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"Novel phage lysins for treating staphylococcal endocarditis: from bench to bedside"

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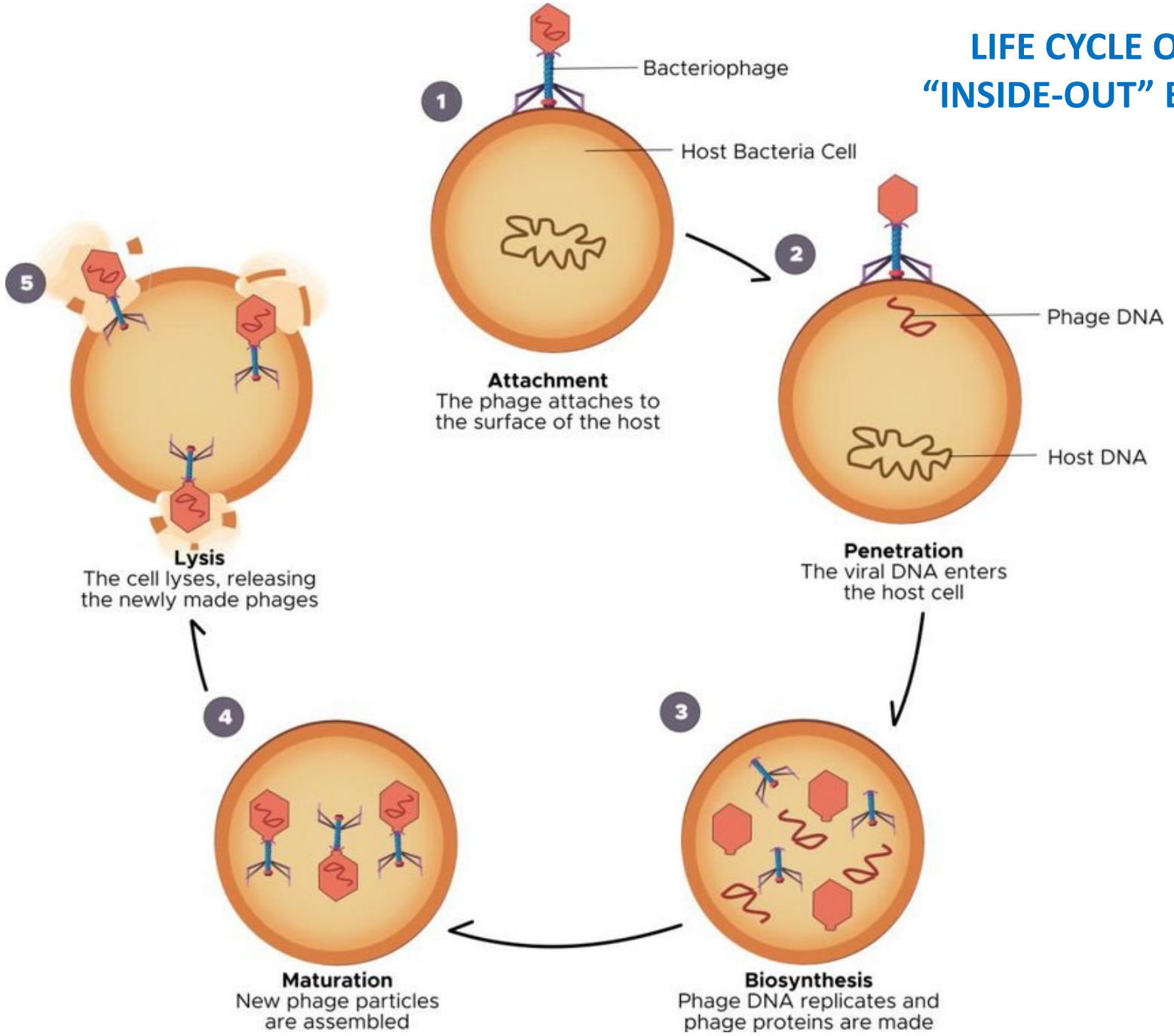
Relevant Disclosures – ContraFect Corp; Lysovant/Roivant Labs; Akagera Medicines

THE LUNDQUIST INSTITUTE
MICROBIOLOGY RESEARCH LABS

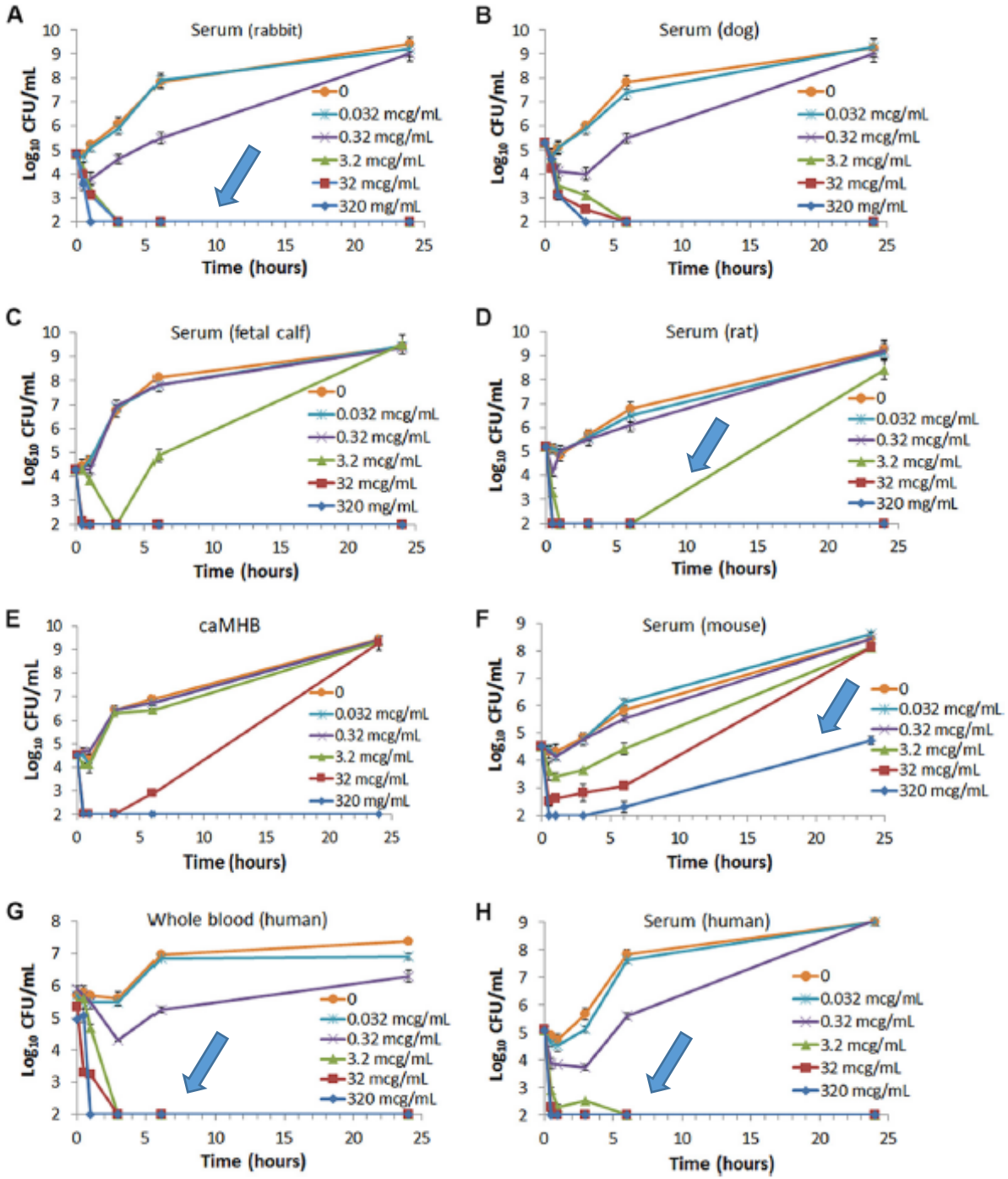
LIFE CYCLE OF LYTIC PHAGES
"INSIDE-OUT" BACTERIAL KILLING



Bacteriophage-Antibiotic Combination Strategy: an Alternative against Methicillin-Resistant Phenotypes of Staphylococcus aureus.
Razieh Kebriaei et al *AAC* July 2020

***The diSArm Trial*. Armata Pharmaceuticals [NCT05184764]**
Staph Bacteremia
Phase 1B-2a
Phage Cocktail + SOC Abs

Gram-Positive Phage Lysins (~~GN~~) – Bullet Points



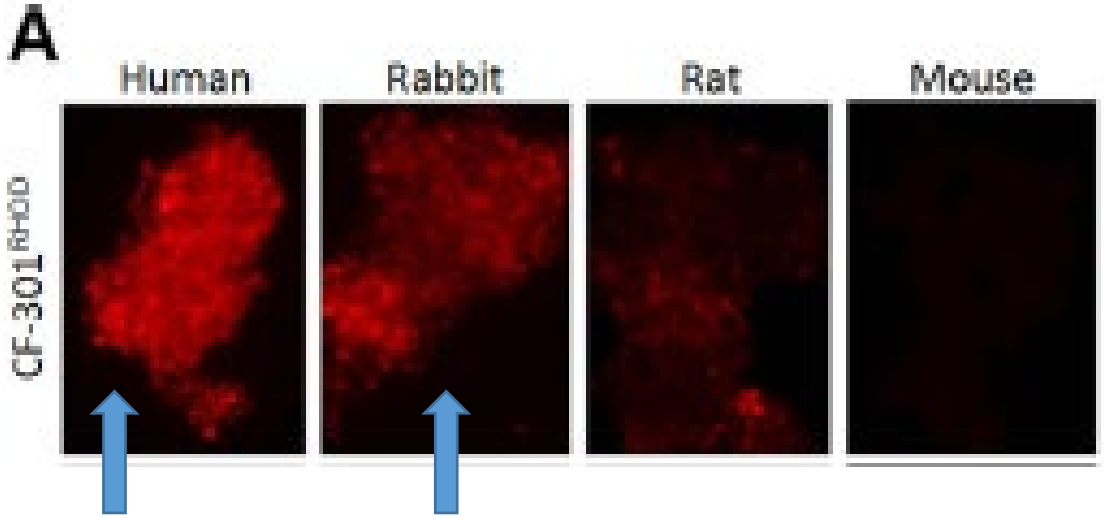
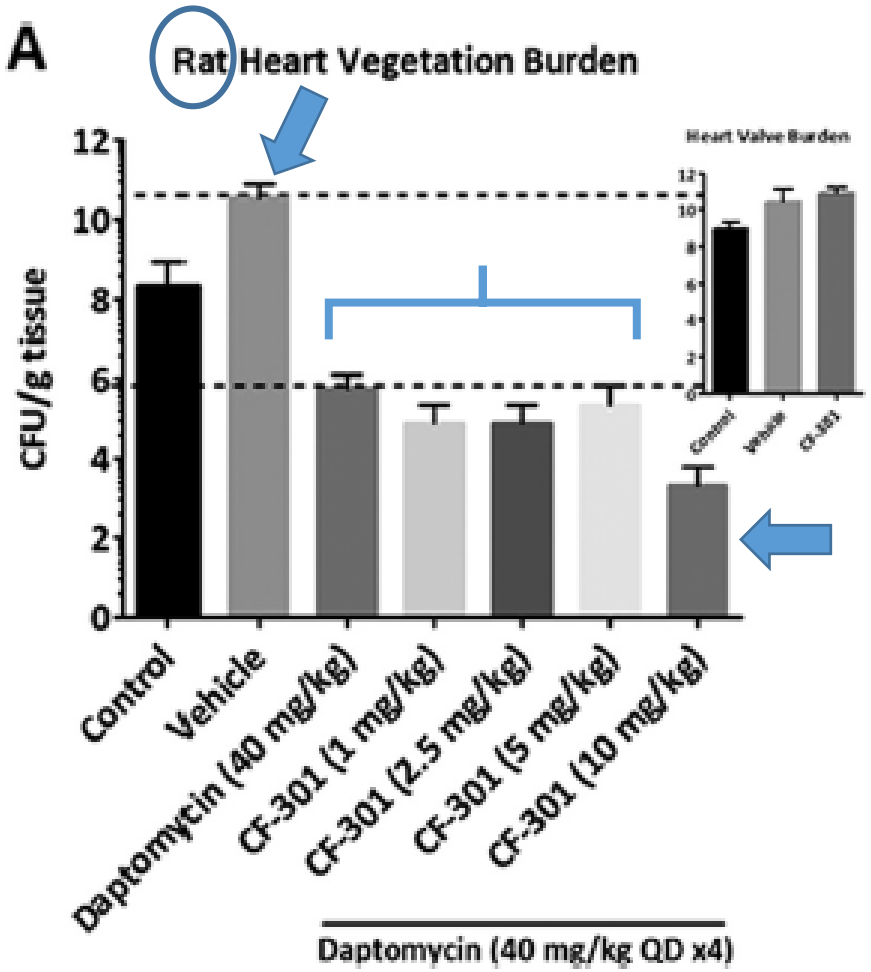


TABLE 1 Comparison of CF-301 MIC values (micrograms per milliliter) determined in caMHB and human serum

		caMHB			Human serum		
S. aureus type	*n*	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
MSSA	74	16	32	8–32	0.5	1	0.25–1
MRSA	75	32	32	2–128	0.5	1	0.25–2
Other[a]	22	4	32	0.5–32	0.5	1	0.25–2



Lysin alone = ineffective in IE model (vs *in vitro;* prophylactic animal models) = ??
reflects heavy biofilm; intra-organ penetration/distribution issues; host factors ??)
"Damages" the org'm = foundational for enhanced Dapto killing

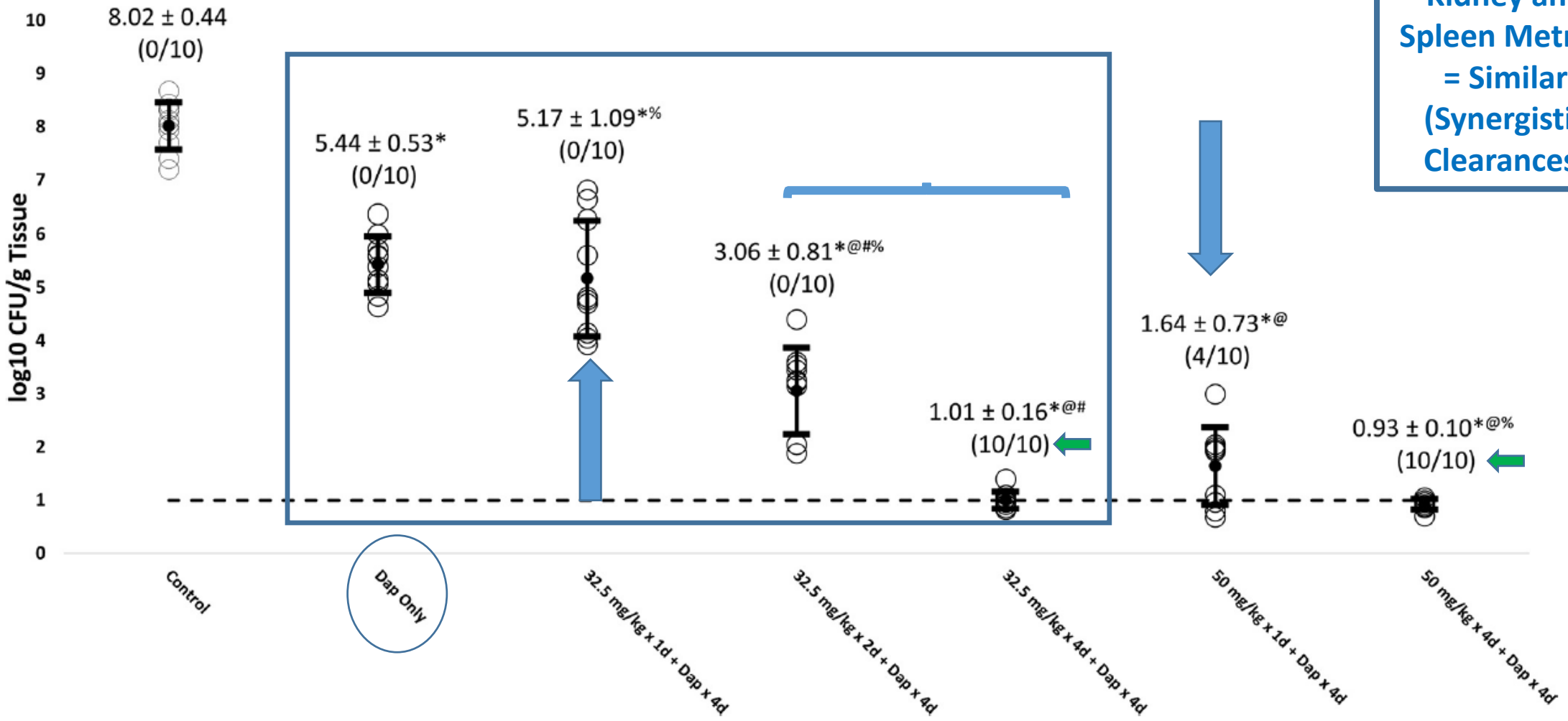
Efficacy of Antistaphylococcal Lysin LSVT-1701 in Combination with Daptomycin in Experimental Left-Sided Infective Endocarditis Due to Methicillin-Resistant Staphylococcus aureus

AAC August 2021

Tonabacase

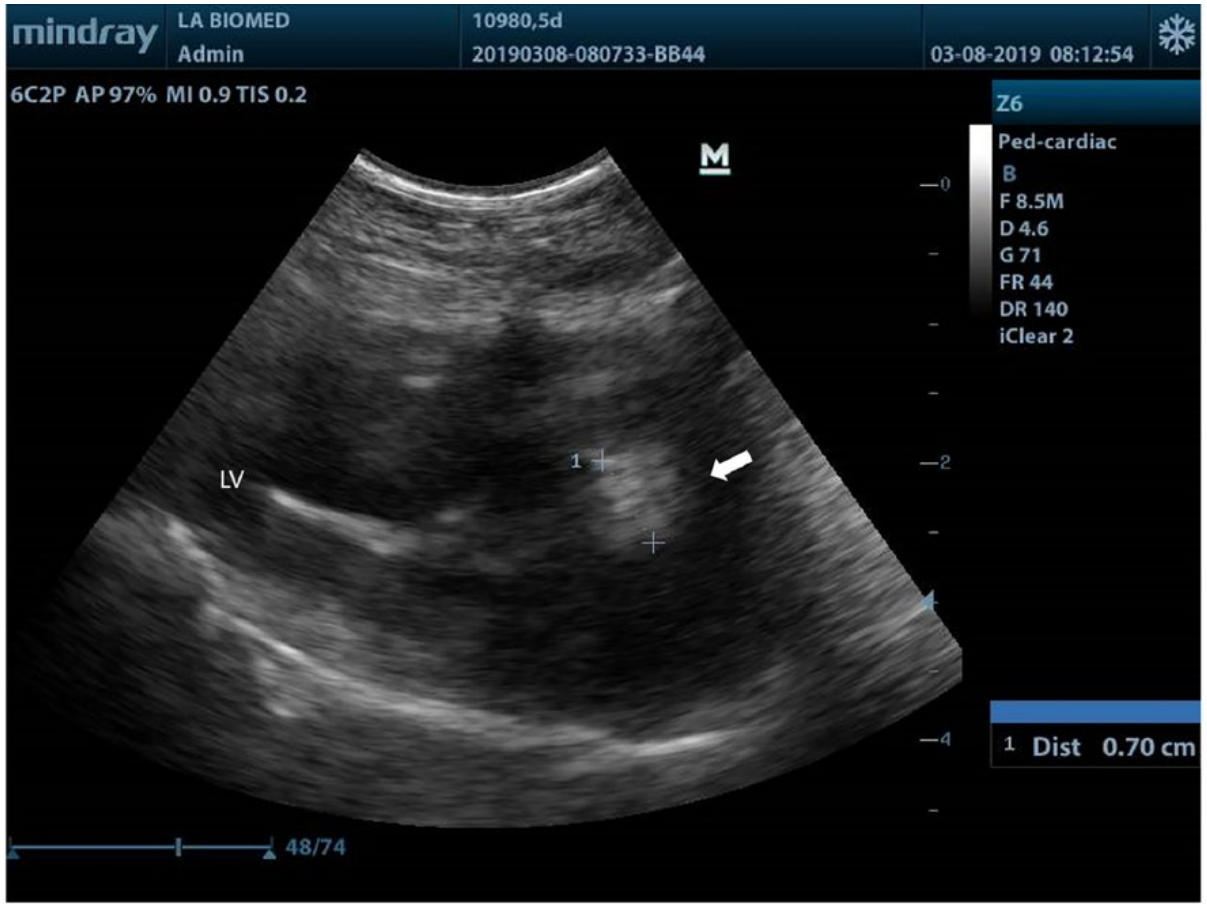
David B. Huang, Eric Gaukel, Nancy Kerzee, Katyna Borroto-Esoda, Simon Lowry, Yan Q. Xiong, Wessam Abdelhady, Arnold S. Bayer

Kidney and Spleen Metrics = Similar (Synergistic Clearances)

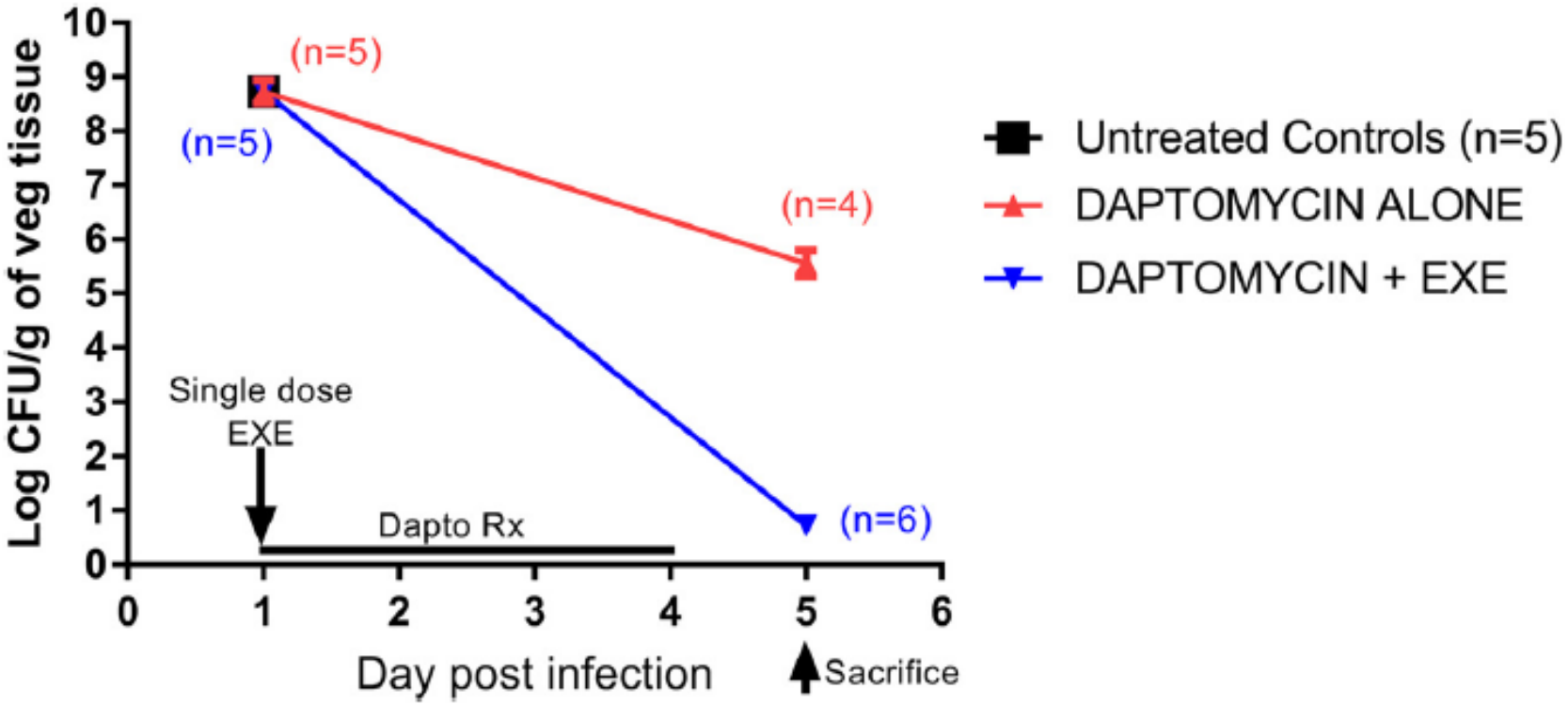


Effect of the Lysin Exebacase on Cardiac Vegetation Progression in a Rabbit Model of Methicillin-Resistant *Staphylococcus aureus* Endocarditis as Determined by Echocardiography.

Shah SU, Xiong YQ, Abdelhady W, Iwaz J, Pak Y, Schuch R, Cassino C, Lehoux D, Bayer AS. *AAC* July 2020



DAP Alone – Four Days



Is the reduction in vegetation size by ECHO in the DAP + lysin group = combination of anti-biofilm effect + rapid reduction in intravegetation MRSA burden >>> blunting of the usual, expected secondary pro-coagulant events??

Clinical Trials of Phage Lysins in Staph IE (1) - Exebacase

Fowler et al. *J Clin Invest* July 2020 (NCT03163446 – Phase II)

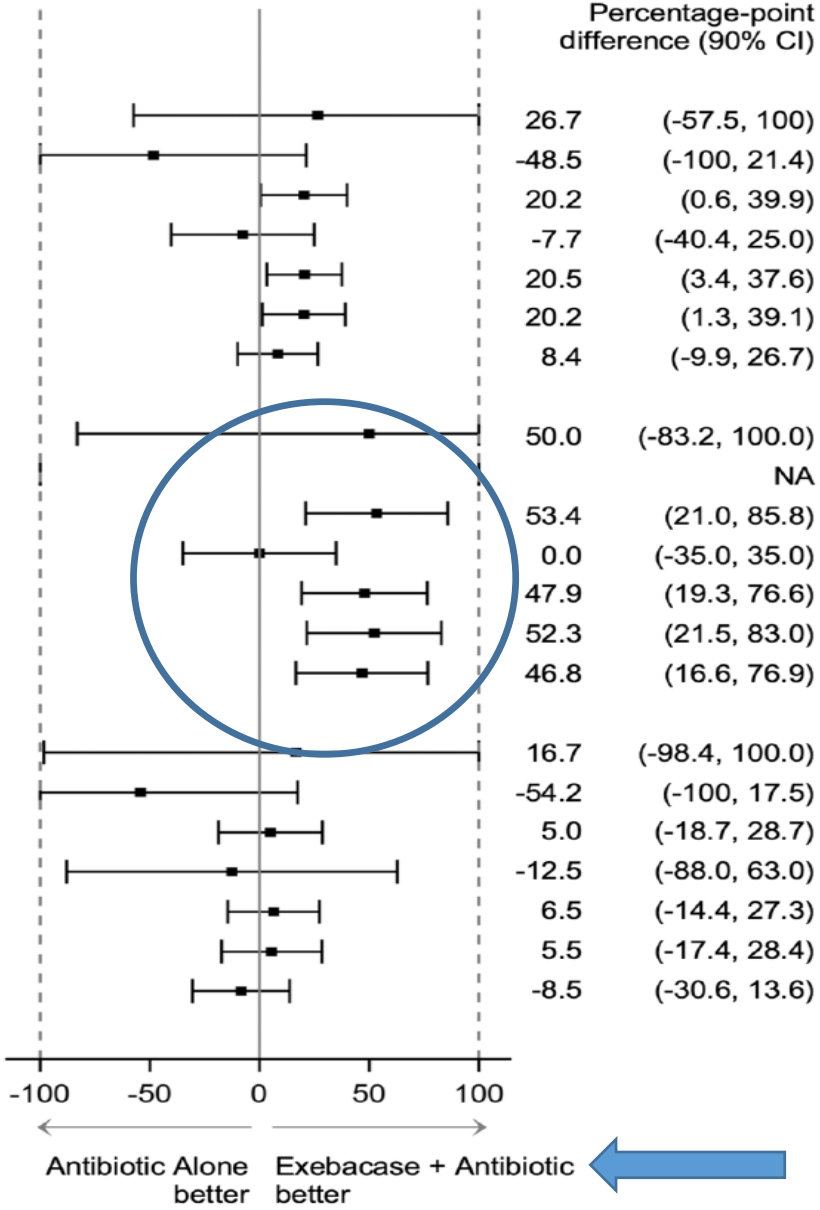
Clinical Trials of Phage Lysins in Staph IE (2)

Fowler et al. *J Clin Invest* July 2020

Clinical Trials of Phage Lysins in Staph IE (3)

Fowler et al. *J Clin Invest* July 2020

Subgroup	Exebacase + Antibiotic Responders/total	(%)	Antibiotic Alone Responders/total	(%)	Percentage-point difference	(90% CI)
Total population						
Endocarditis right-sided	3/5	(60.0)	1/3	(33.3)	26.7	(-57.5, 100)
Endocarditis left-sided	2/11	(18.2)	2/3	(66.7)	-48.5	(-100, 21.4)
BSI complicated	33/42	(78.6)	21/36	(58.3)	20.2	(0.6, 39.9)
BSI uncomplicated	12/13	(92.3)	3/3	(100)	-7.7	(-40.4, 25.0)
BSI/RIE	48/60	(80.0)	25/42	(59.5)	20.5	(3.4, 37.6)
cBSI/RIE	36/47	(76.6)	22/39	(56.4)	20.2	(1.3, 39.1)
cBSI/RIE/LIE	38/58	(65.5)	24/42	(57.1)	8.4	(-9.9, 26.7)
MRSA						
Endocarditis right-sided	1/2	(50.0)	0/1	(0.0)	50.0	(-83.2, 100.0)
Endocarditis left-sided	1/3	(33.3)	0/0	NA		NA
BSI complicated	13/17	(76.5)	3/13	(23/1)	53.4	(21.0, 85.8)
BSI uncomplicated	5/5	(100)	2/2	(100)	0.0	(-35.0, 35.0)
BSI/RIE	19/24	(79.2)	5/16	(31.3)	47.9	(19.3, 76.6)
cBSI/RIE	14/19	(73.7)	3/14	(21.4)	52.3	(21.5, 83.0)
cBSI/RIE/LIE	15/22	(68.2)	3/14	(21.4)	46.8	(16.6, 76.9)
MSSA						
Endocarditis right-sided	2/3	(66.7)	1/2	(50.0)	16.7	(-98.4, 100.0)
Endocarditis left-sided	1/8	(12.5)	2/3	(66.7)	-54.2	(-100, 17.5)
BSI complicated	20/25	(80.0)	18/24	(75.0)	5.0	(-18.7, 28.7)
BSI uncomplicated	7/8	(87.5)	1/1	(100)	-12.5	(-88.0, 63.0)
BSI/RIE	29/36	(80.6)	20/27	(74.1)	6.5	(-14.4, 27.3)
cBSI/RIE	22/28	(78.6)	19/26	(73.1)	5.5	(-17.4, 28.4)
cBSI/RIE/LIE	23/36	(63.9)	21/29	(72.4)	-8.5	(-30.6, 13.6)



Clinical Trials of Phage Lysins in Staph IE (4)
Fowler et al. *J Clin Invest* July 2020

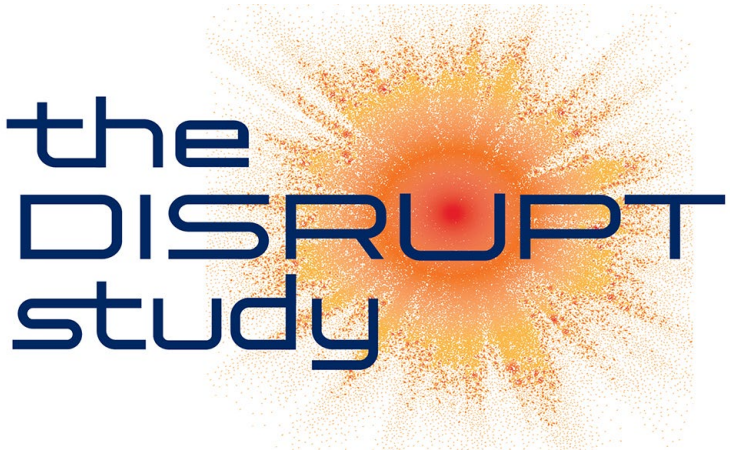
- Limitations:

- 1. Small sample sizes in multiple sub-groups
- 2. cBSI-dominant (22 “pure” IE cases – does that matter?)
- 3. Uneven distributions of IE cases and ‘uncomplicated’ BSI
- 4. Most relevant to MRSA (even though Exebacase has equivalent *in vitro* activities in MSSA vs MRSA).
- 5. Reflects intrinsic efficacy differences of anti-MSSA vs anti-MRSA agents ?
- 6. Sets the stage for an MRSA-focused BSI/IE trial?

Direct Lysis of *Staph Aureus* Resistant Pathogen Trial of Exebacase (DISRUPT) (NCT 04160468)

- Phase 3
- RCT – Estimated enrollment = ~350 patients
- BSI/R-sided IE
- Currently recruiting
- Estimated completion – end of 2022-mid-2023?

Exebacase: First in Class to Enter Phase 3 with FDA "Breakthrough Therapy" Designation

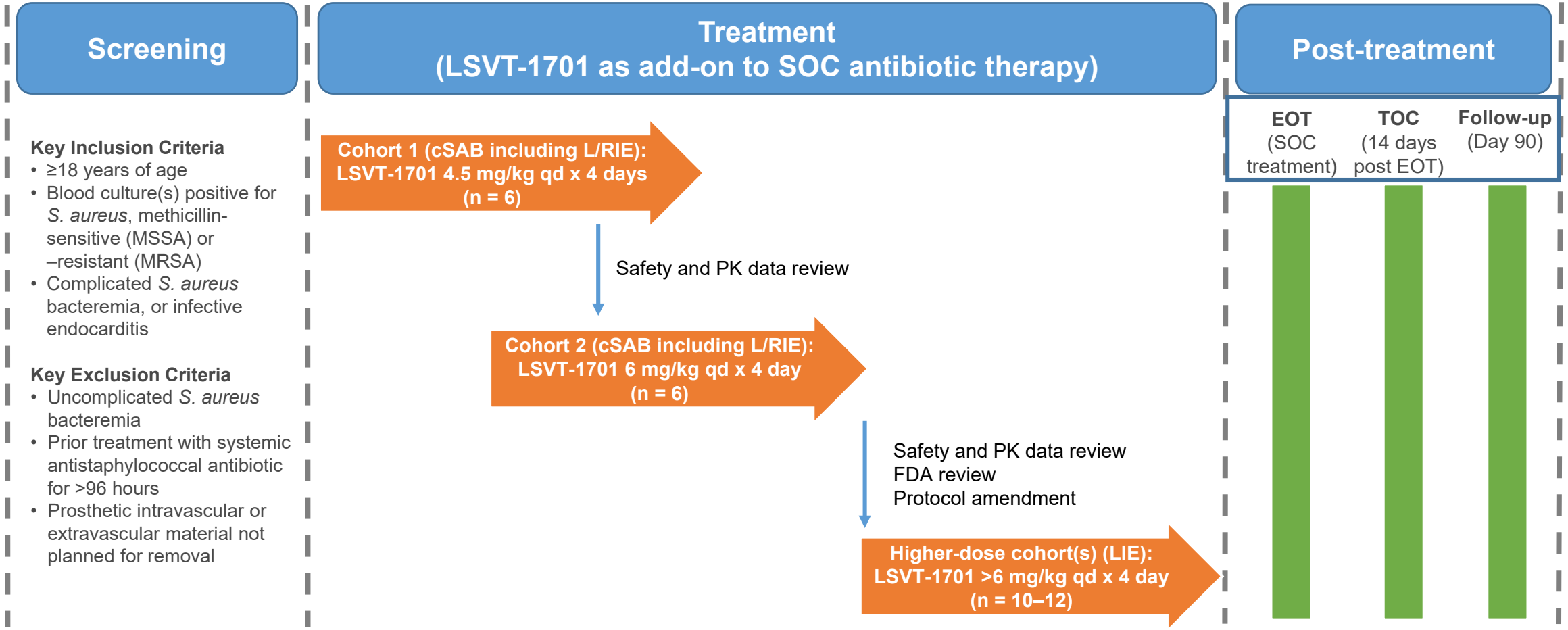


Single, Pivotal Phase 3 Trial –

- **Randomized, double-blind, placebo-controlled**
  - Compares efficacy of single IV dose of Exebacase plus SOCA to SOCA alone
  - Study population includes patients with *S. aureus* (MRSA or MSSA) bacteremia including right-sided endocarditis
  - Number of subjects: ~350 patients - Randomized 2:1 (Exebacase vs. Placebo [SOCA])
- **Primary efficacy endpoint**: Clinical response at Day 14 in patients with **MRSA** bacteremia, including right-sided endocarditis
- **Key secondary endpoints**: Clinical response at Day 14 in All *S. aureus* (MSSA + MRSA) patients; 30 Day 'All Cause Mortality' in MRSA pts

LSVT-1701 (Tonabacase) MAD study - Complicated *Staphylococcus aureus* bacteremia, including left-sided or right-sided infective endocarditis – Phase II

NCT05329168 – June 2022 Launch – 30 + Pts



Primary objective: To evaluate the safety and tolerability of LSVT-1701 as an add-on to SOC antibiotic therapy for the treatment of cSAB, including LIE and RIE
Main secondary objectives: To evaluate the 1) PK of LSVT-1701 and 2) efficacy of LSVT-1701 in the treatment of cSAB, including LIE and RIE

cSAB: complicated *S. aureus* bacteremia; EOT: end of treatment; MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-sensitive *S. aureus*; LIE: left-sided infective endocarditis; RIE: right-sided infective endocarditis; SOC: standard of care; TOC: test of cure.
Clinical response is defined as complete resolution or improvement of attributable signs and symptoms of SAB such that no further antibiotic therapy is necessary, no new signs and symptoms of SAB, no metastatic foci of *S. aureus* infection after Day 7, no further surgery or medical intervention for SAB, and the patient is alive.

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Anti-Staph Phage Lysins - Conclusions and Unresolved Issues

QUESTIONS & COMMENTS??