Novel Phage-Derived Lysins for MRSA IE

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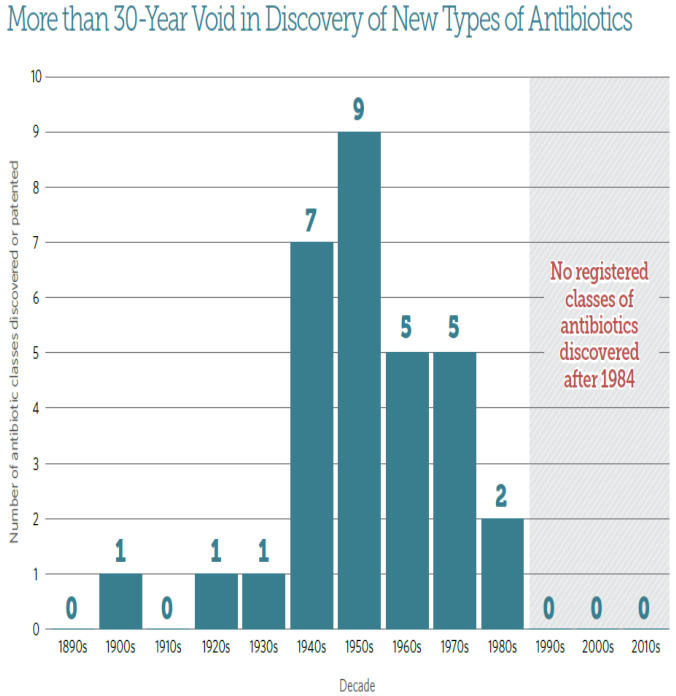
ContraFect is a clinical-stage biotech leading the development of differentiated, first-in-class biologics for the treatment of life-threatening and drug-resistant infections

Effective New Antimicrobial Therapies are Needed

New treatment options are needed for *S. aureus* bacteremia/infective endocarditis, particularly for MRSA

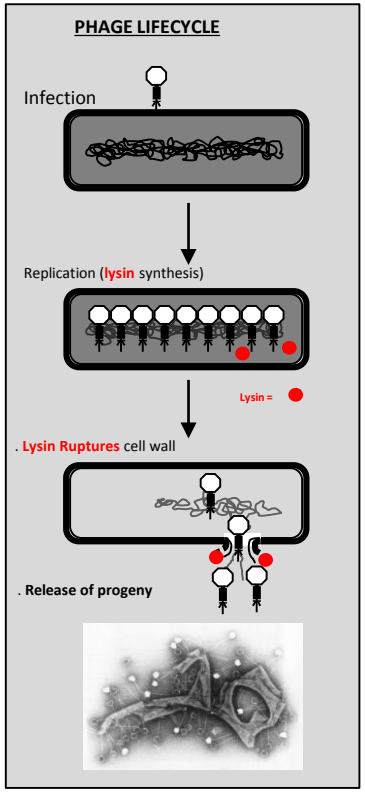
- ~200,000 hospitalizations per year in the US
- Mortality rates of 20-40%, higher for MRSA
- Clinical success rates suboptimal with current antibiotics
- Few treatment options, particularly for MRSA
- No new treatments in over a decade

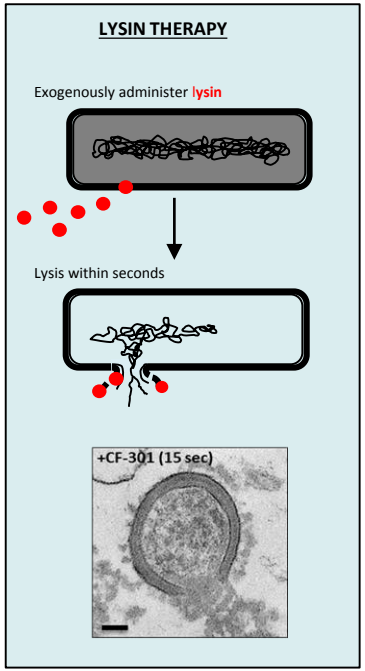
Antimicrobial Resistance Is A Global Health Threat



Kaasch, 2014, CDC, 2013, ECDC, 2007; Source: US CDC 2013, ECDC 2007; Pew Charitable Trusts, “A Scientific Roadmap for Antibiotic Discovery, “ May, 2016

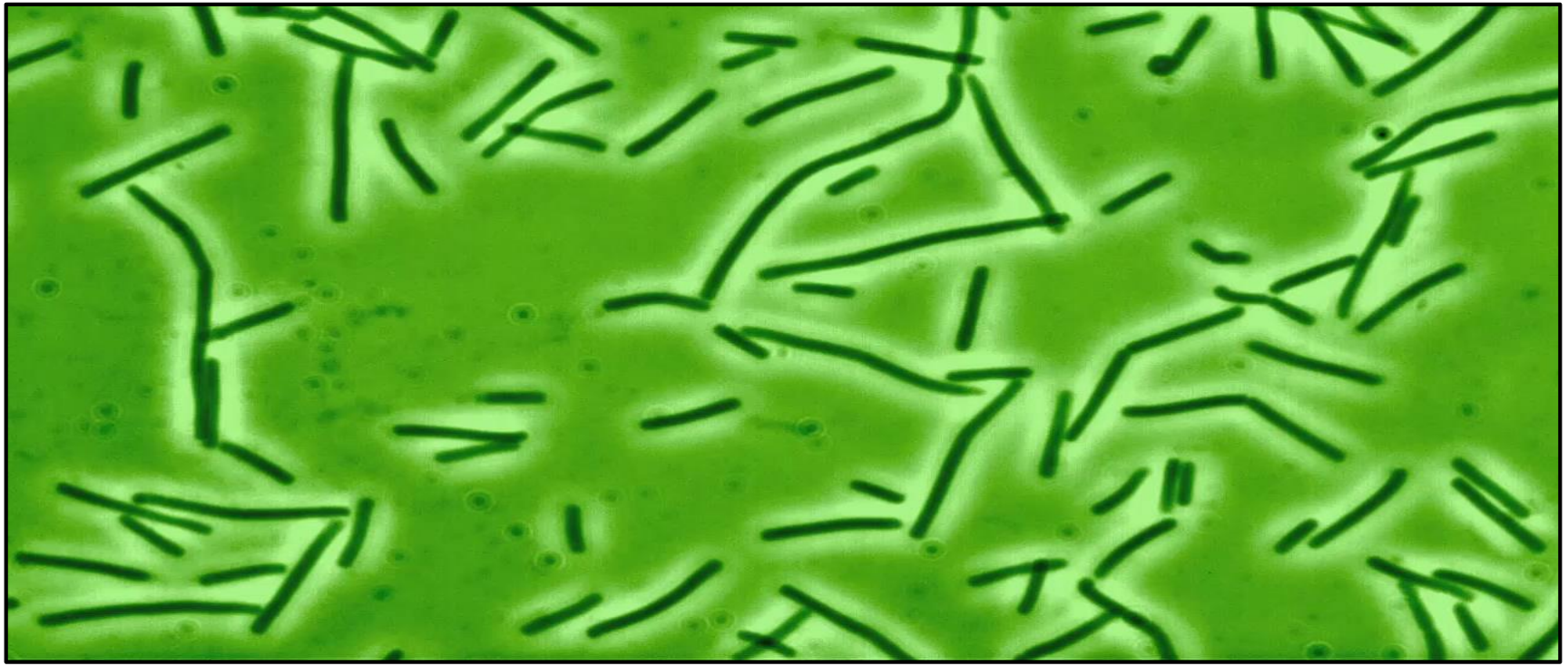
Lysin Technology -The Promise of Direct Lytic Agents





- Novel MOA: Peptidoglycan hydrolysis leading to osmotic lysis
- Rapid, targeted, species-specific killing
- Eradication of biofilms
- Synergy with conventional antibiotics
- Highly active against antibiotic resistant strains
- Low propensity for resistance and no antibiotic cross-resistance
- Suppression of emergence of antibiotic resistance when used together
- Potential to resensitize resistant bacteria to antibiotics

Lysin In Action – Real Time



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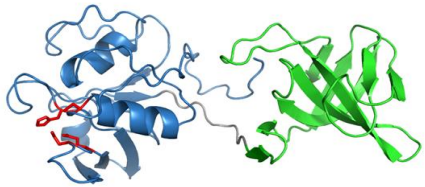
Exebacase (EXE): A Novel Antistaphylococcal Lysin

- Bacterial cell wall (peptidoglycan) hydrolase
- Potent activity against *S. aureus* and associated biofilms and all other *S.* species tested
- Synergistic with conventional antibiotics
- Well tolerated with linear PK in Phase 1
- First lysin to complete Phase 2 study under US IND
  - Novel superiority design study to evaluate the ability of the exebacase to improve clinical outcomes in *S. aureus* bacteremia/endocarditis when used in addition to standard of care antibiotics



Exebacase: Potent, Targeted Activity

Organism	N	CF-301 MIC (μg/mL)		
		MIC_{50}	MIC_{90}	Range
Staph. aureus (MRSA)	315	0.5	1	0.12-1
Staph. aureus (MSSA)	310	0.5	1	0.25-1
Staph. aureus (VRSA)	13	0.5	0.5	0.125-0.5
Staph. epidermidis	54	0.5	0.5	0.12-2
Staph. haemolyticus	22	1	2	0.25-2
Strep. pyogenes	102	1	2	0.5-4
Strep. agalactiae	101	1	2	0.25-4
Strep. pneumoniae	59	4	32	1-64
E. faecalis	23	16	256	0.25-256
E. faecium	6	>256	>256	>256
B. cereus	9	>512	>512	>512
A. baumannii	13	>512	>512	>512
E. coli	7	>512	>512	>512
K. pneumoniae	5	>512	>512	>512
P. aeruginosa	9	>512	>512	>512

- Broad activity against all *Staphylococci* and key *Streptococci,* including erythromycin resistant Group A and clindamycin resistant Group B *strep*
- No activity against GN pathogens – low risk to human GI microbiome

Source: Schuch et al. Oral Presentation, CLSI, 2016

Exebacase: Biofilm Eradication

Biofilm: A major medical problem

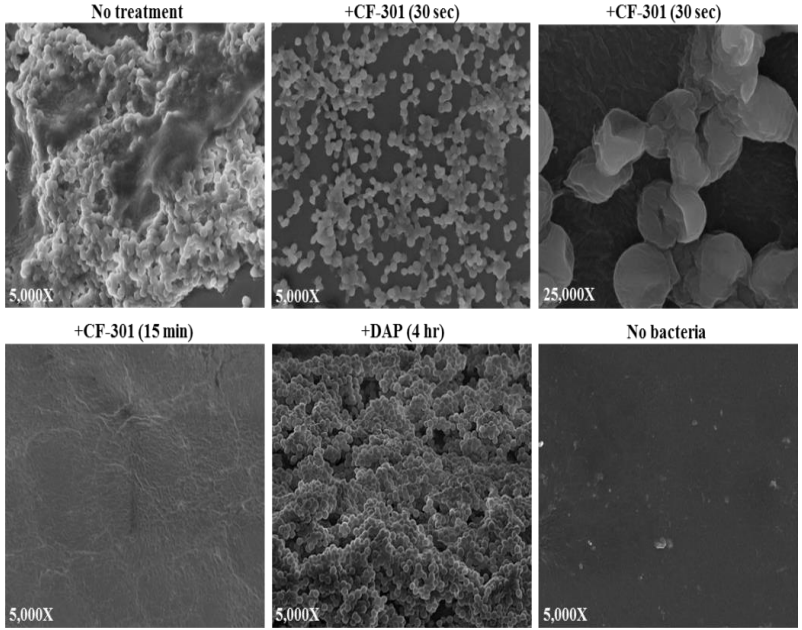
- Biofilms harbor and protect bacteria from immune defenses
- Conventional antibiotics cannot clear or penetrate biofilms
- Biofilms can increase antibiotic resistance 1,000-fold

Mature MRSA biofilms are eradicated by EXE but not Daptomycin in vitro

- EXE $MBEC_{90}$* = 0.25 ug/ml
- DAP $MBEC_{90}$* >1,024 ug/ml

S. aureus biofilms formed on catheter in setting of human infection effectively cleared by EXE, EXE+DAP but not DAP alone at 1xMIC concentrations

Exebacase clears in vitro biofilm in 15 min on a MRSA-infected catheter

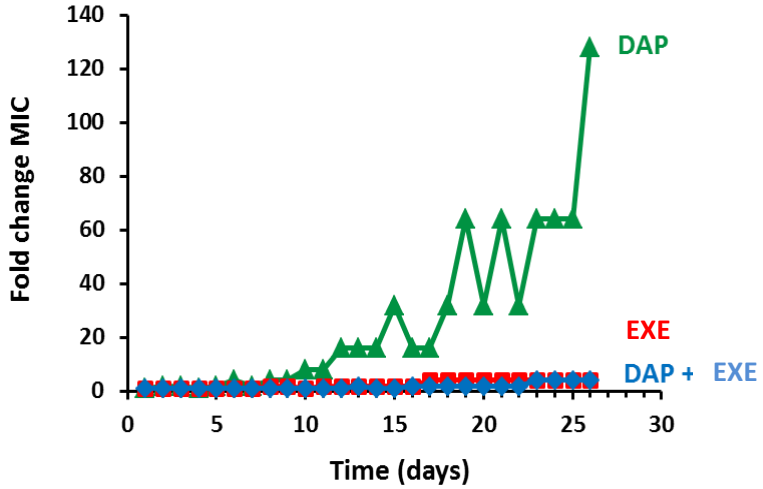


*minimum biofilm-eradicating concentration

Source: Schuch, et al, AAC, 2017.

Exebacase: Low Propensity for Resistance

26-day Serial Passage Resistance Studies with MRSA

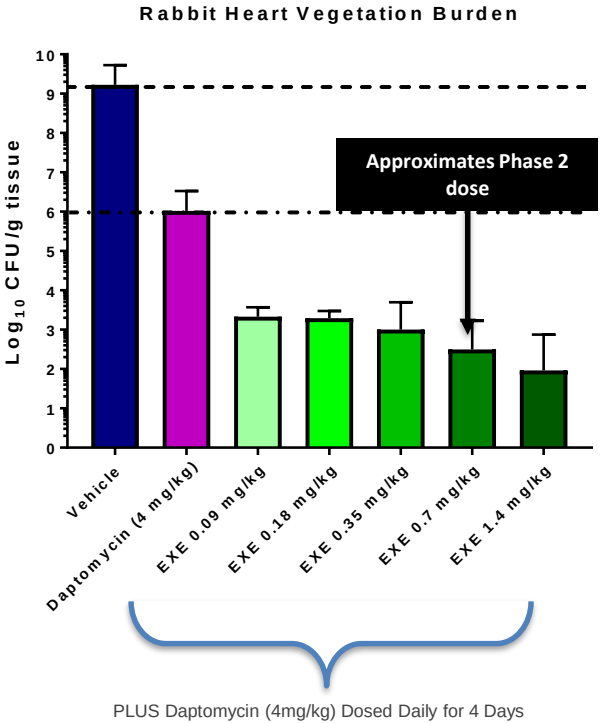


- EXE MIC remained stable (≤2 fold shift) after 26 days[1]
- The addition of EXE to daptomycin (DAP) suppressed emergence of DAP resistance[1,3]
- EXE also suppressed resistance to oxacillin[2] and vancomycin[1,4]

Sources:
1. Schuch et al., 2014, JID, 2014:209
2. Oh and Schuch, 2017, ASM-Microbe, Poster Fri-330
3. Oh et al., 2018, ECCMID, Poster P2452
4. Oh et al., 2018, ASM-Microbe, Poster Sun-535

Exebacase Enhanced Daptomycin Activity in Rat and Rabbit MRSA Infective Endocarditis (IE) Models

- **Single dose of EXE plus DAP (dosed daily for 4 days) in both rat and rabbit IE models resulted in**
  - ~6-$\log_{10}$ reduction in CFUs vs vehicle ($p \leq 0.001$)
  - $\geq$ 3 $\log_{10}$ reduction in CFUs vs. DAP alone ($p \leq 0.002$)
- **In rabbit IE dose ranging study, efficacy maintained at the lowest EXE dose tested (0.09 mg/kg) ($p \leq 0.001$)**
- **Similar efficacy demonstrated with broad range of timing of EXE dose relative to initial dose of DAP**



Source: Indiani et al. (2019) Antimicrob Agents Chemother. AAC.02291-18 (ePub)

Exebacase: Potential To Improve Clinical Outcomes

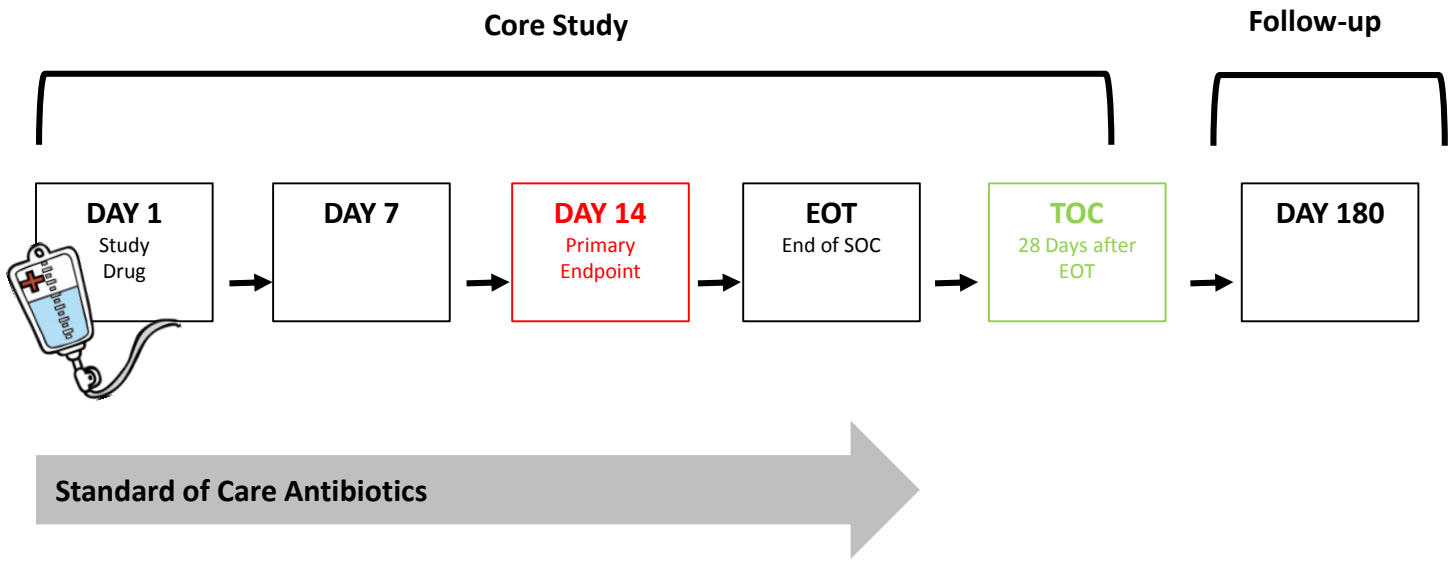
- Novel MOA
- Rapid, potent and targeted
- Eradication of biofilms
- Synergy with antibiotics
- Low propensity for resistance
- Suppression of antibiotic resistance

Improve Cure Rates for Antibiotic Resistant Infections

Phase 2 - Superiority Design Study

- **Randomized, double-blind, placebo-controlled, superiority design study**
  - ***Compared single IV dose of exebacase (EXE) + standard of care antibiotics (SOC) vs SOC alone***
- **Study population**
  - ***Adults with documented S. aureus bacteremia including endocarditis***
- **Study objectives**
  - ***Describe safety and tolerability***
  - ***Estimate clinical outcome rates after study drug administration***
  - ***Describe the pharmacokinetic parameters***
- **Primary endpoint – Clinical Responder Rate at Day 14**
  - ***Determined by independent, blinded Adjudication Committee***
  - ***Defined as "Improvement/resolution of signs/symptoms, no new metastatic foci of infection or complications, and no changes in antibiotic treatment or further medical intervention due to lack of response in patients alive at time of evaluation"***

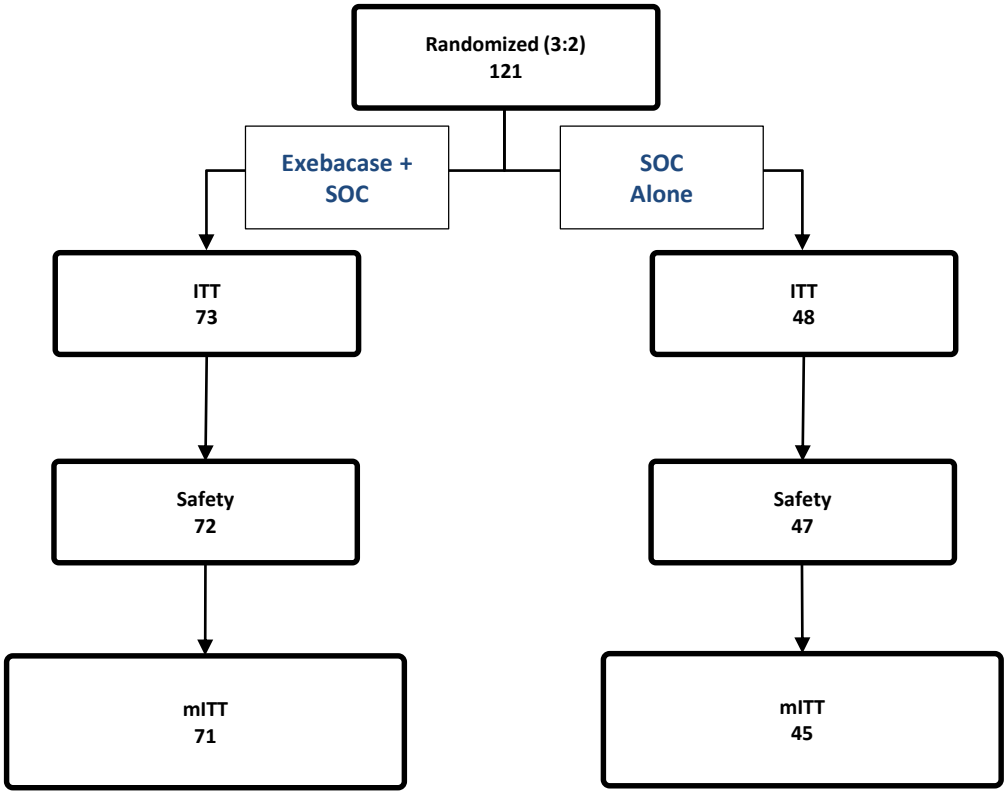
Study Schema



Duration of SOC antibiotic treatment varied widely: mean days, (range)

- EXE + SOC : 33.3 days, (2 – 181 days)
- SOC Alone: 30.5 days, (3 – 91days)

Patient Disposition



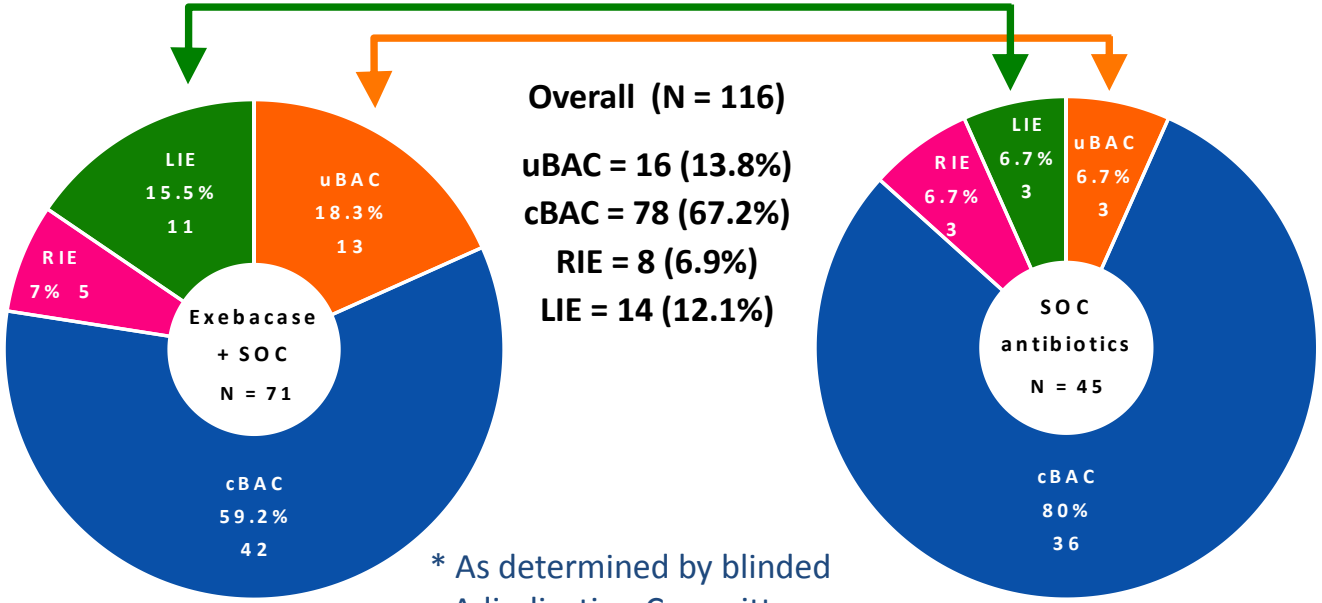
Demographics were Similar in Both Groups

	Exebacase + SOC N = 73	SOC Alone N = 48
Age (years, mean)	56.6	55.0
Age > 50 (n, %)	47 (64.4)	34 (70.8)
Gender (n, %)		
Female	23 (31.5)	16 (33.3)
Male	50 (68.5)	32 (66.7)
Race (n, %)		
Black	14 (19.2)	8 (16.7)
White	51 (69.9)	30 (62.5)
Other	8 (11.0)	10 (20.8)
CrCl (ml/min, n, %)		
<30	28 (38.4)	12 (25.0)
30 to <60	13 (17.8)	7 (14.6)
60 to <90	5 (6.9)	4 (8.3)
≥90	24 (32.9)	23 (47.9)
Missing	3 (4.1)	2 (4.2)

Risk Factors and Infecting Pathogen

	Exebacase + SOC N = 71	SOC Alone N = 45
	n (%)	n (%)
Risk Factor		
Poorly controlled diabetes mellitus	20 (32.3)	8 (20.5)
Injection drug use	6 (9.7)	5 (12.8)
Pre-existing valvular heart disease	1 (1.4)	3 (6.7)
Surgery within prior 30 days	11 (15.5)	5 (11.1)
Extravascular foreign material	9 (12.7)	9 (20.0)
Diagnosis of AIDS	2 (3.2)	1 (2.6)
Hemodialysis	21 (29.6)	8 (17.8)
SIRS[1]	45 (72.6)	27 (69.2)
Infecting Pathogen[2]		
MRSA	27 (38.0)	16 (35.6)
MSSA	44 (62.0)	30 (66.7)

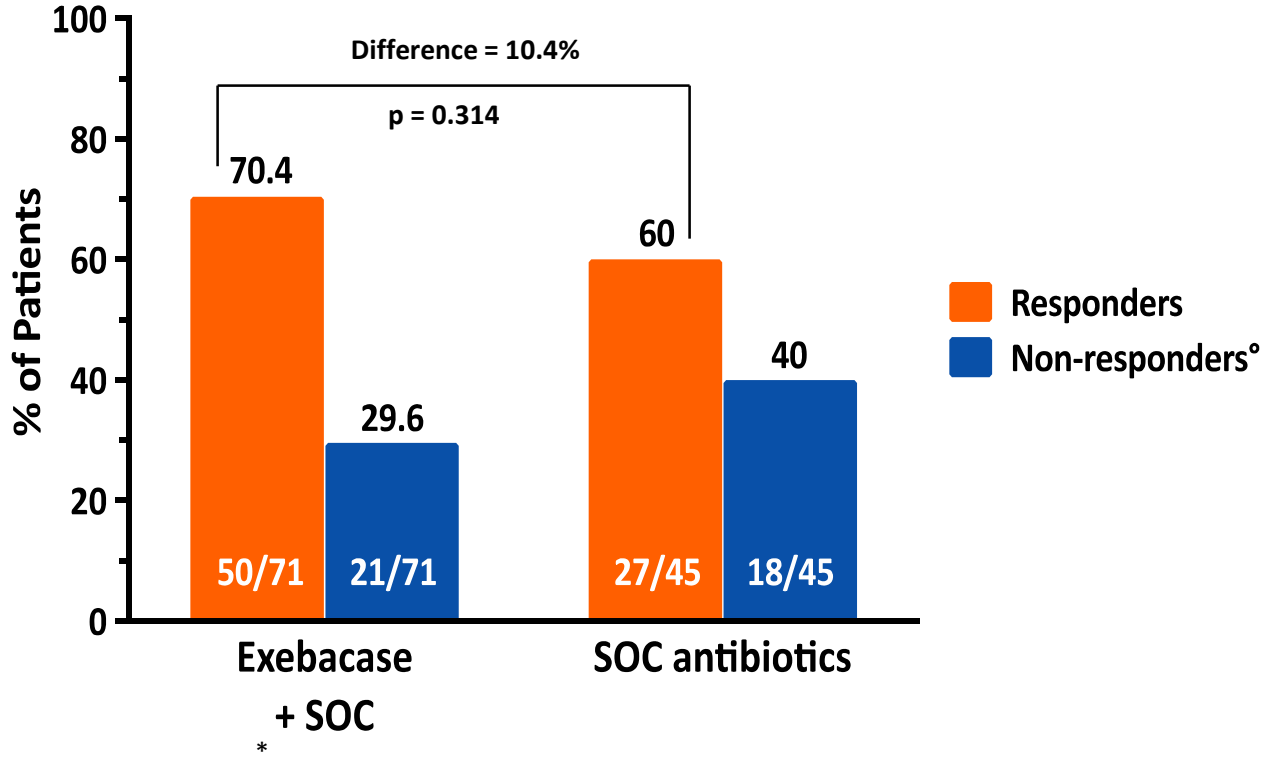
Distribution of Final Diagnoses* Differed Between Treatment Groups



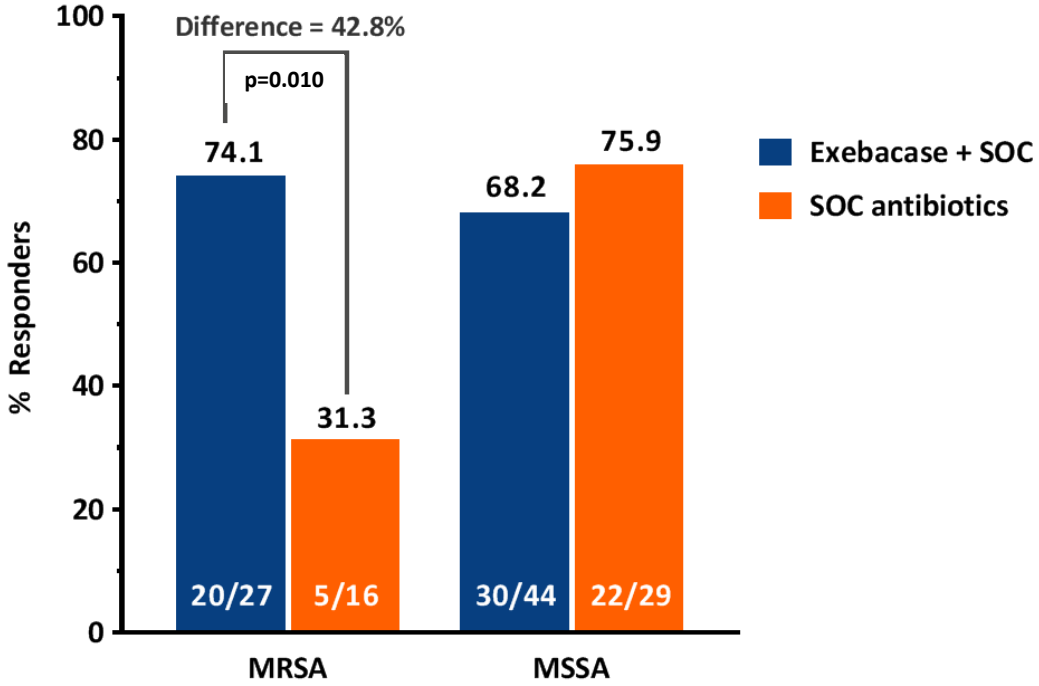
* As determined by blinded Adjudication Committee

uBAC = uncomplicated bacteremia
cBAC = complicated bacteremia
RIE = right-sided endocarditis
LIE = left-sided endocarditis

Primary Efficacy Endpoint: Clinical Responder Rate at Day 14 (mITT)

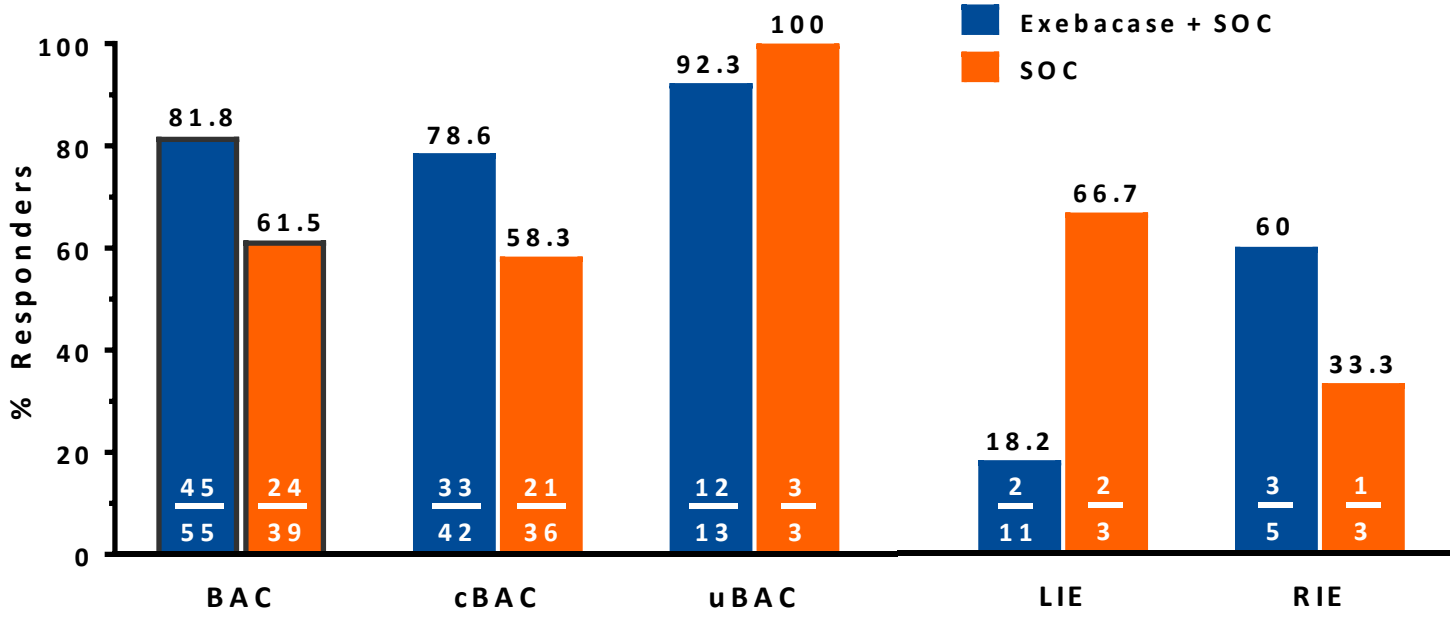


Clinical Responder Rate at Day 14 in Prespecified MRSA Subgroup



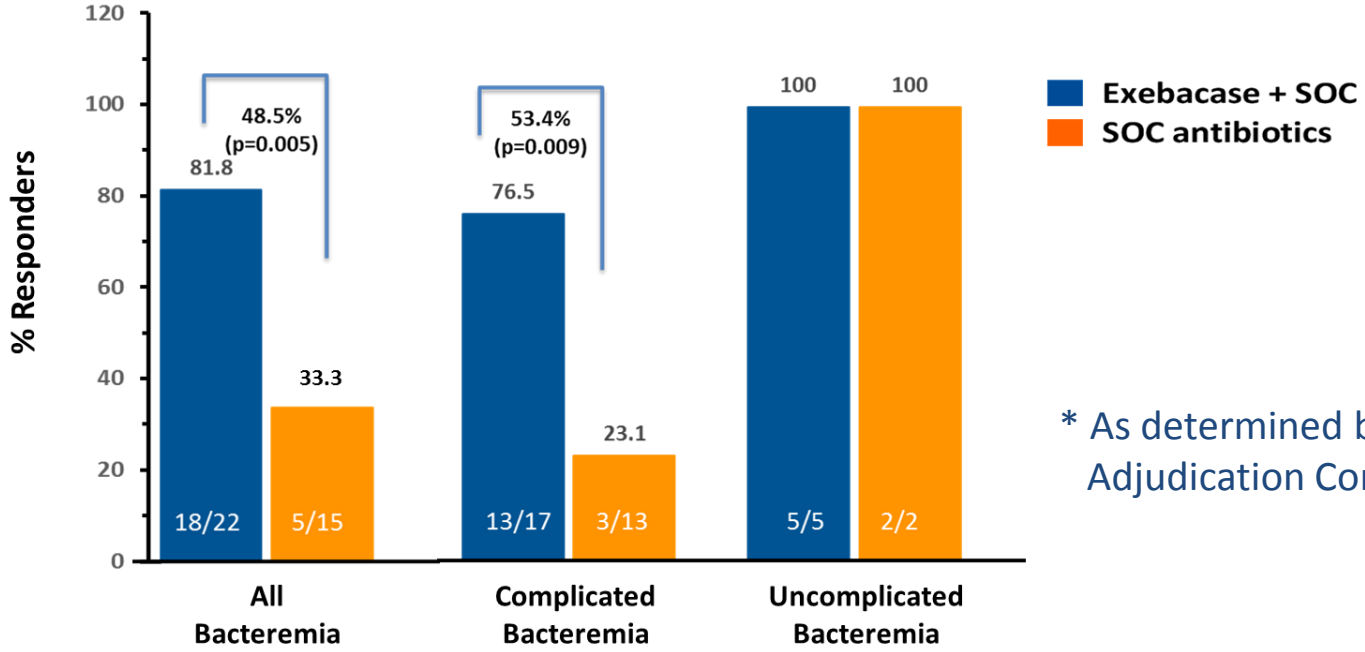
MSSA analysis is affected by the imbalance in LIE: 8 patients in EXE group vs 3 antibiotics alone group had LIE. Excluding LIE, responder rates were 80.6% and 74.1% for EXE and antibiotics alone at Day 14.

Clinical Responder Rates at Day 14 in Prespecified Final Diagnosis* Subgroups (mITT)



* As determined by blinded Adjudication Committee

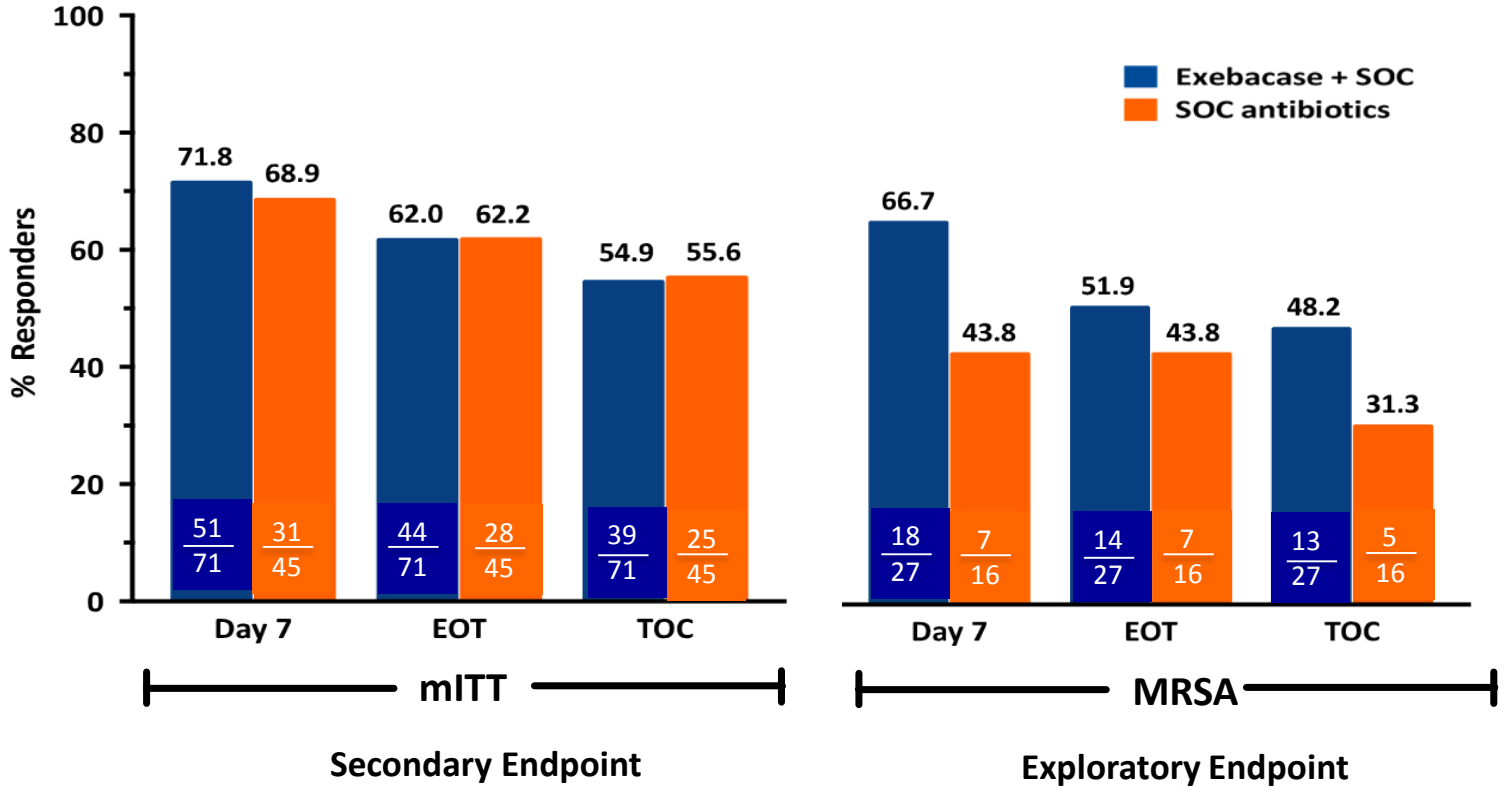
Clinical Responder Rates at Day 14: Final Diagnosis* Subgroups (MRSA)



* As determined by blinded Adjudication Committee

- **Only 6 MRSA patients had IE (5 EXE and 1 SOC)**
- RIE: 1 out of 2 and 0/1 were responders (EXE and SOC, respectively)
- LIE: 1 out of 3 EXE patients was a responder in EXE; no SOC MRSA patients had LIE

Clinical Responder Rates at Day 7, EOT and TOC



Exebacase Was Safe and Well Tolerated Through Day 180

	Exebacase + SOC N = 72 n (%)	**SOC antibiotics N = 47 n (%)**
Adverse events (AEs) through Day 7	48 (66.7)	31 (63.8)
AEs leading to study drug discontinuation	0	0
Hypersensitivity AEs related to EXE	0	
Serious Adverse Events (SAEs) through Day 180	45 (62.5)	28 (59.6)
SAEs determined to be related to EXE	0	
Total deaths through Day 180	17/72 (23.6)	9/47 (19.1)
Total deaths through Day 180 excluding left sided endocarditis	12/61 (19.7)	8/44 (18.2)

TOPLINE – New US Health Economic Data in MRSA

- **Length of stay for MRSA was reduced with exebacase**
  - Median number of hospital days from study drug administration through discharge was 6.0 days in the EXE-treated group vs 10.0 days in SOC-alone group

- **30-day hospital readmission rates among MRSA patients discharged alive from the hospital were lower among EXE-treated patients**
  - **All cause 30-day hospital readmission rates**
    - 16.0% vs 30.8% in the EXE vs SOC antibiotics alone groups, respectively
  - ***S. aureus* 30-day hospital readmission rates**
    - 8.0% vs 15.4% in the EXE vs SOC antibiotics alone groups, respectively

Exebacase – Potential First New Treatment Paradigm for Serious, Antibiotic Resistant Bacterial Infections in Decades

- A first in class direct lytic agent
- In Phase 2, exebacase used in addition to SOC antibiotics :
  - was safe and well tolerated
  - resulted in a 42.8% higher responder rate vs antibiotics alone at Day 14 and trend towards sustained higher Responder rates at all time points in the prespecified MRSA subgroup
  - may require an alternative development approach for left-sided endocarditis
- Results support a definitive Phase 3 study focused on MRSA
- Establishes Proof of Concept for direct lytic agents as potential therapeutics

Questions?