73, TEM-1, OXA-23, OXA-66			V227A A226V, V227A	8 - >8	2	2 - 8 <sup>3(</sup>	,00-005 376-003		300-005 300-006	
days after la					-	al Outcome at 3C m-MITT	ABO		300-006	1	ST <sup>Ox</sup> 436 / 3	ST <sup>Pa</sup> 2	ADC-73, TEM-1, OXA-23, OXA-66			A226V, V227A	8 - >8	. (	0.5	158-004			
dose					pulation arv Safety	Analyses:	OL-R/	Israel	376-001	3	ST <sup>Ox</sup> 451 / ST <sup>Pa</sup> 2 ST <sup>Ox</sup> 457 / ST <sup>Pa</sup> 2		ADC-73, TEM-1, OXA-23, OXA-66-like ADC-73, TEM-1, OXA-23, OXA-66		S14L, V227A, Q277k V227A, P233T	>8	2	2 - 4	60 00 00 00 00 00 00 00 00 00 00 00 00 0	348-0 348- 200-2	Country		
				• Ne	<ul> <li>Primary Safety Analyses:</li> <li>Nephrotoxicity (RIFLE classification)</li> </ul>			Turkey	792-002	2	ST <sup>Ox</sup> 136 / ST <sup>Pa</sup> 2 ST <sup>Ox</sup> 229 / ST <sup>Pa</sup> 25			/I-1, OXA-23, OXA- OXA-23, OXA-64	66	V227A, Q277R V227A	>8		2	2	4 8 8 8 0 0 0 0 0 0 0 0 0	Brazil Greece Hungary Israel Lithuania Russia Taiwan Turkey	
TOC = Test of Cure							l ithu ania	440.000	4				M-1, OXA-23, OXA-66			>8		2					
							Lithuania	440-003 158-001	1	ST <sup>Ox</sup> 195 / ST <sup>Pa</sup> 2 ST <sup>Ox</sup> 789		ADC-73, TEM-1, OXA-23 ADC-30, OXA-66, OX		00	V227A L153V, R181C, V227/	>8 A >8		2 8					
sistant Subsets of Baseline ABC Isolates from ATTACK								Taiwan	158-004	1	ST <sup>Ox</sup> 1806 /			1-1, OXA-23, OXA-66		ΔL9-G12	4		0.5	All COL-R isolates in this study had     previously described or new <i>pmrB</i>			
m-MITT A	BC				SUL-DUR (µg/mL)			Brazil	076-002	1	ST <sup>Ox</sup> 236 / ST <sup>Pa</sup> 15		ADC-181, OXA-23, OXA-51			Baseline: none Day 7: K385I	0.5 >8		2 2	<ul> <li>variants</li> <li>Isolates from sites with more than one COL-R infection were closely related or</li> </ul>			
Isolate ALL	S	N 175	% 100	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC Range 0.25 - 16	Beca COI	Israel	376-002	1	ST <sup>ox</sup> 208 / 3	ST <sup>Pa</sup> 2	ADC-30, OXA-66, OXA-72			Baseline: none EOT: P170L	0.5 >8		2 4	clonal			
CARB-			96	2	4	0.5 - 16		MLST: Multi-loo	ST: Multi-locus sequencing type; ST <sup>OX</sup> : Oxford sequencing type scheme; ST <sup>Pa</sup> : Pasteur sequencing type scheme; BLA: SUL-DUR, sulbactam-durlobactam; EOT, end of therapy														
MDR			96	2	4	0.5 - 16					Outcome	es of F	Patients W	hose ABC	Infec	tions Becam	e Resis	tant to	Study	Drug			
XDR		147	84	2	4	0.5 - 16							-DUR MIC	Colistin MIC				Clinical					
PDR		26	15	2	4	1 - 8		Country	Infectio	ion T	reatment		µg/mL)	(µg/mL)		mortality at 28		outcome		Microbiological Outcome			
COL-F	२	30	17	2	4	0.5 - 8		Country	typ	9	arm	SCR	тос	SCR	тос		EOT	тос	LFU	EOT	тос	LFU	
								Greece	VAB	P S	SUL-DUR	4	8	>8	>8	alive	cure	cure	fail	persistent	persistent	eradicated	
<ul> <li>m-MITT patients were enrolled at 59 sites across 16 countries in the US, Latin America, Europe, Southeast Asia and China</li> <li>The majority of colistin-resistant ABC infections came from 5 clinical sites in Europe</li> <li>No colistin-resistant ABC isolates were detected at baseline in the</li> </ul>							Brazil	HAB	P	COL	2	2	0.5	>8	dead	cure	cure	fail	persistent	persistent	presumed persistent		
							Israel VABP COL 2 4 0.5 >8 dead cure fail fail persi							persistent	persistent	presumed persistent							
Most of th	<ul> <li>Americas or China</li> <li>Most of the colistin-resistant ABC isolates were PDR but susceptible</li> </ul>								HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; SUL-DUR, sulbactam-durlobactam; COL, colistin; SCR, screen; EOT, end of therapy; TOC, test of cure; LFU, late follow up; A microbiological outcome is presumed persistent if the clinical outcome was Fail, respectively, and no culture sample was obtained at that time														
	to SUL-DUR (preliminary breakpoint ≤ 4 μg/mL)								Conclusions														
<b>3C Infection</b>	C Infections Treated with Sulbactam-Durlobactam								A large number of ABC infections in ATTACK were colistin-resistant; most of which were in Europe.														
								• The majority of colistin-resistant isolates belonged to ST <sup>Pa</sup> 2 (IC2) and had mutations in <i>pmrB</i> , consistent with previous reports.															
art A	Art A Part B Patients with COL-R															PDR subsets o				ACK.			
DL arm (all received SUL-DUR) ABC Infections who received SUL-DUR													ical and microb										
(n/N)	% (n/N) % (n/							-						it to study drug	-			-					
% (20/62)	18% (5/28) 22.7% (5/22)					<ul> <li>The single VABP patient in the SUL-DUR arm whose ABC infection showed elevated SUL-DUR MIC values over time survived to 28 days.</li> <li>If approved, SUL-DUR could be an important therapy option for patients with infections due to ABC, including MDR and COL-R isolates.</li> </ul>																	
% (25/62)	71.4% (20/28)				77.3%	(17/22)										ences							
% (26/62)	78.6% (22/28)				77.3% (17/22)			•	· ·		-	•	(2012) CMI, 19:2 7, 11 <sup>th</sup> ed. 2018.		ll et al. (2	2015) Antimicrob Ag	ents Chemot	her. 59: 16	i80-1689 <b>4</b>	. Durand-Reville,	T. <i>et al.</i> (2017)	Nature	

ATTACK Trial Design										Whole Genome Sequencing Results for Colistin-Resistant ABC Isolated from Patients in ATTACK													
nase 3, multinational, randomised, controlled, noninferiority trial conducted to evaluate the efficacy and safety of SUL- n, both in combination with imipenem/cilastatin as background therapy, for patients with serious infections due to ABC, nem-resistant ABC (CRABC) strains										Country	Clinical Site ID		MLST		β-lactamase gen	es	PmrB variar		IC	UL-DUR MIC µg/mL)	076-002 158-002	Country	oot should sh
Treatment duration 7–14 days									Hungary	348-003	9	ST <sup>Ox</sup> 195 / ST <sup>Pa</sup>	2 ADC	C-73, TEM-1, OXA-23, OXA	-58, OXA-66	T13A, I23L, P96 V117D, V227A, Q2 N305Y, N353I, A4	277R, <b>8</b> -	>8	1 - 4	<sup>6.007</sup> <sup>376.007</sup>		643.002	
	SUL-DUR (1g						-	use mortality in	(D	Russia	643-002	7	ST <sup>Ox</sup> 195 / ST <sup>Pa</sup>	<sup>a</sup> 2	ADC-73, OXA-23, OXA	<b>\-66</b>	V227A	>	8	2			643-002
	IMI (1g/1g		<b>→</b>	Late	follow-up	th	e CRABC r	-	eline		300-002	1	ST <sup>Ox</sup> 436 / ST <sup>Pa</sup>	2	ADC-73, TEM-1, OXA-23,	OXA-66	A226V, V227	\ >	8	4 30	0-005		643-002
nted 1:1			тос	7±2 days after		population Secondary Efficacy Endpoints:			) as(				ST <sup>Ox</sup> 195 / ST <sup>Pa</sup>	2	ADC-73, OXA-23, OXA	<b>\-66</b>	V227A				0.005	T /	300-005
SI) Colistin (2.5 mg/kg) q12h			→ <b>TOC</b> 7±2	TOC		• CI	Clinical Cure and Favorable			Greece	300-005	4	ST <sup>Ox</sup> 425 / ST <sup>Pa</sup>	2	ADC-73, TEM-1, OXA-23,	OXA-66	A226V, V227	8 -	>8	2 - 8 <sup>3(</sup>	376-003		300-006
	plus			days Su			Microbiological Outcome at TOC in CRABC m-MITT				300-006	1	ST <sup>Ox</sup> 436 / ST <sup>Pa</sup>	2	ADC-73, TEM-1, OXA-23,	OXA-66	A226V, V227	8 -	>8	0.5	158-004		300.002
	IMI (1g/1g) q6h			t assessed at Day 28			population						ST <sup>Ox</sup> 451 / ST <sup>Pa</sup>	<sup>a</sup> 2 AI	ADC-73, TEM-1, OXA-23, O	KA-66-like	S14L, V227A, Q2		_		440.002 003		UP COO3
nted	ed SUL-DUR (1g/1g) q6h plus			dose Day 28			Primary Safety Analyses:			Israel	376-001	3	ST <sup>Ox</sup> 457 / ST <sup>Pa</sup>	2	ADC-73, TEM-1, OXA-23,	3, TEM-1, OXA-23, OXA-66		- >	8	2 - 4	348.00;	348-0 348- 200-2	Country
Δ						• N	<ul> <li>Nephrotoxicity (RIFLE</li> </ul>						ST <sup>Ox</sup> 136 / ST <sup>Pa</sup>	2	ADC-73, TEM-1, OXA-23, OXA-66		V227A, Q277I	ς >	8	2	Ċ	848 000 00 00 00 00 00	Brazil Greece
or	IMI (1g/1g	ı) q6h					classification)			Turkey	792-002	2	ST <sup>Ox</sup> 229 / ST <sup>Pa</sup>				V227A		8	2			<ul> <li>Hungary</li> <li>Israel</li> <li>Lithuania</li> <li>Russia</li> <li>Taiwan</li> <li>Turkey</li> </ul>
TOC = Test of Cure									Lithuania	440-003	1	ST <sup>Ox</sup> 195 / ST <sup>Pa</sup>		ADC-73, TEM-1, OXA-23,		V227A		8	2				
											158-001		ST <sup>Ox</sup> 789		ADC-30, OXA-66, OXA		L153V, R181C, V2		-	8		alataa in thia	atudu (bad
ained <i>In Vitro</i> Activity Across Drug-Resistant Subsets of Baseline ABC Isolates from ATTACK										Taiwan	158-004		ST <sup>Ox</sup> 1806 / ST <sup>P</sup>	<sup>a</sup> 2	ADC-30, TEM-1, OXA-23,	OXA-66	ΔL9-G12	4	4	0.5	All COL-R is previously d	escribed or ne	•
										Brazil	076-002	1	ST <sup>Ox</sup> 236 / ST <sup>Pa</sup>	15	ADC-181, OXA-23, OX	۸ 51	Baseline: non	e 0.	.5	2	variants		
sceptibility of ABC baseline isolates m-MITT ABC N % SUL-DUR (µg/mL)						ame JL-R	Diazii	070-002		31 - 230 / 31 -	15	ADC-181, OAA-23, OA	h-0 I	Day 7: K385I	>	•8	2			ore than one sely related or			
	tion (N = 175)		Isolates			MIC <sub>50</sub>	MIC <sub>90</sub>	MIC Range	Beo	Israel	376-002	1	ST <sup>Ox</sup> 208 / ST <sup>Pa</sup>	<sup>a</sup> 2	ADC-30, OXA-66, OXA	-72	Baseline: non EOT: P170L		.5 •8	2	clonal		, <b>,</b>
		AMK	ALL	175		2	4	0.25 - 16		MLST: Multi-I	ocus sequencing	j type; ST <sup>ox</sup> : (	Oxford sequencing type	scheme; ST	ST <sup>Pa</sup> : Pasteur sequencing type so	heme; BLA: SL			-	-			
	MIC <sub>90</sub>	1 = 1	CARB-R		96	2	4	0.5 - 16															
7	/ /	CPZ-SUL	MDR XDR	168	96 84	2	4	0.5 - 16 0.5 - 16					Outcomes o	of Pat	tients Whose A	BC Infe	ctions Beca	ime Res	istant t	to Study	Drug		
/ /		IPM	PDR	26		2	4	1 - 8			Infec				DUR MIC Colistin MIC μg/mL) (μg/mL)		mortality		Clinical		Microbiological Outcome		utcome
		MEM	COL-R		17 2	2	4	0.5 - 8		Country	typ		arm			ig/mL)	at 28		outcome				
		LVX				_								SCR	TOC SCR	TOO	c days	EOT	TOC	LFU	EOT	тос	LFU
		MIN .	m-MITT pa	tients were ei	nrolled at 59	9 sites ac	cross 16 cou	untries in the		Greece	VAI	BP S	SUL-DUR	4	8 >8	>8	alive	cure	cure	fail	persistent	persistent	eradicated
				<ul> <li>US, Latin America, Europe, Southeas</li> <li>The majority of colistin-resistant ABC</li> </ul>				Asia and China			HA	BP	COL	2	2 0.5	>8	dead	cure	cure	fail	persistent	persistent	presumed persistent
MIC (µg/mL) site				No colistin-resistant ABC isolates were detected at baseline in the						Israel	VA	BP	COL	2	4 0.5	>8	dead	cure	fail	fail	persistent	persistent	presumed persistent
•	n microdilution according to CLS	•	Americas o Most of the	r China colistin-resis	tant ARC is	olates we	ere PDR hu	t suscentible							neumonia; SUL-DUR, sulbactam time	durlobactam; C	OL, colistin; SCR, scree	n; EOT, end of the	erapy; TOC, te	est of cure; LFU, la	ate follow up; A microbi	ological outcome is	presumed persistent if
	perazone-sulbactam (2:1); COL ı; MIN,  minocycline; SUL, sulba			R (preliminary						the clinical outcome was Fail, respectively, and no culture sample was obtained at that time													
									_	Onclusions     A large number of ABC infections in ATTACK were colistin-resistant; most of which were in Europe.													
for Patien	ts with Colistin-R	esistant ABC	Infections	Treated	with Sul	bactar	n-Durlol	oactam		•									-	sot with or		40	
							Dationto w			•					onged to ST <sup>Pa</sup> 2 (I			•		-		TS.	
	Part A	Part		Part B			Patients with COL-R ABC Infections who		•	<ul> <li>SUL-DUR maintained in vitro activity against colistin-resistant, XDR and PDR subsets of ABC isolates from ATTACK.</li> <li>Batients with COL B infections treated with SUL DUB had favorable clinical and microbiological outcomes.</li> </ul>													
T Patients	SUL-DUR arm COI		rm	(all receive	II received SUL-DUR)		) received SUL-DUR		<ul> <li>Patients with COL-R infections treated with SUL-DUR had favorable clinical and microbiological outcomes.</li> <li>Two patients with respiratory infections in the COL arm became resistant to study drug; neither survived to 28 days.</li> </ul>														
	% (n/N)	% (n/l	N)	% (n/N)			% (n/N)		<ul> <li>The single VABP patient in the SUL-DUR arm whose ABC infection showed elevated SUL-DUR MIC values over time survived to 28 days.</li> </ul>														
e Mortality	19% (12/63)	32.3% (2	(20/62) 18% (5/28)				22.7%	(5/22)		•					therapy option fo							-	
at TOC	61.9% (39/63) 40.3% (25/62)		5/62)	62) 71.4% (20/28)			77.3%	(17/22)		References													
Favorable TOC	able 68.3% (43/63) 41.9% (26/62)			78.6%	(22/28)		77.3%	(17/22)		•	,		2 <b>2.</b> Magiorakis <i>et</i> ed. 2020. <b>6.</b> CLSI	•	l2) CMI, 19:268-81 <b>3.</b> Pe 1 <sup>th</sup> ed. 2018.	enwell <i>et al.</i>	(2015) Antimicrob	Agents Chen	nother. 59:	1680-1689 <b>4</b>	. Durand-Reville,	T. <i>et al.</i> (2017)	Nature

**Disclosures:** All authors are full-time employees of Entasis Therapeutics

## Entasis Therapeutics 35 Gatehouse Dr. Waltham, MA 02151 1-781-810-0121 Sarah.McLeod@entasistx.com

