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Exebacase (Lysin CF-301) Activity Against *Staphylococcus aureus* (*S. aureus*) Isolates from Bacteremic Patients Enrolled in a Phase 2 Study (CF-301-102)

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BACKGROUND

Exebacase (EXE) is a novel, recombinantly-produced lysin (cell wall hydrolase) which is the first member of the Direct Lytic Agent (DLA) family to report Phase 2 (Ph2) data. The Ph2 trial was a randomized, double blind, placebo controlled superiority designed study which evaluated clinical responder rates with EXE used in addition to standard of care (SoC) antibiotics vs. SoC alone in adult patients with *S. aureus* bacteremia including endocarditis. Clinical response at Day 14, determined by an endpoint adjudication committee, was the primary study endpoint. Here, we examined EXE activity by broth microdilution (BMD) against baseline methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) isolates from each participant in the recently completed EXE 'first in-patient' Ph2 study (NCT03163446).

PURPOSE

The objective of this work was to determine the MIC distribution of EXE against Ph2 clinical *S. aureus* isolates for this First in Patient study. The clinical response rate for each EXE MIC value within the MRSA subgroup was also determined.

INTRODUCTION

With the increasing worldwide prevalence of antibiotic resistant bacteria, lysins are a promising novel alternative to small molecule antibiotics. Lysins are recombinantly produced peptidoglycan hydrolases which are rapidly bacteriolytic when applied to target bacteria (see **Fig. 1**). EXE is an anti-staphylococcal lysin that recently completed a Phase 2 clinical study. Hallmark features of CF-301 include a rapid bacteriolytic effect against a range of *S. aureus* isolates, potent anti-biofilm activity, a low propensity for resistance, and synergy with antibiotics.

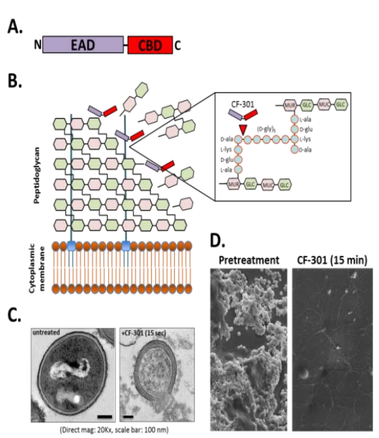

Fig. 1. Characteristics of lysins including EXE. **(A)** Lysins have N-terminal enzymatically active domain (EAD) fused to a C-terminal cell wall binding domain (CBD). **(B)** Lysins rapidly degrade cell wall peptidoglycan to trigger osmotic lysis. The EXE-sensitive bond is indicated. **(C)** Bacteriolytic effect of EXE against *S. aureus* strain MW2. **(D)** Eradication of catheter biofilm by EXE.

METHODS

Patients with complicated bacteremia or endocarditis caused by *S. aureus* were enrolled into Study CF-301-102 at centers in the US, EU, Latin America, Israel, and Russia from 2017 and 2018. The majority of patients recieved appropriate SoC antibacterial therapy (94.4% and 97.8% in the EXE and placebo groups, respectively), defined as receipt of an antibiotic, in the 2 days prior or 2 days after study drug dosing, to which the baseline pathogen was susceptible based on MIC data. Baseline qualifiying isolates from blood cultures of 115 patients were collected prior to administration of exebacase. MICs were determined by broth microdilution in TREKS (ThermoFisher) panels at a central laboratory (ACM Global Laboratories; Rochester, NY) using a nonstandard medium approved for use with EXE AST by the CLSI. The medium is comprised of CAMHB supplemented with horse serum (final concentration of 25%) and dithiothreitol (final concentration of 0.5 mM).

RESULTS

Table 1. Exebacase MICs against *S. aureus* baseline isolates from Ph2 Study CF-301-102

Organism	N	MIC (µg/mL)					MIC_{50}	MIC_{90}
		0.125	0.25	0.5	1	2		
All *S.aureus*	116*	1	13	49	43	10	0.5	1
MSSA	74	1	8	34	26	5	0.5	1
MRSA	42	0	5	15	17	5	1	2

*One patient had both MRSA and MSSA and was counted in both subgroups

Table 2. Clinical Response at Day 14 by Baseline EXE MIC - MRSA

MIC (µg/mL)	Number of patients exhibiting clinical response (%) in the exebacase and placebo groups	
	EXE + SoC	SoC alone
0.12	0	0
0.25	3/3 (100)	0/2 (0)
0.5	9/11 (81.8)	2/4 (50.0)
1.0	6/9 (66.7)	3/8 (37.5)
2.0	1/3 (33.3)	0/2 (0)

- The Ph2 trial demonstrated 42.8% higher clinical responder rates with a single dose of EXE used in addition to SoC vs SoC alone for the treatment of MRSA bacteremia including endocarditis
- EXE MICs of baseline isolates ranged from 0.125 – 2 µg/mL, with $MIC_{50/90}$ of 0.5/1 µg/ml (for MSSA) and MRSA (0.5/2 µg/ml) subgroups
- In the MRSA population, clinical responder rates were higher in the EXE treated group compared to the SoC alone across all EXE MIC values among MRSA isolates (which will be the focus of Ph3 studies)
- No significant differences were observed in response rates at different EXE MICs; further analysis of efficacy at different MICs will be addressed in Ph3 trial with a larger data set

CONCLUSIONS

- Exebacase had low MICs against all baseline *S. aureus* isolates obtained from bacteremic patients enrolled in the Ph2 study
- Favorable clinical responses for EXE (compared to placebo) were seen for MRSA isolates across the entire range of EXE susceptibilities
- Our Ph2 findings suggest that MRSA strains with EXE MICs of ≤2 will be susceptible to EXE, and are in agreement with previously presented exposure target attainment animal studies, PK/PD modeling and preliminary non-clinical breakpoint assessments which indicate that strains with MIC values of ≤2 µg/mL will be susceptible to the Ph2 clinical EXE dose