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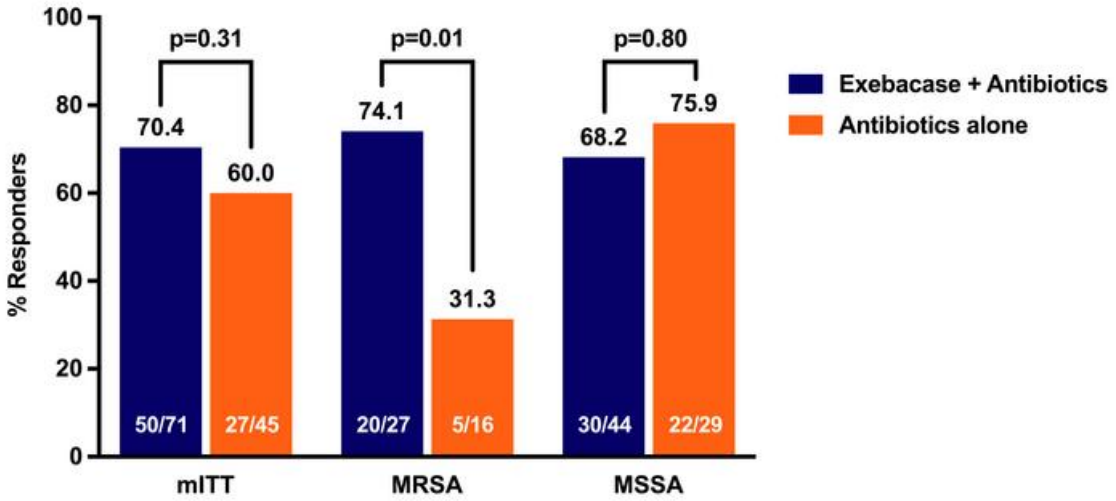
Graphical abstract



Exebacase For Patients with *Staphylococcus aureus* Bloodstream Infection and Endocarditis

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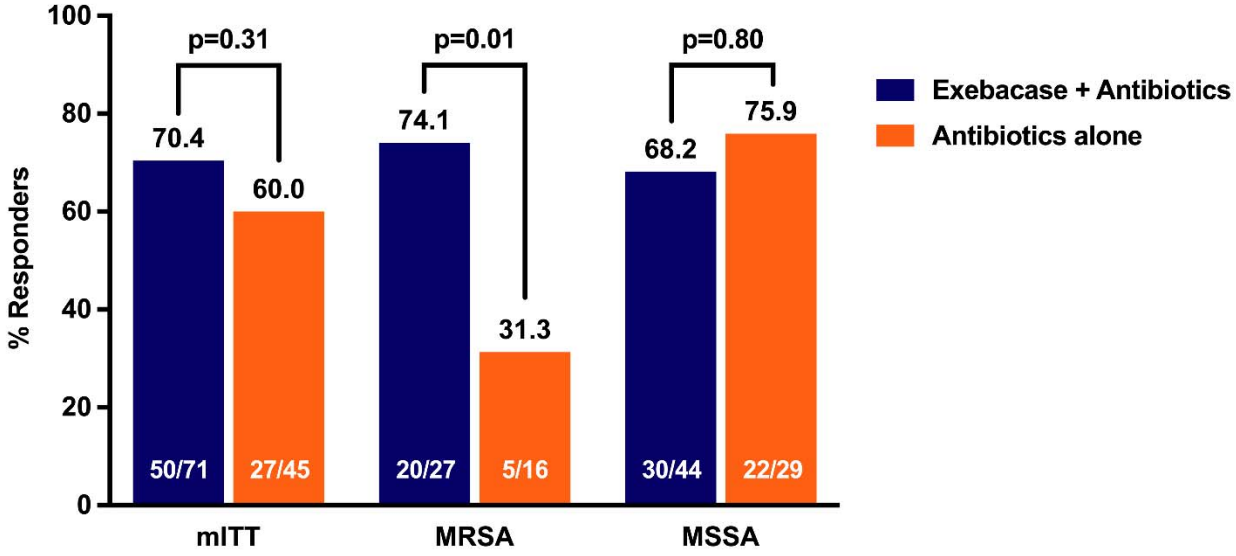
GRAPHICAL ABSTRACT



Abbreviations: mITT= microbiological intent-to-treat; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-sensitive *S. aureus*.

Note: The p-values for the MRSA and MSSA subgroups are ad-hoc p-values.

ABSTRACT

BACKGROUND

Novel therapeutic approaches are critically needed for *Staphylococcus aureus* bloodstream infections (BSI), particularly for methicillin-resistant *S. aureus* (MRSA). Exebacase, a first-in-class antistaphylococcal lysin, is a direct lytic agent that is rapidly bacteriolytic, eradicates biofilms, and synergizes with antibiotics.

METHODS

In this superiority-design study, we randomly assigned 121 patients with *S. aureus* BSI/endocarditis to receive a single dose of exebacase or placebo. All patients received standard-of-care antibiotics. The primary efficacy endpoint was clinical outcome (responder rate) at Day 14.

RESULTS

Clinical responder rates at Day 14 were 70.4% and 60.0% in the exebacase + antibiotics and antibiotics alone groups, respectively (difference=10.4, 90% CI [-6.3, 27.2], p-value=0.31), and were 42.8 percentage points higher in the pre-specified exploratory MRSA subgroup (74.1% vs. 31.3%, difference=42.8, 90% CI [14.3, 71.4], ad hoc p-value=0.01). Rates of adverse events (AEs) were similar in both groups. No AEs of hypersensitivity to exebacase were reported. Thirty-day all-cause mortality rates were 9.7% and 12.8% in the exebacase + antibiotics and antibiotics alone groups, respectively, with a notable difference in MRSA (3.7% vs. 25.0%, difference= –21.3, 90% CI [-45.1, 2.5], ad hoc p-value=0.06). Among MRSA patients in the United States, median length-of-stay was 4-days shorter and 30-day hospital readmission rates were 48 percentage points lower in the exebacase-treated group compared with antibiotics alone.

CONCLUSIONS

This study establishes proof-of-concept for exebacase and direct lytic agents as potential therapeutics and supports conduct of a confirmatory study focused on exebacase to treat MRSA BSI.

TRIAL REGISTRATION: Clinicaltrials.gov NCT03163446

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INTRODUCTION

Complicated *Staphylococcus aureus* (*S. aureus*) bloodstream infections (BSI) cause substantial morbidity and mortality (1), which is highest for methicillin resistant *S. aureus* (MRSA) BSI (2, 3, 4, 5). Mortality rates for patients with *S. aureus* BSI have not changed significantly for decades despite new antibiotics with activity against MRSA (6, 7, 8). Hence, there is an urgent need for novel approaches to improve clinical outcomes for *S. aureus* BSI, particularly MRSA.

Exebacase, an antistaphylococcal lysin, is an entirely new antibacterial treatment modality (9, 10). As a peptidoglycan hydrolase, recombinantly-produced as a purified protein, exebacase results in rapid, pathogen-targeted bacteriolysis, potent biofilm eradication, synergy with antibiotics, low propensity for resistance, and the potential to suppress antibiotic resistance when used together with antibiotics (9, 10, 11, 12). Exebacase represents a first-in-field, first-in-class, non-antibiotic antimicrobial direct lytic agent with the potential to improve clinical outcomes of *S. aureus* BSI. Here, we report the safety and efficacy of exebacase used in addition to standard antibiotic therapy to treat *S. aureus* BSI including endocarditis in a superiority-design, proof-of-concept study.

RESULTS

Trial Population

This randomized, double-blind, placebo-controlled, superiority-design, first-in-patient, proof-of-concept study (clinicaltrials.gov identifier: NCT03163446) was conducted at 42 sites in 11 countries between May 2017 and March 2019. A total of 3729 patients were pre-screened for eligibility, of which 121 patients were randomized (intent-to-treat [ITT] population), 119 patients received study drug (exebacase or placebo) (safety population), and 116 patients had confirmed *S. aureus* BSI and were included in the primary efficacy analysis population (the microbiological intent-to-treat [mITT] population) (Figure 1). The majority of patients were enrolled in the United States (U.S.) (79.3%). Small numbers of patients were enrolled in each of the other 10 countries. The average patient was approximately 56 years of age, white (68.1%), and male (67.2%).

Approximately one-third of patients in both treatment groups had MRSA (Table 1) resulting in 27 and 16 patients in the MRSA subgroup in the exebacase + antibiotics group and the antibiotics alone group, respectively. More than twice as many patients in the exebacase + antibiotics group compared with the antibiotics alone group had left-sided endocarditis (15.5% vs. 6.7%) and uncomplicated BSI (18.3% vs. 6.7%). Renal and cardiovascular comorbidities were also more common in the exebacase + antibiotics group compared to the antibiotics alone group: 56.3% and 37.8% had moderate to severe renal insufficiency, 71.8% and 53.3% had diabetes, and 38.0% and 27.8% had more than one baseline cardiac diagnosis, respectively. Among patients with BSI, the most common source of infection was skin and soft tissue in the exebacase + antibiotics group and intravascular (hemodialysis access or other catheter) in the antibiotics alone group. In the MSSA subgroup, 8 (18.2%) patients in the exebacase + antibiotics group compared with 3 (10.0%) patients in the antibiotics alone group had left-sided endocarditis. There were other clinically important differences between the exebacase + antibiotics and antibiotics alone groups with respect to baseline comorbidities including moderate to severe renal insufficiency (61.4% vs. 40.0%), poorly controlled diabetes (36.4% vs. 16.7%), and hypertension (75.0% vs. 56.7%).

All patients in the mITT population received an antibiotic to which the baseline pathogen was susceptible within 2 days of study drug administration. Vancomycin and beta-lactams were the most frequently used antibiotics through Day 14. The median duration of antibiotic therapy from the start of study drug was the same in both treatment groups (29 days, range: 2 to 181 days and 2 to 91 days in the exebacase + antibiotics and antibiotics alone groups, respectively) (Table 2).

Efficacy Analyses

In the mITT population, 70.4% of the exebacase + antibiotics and 60.0% of the antibiotics alone groups were clinical responders at Day 14 (difference=10.4, 90% CI [-6.3, 27.2], p-value=0.31) (Table 3). In the pre-specified exploratory MRSA subgroup, the clinical responder rate at Day 14 was 42.8 percentage points higher among exebacase-treated patients compared to those who received antibiotics alone (74.1% vs. 31.3%, difference=42.8, 90% CI [14.3, 71.4], ad hoc p-value=0.01). Responder rates in the methicillin-sensitive *S. aureus* (MSSA) subgroup were similar between treatment groups. There was 1 patient in the antibiotics alone group who had both MRSA and MSSA and was counted in each subgroup for the analyses. A sensitivity analysis was completed whereby this patient was excluded from the MRSA and MSSA subgroup analyses. Since this patient was a non-responder, the responder rate in the antibiotics alone group increased slightly, however, the conclusions were unchanged. The exploratory analysis of clinical outcome at Day 14 in the clinically evaluable population is provided in Supplemental Table 1 available online with this article.

The disproportionately high number of left-sided endocarditis patients randomized to exebacase appeared to affect the efficacy analysis due to the inherent lethality of this disease. An ad hoc analysis of patients with BSI/right-sided endocarditis (i.e., excluding left-sided endocarditis) (Figure 2) found 80.0% and 59.5% of patients in the exebacase + antibiotics and antibiotics alone groups, respectively, were clinical responders (difference=20.5, 90% CI [3.4, 37.6], ad hoc p-value=0.03). Results in MRSA patients with BSI/right-sided endocarditis were similar to the overall MRSA population.

The clinical response pattern observed at Day 14 persisted at subsequent timepoints in both the mITT population and MRSA and MSSA subgroups (Table 3). A bar graph showing clinical outcome at Day 7, Day 14, EOT, and TOC is provided in Supplemental Figure 1 available online with this article).

Microbiological response was similar between the exebacase + antibiotics and antibiotics alone groups at Day 7 (83.1% vs. 86.7%) and Day 14 (90.1% vs. 84.4%). In the MRSA subgroup, microbiologic response at Day 14 in the exebacase + antibiotics and antibiotics alone groups was 92.6% vs.75.0%, and in patients with MSSA, 88.6% vs. 90.0%. All patients that were clinical responders at Day 14 had negative blood cultures by Day 14. The exploratory analysis of microbiologic response at Days 7 and 14 in the microbiologically evaluable population is provided in Supplemental Table 2 available online with this article.

Kaplan-Meier curves of time to symptom resolution, time to defervesence, and time to clearance of bacteremia are in Supplemental Figures 2, 3, and 4, respectively, available online with this article.

Safety Analyses

The incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs was similar in both groups (Table 4). No TEAEs of hypersensitivity to exebacase were reported, and no TEAEs resulted in withdrawal of study drug. One serious TEAE, which occurred on Day 30 after exebacase dosing, was considered related to study drug by an investigator. The 30-day all-cause mortality rate was 9.7% (7/72) and 12.8% (6/47) in the exebacase + antibiotics and antibiotics alone groups. In the MRSA subgroup, the 30-day all-cause mortality rate was 3.7% (1/27) in the exebacase + antibiotics group and 25.0% (4/16) in the antibiotics alone group (difference= –21.3, 90% CI [-45.1, 2.5], ad hoc p-value=0.06). Through test-of-cure (TOC), which occurred 28 days after the end-of-treatment with antibiotics (EOT), mortality rates were 19.4% (14/72) and 14.9% (7/47) in the exebacase + antibiotics and antibiotics alone groups, respectively (difference= 4.6, 90% CI [-8.7, 17.8], ad hoc p-value=0.63); a similar trend was observed through Day 180.

Immunogenicity

At baseline, 20.8% and 14.9% of patients had pre-existing exebacase cross-reactive anti-drug antibodies (ADA) in the exebacase + antibiotics and antibiotics alone groups, respectively (Table 5). Clinical responder rates at Day 14 were similar among exebacase patients who were ADA-positive and ADA-negative at baseline (73.3% and 69.6%, respectively), as were TEAE rates (100.0% and 91.2%, respectively). Of patients who were ADA-negative at baseline and had evaluable post-dose ADA samples, 71.2% (37/52) of exebacase-treated patients and 25.0% (8/32) in the antibiotics alone group developed treatment-emergent ADA.

One patient had detectable, low titer exebacase-cross reactive immunoglobulin E (IgE) at baseline, which remained low after dosing with exebacase. Six patients who received exebacase and none who received antibiotics alone developed treatment-emergent IgE, which were of low titer and transient.

Health Resource Utilization

Among U.S. patients with MRSA who were alive at hospital discharge, the median length-of-stay was 6 days in the exebacase + antibiotics group compared with 10 days in the antibiotics alone group (Table 6). All-cause 30-day readmissions occurred in 16.0% and 30.8% of patients in the exebacase + antibiotics and antibiotics alone groups, respectively. Among U.S. patients with MSSA who were alive at hospital discharge, the median length-of-stay was 8 and 7 days in the exebacase + antibiotics and antibiotics alone groups, respectively; all-cause 30-day readmissions occurred in 27.6% and 43.5% of patients in the exebacase + antibiotics and antibiotics alone groups, respectively.

DISCUSSION

Exebacase, a first-in-class direct lytic agent, is an entirely new modality for treatment of serious infections caused by *S. aureus* and a member of a new class of non-antibiotic antimicrobials known as lysins (cell wall hydrolase enzymes), which may represent the post-antibiotic generation of treatments (9, 10).

This first-in-patient, proof-of-concept study tested the utility of exebacase as adjunctive therapy to improve clinical outcomes for *S. aureus* BSI including endocarditis. Since exebacase was added to standard-of-care antibiotics, this study utilized a superiority design uncommon in contemporary antibiotic drug development, which typically compares investigational antibiotic vs. standard antibiotic in a noninferiority design). While a treatment difference of 10 percentage points was observed in the mITT population at Day 14 (70.4% vs. 60.0%), treatment with exebacase was associated with a 42.8 percentage point higher clinical responder rate in the MRSA subgroup at the primary Day 14 efficacy timepoint (74.1% vs. 31.3%). The higher responder rates among MRSA patients that received exebacase were sustained at later time points and are supported by reductions in length-of-stay and readmission rates. Responder rates in the MSSA subgroup were similar between treatment groups. The low responder rate of 31.3% among MRSA patients in the placebo group is consistent with historically worse outcomes with MRSA, compared with MSSA, and allows for the larger treatment difference in patients with MRSA. Based on in vitro microbiologic studies and contemporary surveillance studies (13, 14), which demonstrate similar activity of exebacase against MRSA and MSSA, there is no evidence of inherent underlying biologic differences in the activity of exebacase against MRSA and MSSA. However, while exebacase exhibited no biological differences by itself against MRSA and MRSA, the biological effects of antibiotics used to treat MRSA and MSSA (e.g., vancomycin vs beta-lactam) to which exebacase was added are very different. Therefore, it is possible that the additive effect of exebacase in patients with MRSA may be due to the drugs to which it is added. The differences in

responder rates in the MSSA subgroup may have also been influenced by differences in underlying serious comorbidities and the distribution of left-sided endocarditis between treatment groups.

The results of this study have several key implications. Complicated *S. aureus* BSI are serious, common, and potentially lethal infections (15), and MRSA has been identified as a serious threat by both the Centers for Disease Control and the World Health Organization (16, 17). The introduction of vancomycin, a major advance in the treatment of MRSA bacteremia, was over 60 years ago. Daptomycin, the newest drug developed for *S. aureus* BSI, is over 13 years old and was approved based on noninferiority to older antibiotics, with MRSA clinical success rates of 44.4% for daptomycin and 31.8% for vancomycin (18). Subsequent attempts to develop new antibiotics for *S. aureus* bacteremia have failed (19, 20). The addition of adjunctive agents such as immunotherapeutics (21, 22, 23, 24) or antibiotics (e.g., gentamicin [25], rifampin [26], or beta-lactams [27]) to standard therapy for *S. aureus* or MRSA BSI has generally shown disappointing results in clinical trials with the exception of a recent open-label pilot study of the initial combination of daptomycin and ceftaroline, which showed potentially promising results to be confirmed in a larger randomized clinical trial (28). Thus, the urgent need for effective new treatments for *S. aureus* BSI, and MRSA BSI in particular, remains unaddressed.

Based on the novel properties of lysins which are complimentary to and synergistic with antibiotics (9, 10, 11, 12, 33), and the unmet need for agents to improve clinical outcomes for *S. aureus* BSI/endocarditis associated with conventional antibiotics alone, exebacase is being developed as adjunctive therapy. The current study is the first to show promising improvements in clinical outcomes among patients with *S. aureus* BSI who received adjunctive lysin therapy. This improvement was particularly marked in the pre-specified exploratory MRSA subgroup. Exebacase was generally safe and well tolerated, with adverse events consistent with those expected in critically ill, hospitalized patients with potentially life-threatening *S. aureus* BSI, including endocarditis and/or underlying comorbid conditions. Overall, 30-day all-cause mortality rate was 9.7% in the exebacase-treated group and 12.8% in the antibiotics alone group, with a greater difference in the MRSA subgroup (3.7% vs. 25.0%). These

findings are important considering that 28-day mortality has been used as a standard for assessment of survival in hospitalized patients with serious infections (e.g., hospital-acquired and ventilator-associated bacterial pneumonia [HABP/VABP]) (29, 30), and is an FDA-recommended endpoint in HABP/VABP trials (31). All-cause mortality rates in both groups were higher at the TOC timepoint, which varied widely between patients (up to 180 days after dosing) allowing time for mortality due to medical events unrelated to the infection under study. The TOC all-cause mortality rates of 19.4% and 14.9% in the exebacase + antibiotics and antibiotics alone groups may have been affected by the higher number of comorbidities and patients with left-sided endocarditis in the exebacase-treated group.

Importantly, no hypersensitivity reactions to exebacase were reported, despite the fact that 20% of exebacase-treated patients had baseline exebacase ADA. The pre-existing ADA did not affect efficacy or safety outcomes and exebacase does not appear to be sensitizing for allergic hypersensitivity. The presence of baseline antibodies to exebacase may be explained by recent findings that exposures to *S. aureus* (and likely other pathogens, including streptococci) results in human antibody responses against a range of cell wall proteins, including autolysins (32), which would be expected to share common structural motifs and antigenic domains with exebacase. Prior exposures to staphylococci or streptococci (and the generation of antibodies) may occur during the course of infection, or during carriage of these organisms in microbiome environments.

Among U.S. patients with MRSA, exebacase was associated with lower median length-of-stay and 30-day hospital readmission rates compared with antibiotics alone. This orthogonal analysis further supports the clinical efficacy observed in the MRSA subgroup. While the precise drivers of these reductions in health resource utilization are not known, the hallmark antibacterial actions of exebacase, including rapid bactericidality, eradication of S. *aureus* biofilms, and potent synergy with antibiotics which have been well described in vivo and in vitro (9, 10, 11, 12, 33) may have played a role.

A limitation of the study was the relatively small sample size, especially in the MRSA subset, given this was a first-in-patient, proof-of-concept rather than a confirmatory study. The sample size for the MRSA subset was not pre-specified since the analysis in this population was an exploratory objective of the protocol. Another limitation was the difference in the proportion of patients with left-sided endocarditis and uncomplicated BSI between treatment groups. The baseline difference in left-sided endocarditis may have affected the efficacy and safety analyses, given that these patients have poor outcomes and generally require surgical intervention. The results in the MSSA subset may also be difficult to interpret given differences between treatment groups in clinically important serious underlying comorbidities. In addition, EOT and TOC were not fixed time points, which may affect the interpretation of the efficacy findings at these timepoints. The 30-day mortality rates in this study were lower than those seen in cohort studies (1, 6), but are similar to mortality rates in recent clinical trials of *S. aureus* bacteremia (18, 20, 27). This difference in mortality rates in cohort studies vs. interventional trials reflects the intrinsic difference in the purpose of clinical medicine vs. clinical trials. Because clinical trials primarily seek to evaluate the efficacy of a product, stringent inclusion/exclusion criteria are in place to exclude those patients who are likely to have poor clinical outcome due to factors unrelated to *S. aureus* BSI (e.g., malignancy). Given the unmet medical need to improve the clinical success rates for *S. aureus*/MRSA BSI with antibiotics alone, this study evaluated exebacase used in addition to standard therapy. The efficacy of exebacase as a monotherapy was not evaluated in this study. The potential use of exebacase as monotherapy could be explored, as appropriate, for discrete clinical problems for which standard antibiotic therapy is not available (e.g., resistant pathogens).

In summary, this study establishes proof-of-concept for exebacase and the emerging new class of direct lytic agents as potential therapeutics for BSI caused by MRSA. Moreover, these data support the testing of exebacase in a confirmatory study with a focus on MRSA. Given the consistently poor outcomes of MRSA BSI treated with standard antibiotic therapy and the long list of failed attempts to develop new

treatments, these data suggest that exebacase may be the first tangible opportunity in decades to improve clinical responder rates and reduce mortality for MRSA BSI.

METHODS

Trial Design and Oversight

An independent Data Safety Monitoring Board reviewed unblinded safety and pharmacokinetic data at pre-specified points. Clinical response was assessed by the investigator. An independent, blinded Adjudication Committee adjudicated eligibility, final diagnosis including endocarditis determination, and clinical response. Echocardiograms were adjudicated by a blinded cardiologist at an echocardiography laboratory according to standard methodology (34). *S. aureus* identification and susceptibility were confirmed by a central microbiology laboratory.

ContraFect Corporation, as study Sponsor, designed and conducted the study in collaboration with the principal investigator. ContraFect prepared the statistical analysis plan, conducted the analyses, and interpreted the data in conjunction with the authors. The protocol is included in the supplemental material available online with this article.

Patient Population and Treatment

Eligible patients were at least 18 years of age, met screening criteria, and had Gram-positive cocci in clusters on Gram stain plus positive direct tube coagulase test or blood culture positive for *S. aureus* within 72 hours before randomization. Echocardiography was performed within 3 days of randomization (35). Removable sources of infection (e.g., intravascular line, abscess, dialysis graft) were removed or debrided within 72 hours after randomization. All patients received antibiotics selected by the investigator according to the protocol consisting of semisynthetic penicillins or first-generation cephalosporins for MSSA and vancomycin or daptomycin for MRSA. Patients were randomly assigned in a 3:2 ratio using a blocked randomization scheme to receive a single 2-hour intravenous infusion of blinded study drug (exebacase or placebo). A 3:2 randomization ratio was used so as to expose a larger proportion of patients to exebacase compared to placebo, but also maximize the sample size in the placebo group. Exebacase was dosed at 0.25 mg/kg based on target attainment studies in animals and Phase 1 data in humans. While the study was ongoing, review of PK data by the Data Safety Monitoring

Board resulted in dose adjustment to 0.12 mg/kg for patients with creatinine clearance <60 mL/min and/or age >50.

Analysis Population, Endpoints, and Assessments

The ITT population included all randomized patients. The safety population included all patients who received study drug. The primary efficacy analysis population, mITT, included all patients with confirmed *S. aureus* BSI who received study drug.

Patient assessments occurred at Day 7, Day 14, EOT, and TOC 28 days after EOT, with long-term follow-up of immunogenicity and safety at Day 180 after study drug dosing.

The primary objectives were to describe safety and tolerability and estimate clinical outcome at Day 14 of exebacase + antibiotics compared with antibiotics alone. Day 14 was selected as the primary efficacy endpoint because it was hypothesized that exebacase's novel, rapid mechanism of action and hallmark properties (9, 10, 11, 12, 33) would lead to a more rapid resolution of clinical signs and symptoms of infection. The Day 14 timepoint allowed for evaluation of the clinical effect of exebacase in a superiority-design study with less likelihood of confounding by adverse medical occurrences unrelated to the disease under study which may occur at later timepoints.

Key secondary and exploratory objectives were to estimate clinical outcome at Day 7, EOT, and TOC, estimate microbiologic outcome at Days 7 and 14, describe clinical outcomes in patients with MRSA and by diagnosis, describe post-dose immunological response to exebacase, and explore health resource utilization. Uncomplicated or complicated BSI and right- or left-sided endocarditis were mutually exclusive diagnoses for the analyses. Clinical response was defined as survival with improvement or resolution of attributable signs and symptoms, and without new signs or symptoms, new foci of infection, change in antibiotics due to non-response, complications of *S. aureus*, or further surgery or medical intervention to treat *S. aureus*. Microbiological response was defined as two consecutive blood cultures collected on different days yielding no *S. aureus* growth.

Safety assessments included adverse events (AEs), vital signs, electrocardiograms, and clinical laboratory tests. Treatment emergent AEs (TEAEs) were those with an onset or worsening of severity that occurred at or after administration of study drug through TOC.

Statistics

The study was designed to provide proof-of-concept and an initial assessment of efficacy and was not considered a confirmatory trial. The sample size of approximately 70 and 45 patients in the exebacase + antibiotics and antibiotics alone groups, respectively, provided at least 80% power to detect a treatment difference of 25 percentage points in clinical response at Day 14, based on expected clinical responder rates of 60% in the antibiotics alone group and 85% in the exebacase + antibiotics group.

Clinical outcome at Day 14, as assessed by the Adjudication Committee, was the primary efficacy variable. For the primary analysis, once a patient was assessed as a clinical non-responder (i.e., failure) due to death, new metastatic foci, complications or surgery due to *S. aureus*, or change in antibiotics due to non-response, the patient was a clinical non-responder for all subsequent visits through TOC. The clinical responder rates at Day 14 were compared between treatment groups using Fisher's exact test. Statistical significance was based on a two-sided alpha level of 0.05. No adjustment was made for multiple comparisons as confirmatory inferential analyses were not conducted for secondary outcomes or subgroup analyses of clinical response at Day 14 (statistical comparisons were an ad hoc analysis). Two-sided 90% confidence intervals for the difference in outcome rates between treatment groups were calculated using a continuity corrected Z-statistic.

Study Approvals

This trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The institutional review board (IRB) for each site approved the protocol, and written informed consent was obtained for all patients. The central IRB was Western Institutional Review Board (Puyallup, WA, U.S.). A list of the IRB for each site is provided Supplemental Table 3 available online with this article.

Author Contributions

VGF, CC, AFD, JLD, and RS contributed to the design of the clinical study. AFD performed the statistical analysis. VGF, CC, AD, JLD, RS, and RP contributed to data interpretation. VGF was the principal investigator for the study. LJP, AB, DE, GJM, and MER were investigators and enrolled patients into the study. RW, GRC, and MZ were adjudicators for the study. PSD interpreted echocardiograms. JLD was responsible for writing the manuscript. All authors reviewed and edited the manuscript.

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REFERENCES

1. Fowler VG, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Arch Intern Med*. 2003;163:2066–2072.

2. Melzer M, Eykyn SJ, Gransden WR, Chinn GS. Is methicillin-resistant *Staphylococcus aureus* more virulent than methicillin-susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and bacteremia. *Clin Infect Dis*. 2003;37(11):1453–1460.

3. Cosgrove S, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin- susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis*. 2003;36(1):53–59.

4. deKraker MEA, Wolkewitz M, Davey PG, Grundman H. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant *Staphylococcus aureus* bloodstream infections. *Antimicrob Agents Chemother*. 2011b;55(4):1598–1605

5. World Health Organization. Antimicrobial resistance: global report on surveillance. https://www.who.int/drugresistance/documents/surveillancereport/en/ Updated April 2014. Accessed January 03, 2020.

6. Souli M, et al. Changing characteristics of *Staphylococcus aureus* bacteremia: results from a 21-year, prospective, longitudinal study. *Clin Infect Dis*. 2019;69(11):1868–1877.

7. Tong SYC, Davis JS, Eichenberger E, Holland TL, Fowler VG. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev*. 2015;28:603–661.

8. Turner NA, et al. Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research. *Nat Rev Microbiol*. 2019;17:203–218.

9. Schuch R, Khan BK, Raz A, Rotolo JA, Wittekind M. Bacteriophage lysin CF-301, a potent antistaphylococcal biofilm agent. *Antimicrob Agents Chemother*. 2017;61(7):e02666–16.

10. Indiani C, et al. The antistaphylococcal lysin, CF-301, activates key host factors in human blood to potentiate methicillin-resistant Staphylococcus aureus bacteriolysis. *Antimicrob Agents Chemother*. 2019;63(4):e02291–18.

11. Schuch R, et al. Combination therapy with lysin CF-301 and antibiotic is superior to antibiotic alone for treating methicillin-resistant Staphylococcus aureus-induced murine bacteremia. *J of Infect Dis*. 2014;209:1469–78.

12. Watson A, Sauve K, Cassino C, Schuch R. Exebacase demonstrates in vitro synergy with a broad range of antibiotics against both methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2020;64:e01885–19.

13. Watson A, Oh JT, Sauve K, Bradford PA, Cassino C, Schuch R. Antimicrobial activity of exebacase (lysin CF-301) against the most common causes of infective endocarditis. *Antimicrob Agents Chemother.* 2019;63(10):e01078–19.

14. Traczewski M, Oh J, Cassino C, Schuch R. In vitro activity of exebacase (CF-301) against clinical *Staphylococcus aureus* surveillance isolates from the United States, Europe, and Latin America, 2015-2017. Diagn *Microbiol Infect Dis*. 2019;95(4):114879.

15. Kourtis AP, et al. Vital signs: epidemiology and recent trends in methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* blood stream infections. *MMWR Morb Mortal Wkly Rep*. 2019;68:214–219.

16. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Updated 2019. Accessed January 3, 2020.

17. World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua%EF%80%BD1. Updated February 27, 2017. Accessed January 3, 2020.

18. Fowler VG, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355:653–665.

19. A Phase 3 Telavancin *Staphylococcus Aureus* (*S. Aureus*) Bacteremia Trial. ClinicalTrials.gov Identifier: NCT02208063. https://clinicaltrials.gov/ct2/show/NCT02208063?term=vibativ&cond=bacteremia&rank=1. Updated January 15, 2019. Accessed January 3, 2020.

20. Holland TL, et al. Considerations for clinical trials of *S. aureus* bloodstream infections in adults. *Clin Infect Dis*. 2019;68(5):865–872.

21. Weems JJ, et al. Phase II, randomized, double-blind, multicenter study comparing the safety and pharmacokinetics of tefibazumab to placebo for treatment of *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2006;50(8):2751–2755.

22. Rupp ME, et al. Phase II, randomized, multicenter, double-blind, placebo-controlled trial of a polyclonal anti-*Staphylococcus aureus* capsular polysaccharide immune globulin in treatment of *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2007;51(12):4249–4254.

23. Weisman LE, Thackray HM, Steinhorn RH. A randomized study of a monoclonal antibody (pagibaximab) to prevent staphylococcal sepsis. *Pediatrics.* 2011;128(2):271–279.

24. Otto M. Novel targeted immunotherapy approaches for staphylococcal infection. *Expert Opin Biol Ther*. 2010;10(7):1049–1059.

25. Cosgrove SE, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis*. 2009;199:201–208.

26. Thwaites GE, et al., Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391:668–678.

27. Tong SYC, Lye DC, Yahav D. Effect of vancomycin or daptomycin with vs without an antistaphylococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia. A Randomized Clinical Trial. *JAMA*. 2020;323(6):527–537.

28. Geriak M, et al. Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2019;63(5):e02483–18.

29. Spellberg B, Talbot G. Recommended design features of future clinical trials of antibacterial agents for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis*. 2010;51(Suppl 1):S150–S170.

30. Weiss E, Essaied W, Adrie C, Zahar JR, Timsit JF. Treatment of severe hospital-acquired and ventilator-associated pneumonia: a systematic review of inclusion and judgment criteria used in randomized controlled trials. *Crit Care*. 2017;21:162.

31. Food and Drug Administration (FDA). Guidance for Industry. Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia: developing drugs for treatment. Draft guidance. https://www.fda.gov/media/79516/download. Updated May 2014. Accessed January 3, 2020.

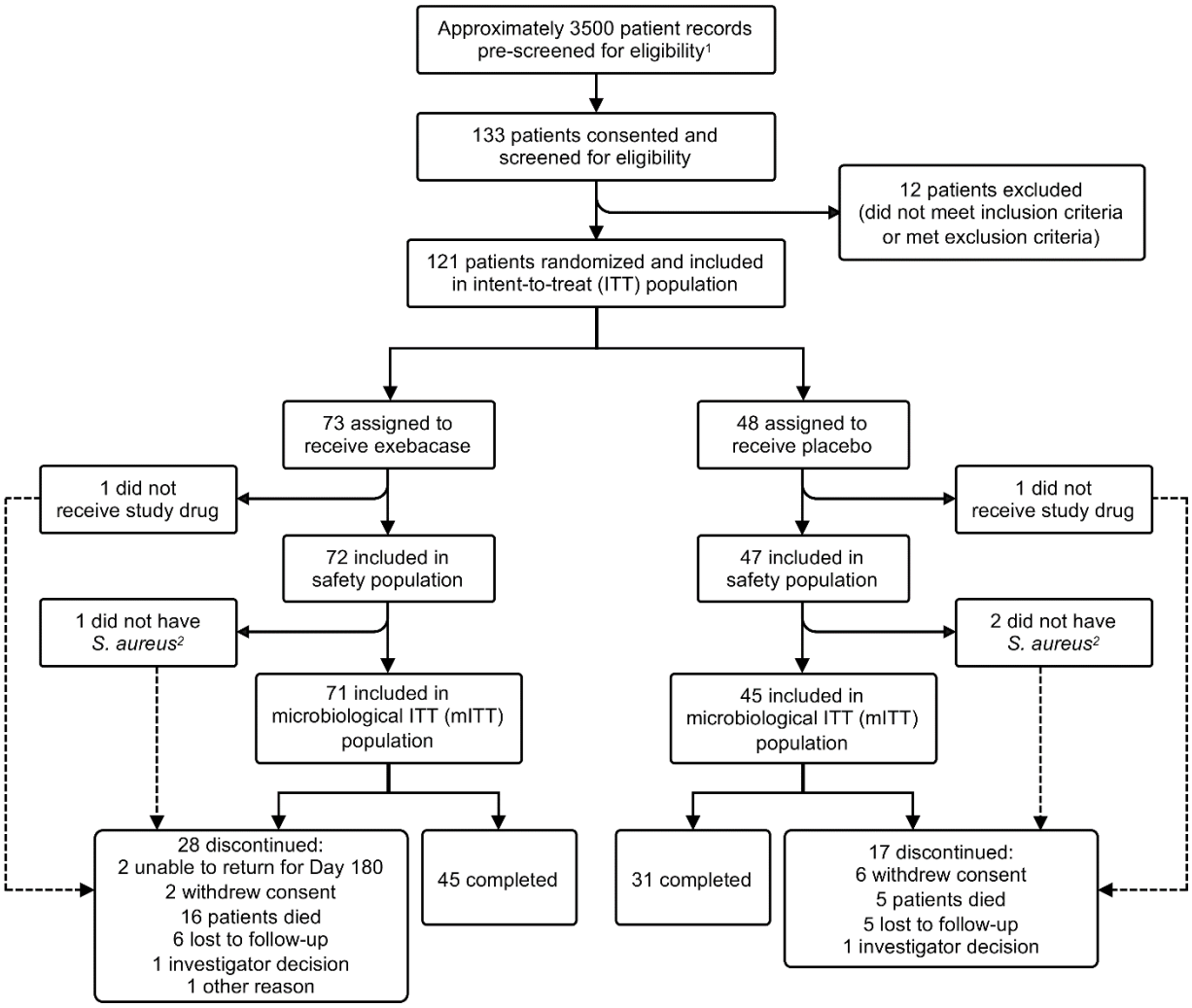
32. Pastrana FR, et al. Human antibody responses against non-covalently cell wall-bound *Staphylococcus aureus* proteins. *Sci Rep*. 2018;8:3234.

33. Oh J, Cassino C, Schuch R. Postantibiotic and sub-MIC effects of exebacase (lysin CF-301) enhance antimicrobial activity against *Staphylococcus aureus*. *Antimicrob Agents and Chemother*. 2019;63(6):e02616–18.

34. Douglas PS, et al. Echocardiographic imaging in clinical trials: American Society of Echocardiography standards for echocardiography core laboratories: endorsed by the American College of Cardiology Foundation. *J Am Soc Echocardiogr*. 2009;22:755–766.

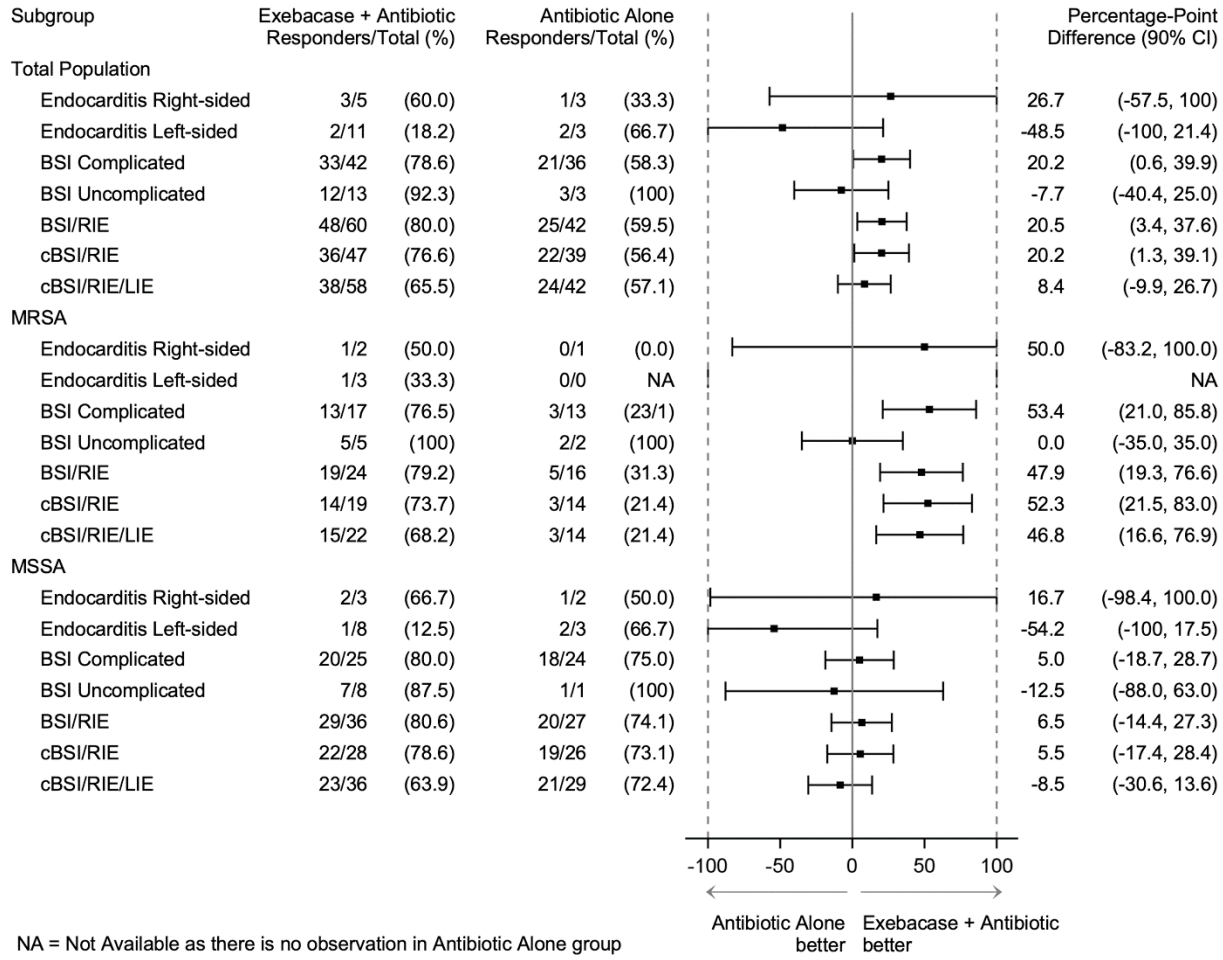
35. Baddour LM, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications, a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.

Figure 1: Patient Disposition



1 The reasons pre-screened patients were deemed to be ineligible are summarized in Supplemental Table 4.
2 The local laboratory identified Gram-positive cocci in clusters on Gram stain plus positive direct tube coagulase test and the patients were enrolled; however, the central laboratory subsequently determined that the isolates were *S. epidermidis*.

Figure 2: Forest Plot of Clinical Responders by Diagnosis



Abbreviations: BSI=bloodstream infection; cBSI=complicated bloodstream infection; CI=confidence interval; LIE=left-sided endocarditis; RIE=right-sided endocarditis.

Table 1. Baseline Disease Characteristics and Risk Factors/Comorbidities (mITT Population)

	Total Population		MRSA[1]		MSSA[1]	
	Exebacase + Antibiotics (N=71) n (%)	Antibiotics Alone (N=45) n (%)	Exebacase + Antibiotics (N=27) n (%)	Antibiotics Alone (N=16) n (%)	Exebacase + Antibiotics (N=44) n (%)	Antibiotics Alone (N=30) n (%)
Disease Characteristics						
Final Diagnosis by Adjudication Committee						
Endocarditis	16 (22.5)	6 (13.3)	5 (18.5)	1 (6.3)	11 (25.0)	5 (16.7)
Right-sided endocarditis	5 (7.0)	3 (6.7)	2 (7.4)	1 (6.3)	3 (6.8)	2 (6.7)
Left-sided endocarditis	11 (15.5)	3 (6.7)	3 (11.1)	0	8 (18.2)	3 (10.0)
BSI	55 (77.5)	39 (86.7)	22 (81.5)	15 (93.8)	33 (75.0)	25 (83.3)
Complicated BSI	42 (59.2)	36 (80.0)	17 (63.0)	13 (81.3)	25 (56.8)	24 (80.0)
Uncomplicated BSI	13 (18.3)	3 (6.7)	5 (18.5)	2 (12.5)	8 (18.2)	1 (3.3)
Primary source of infection in BSI patients[2]						
Unknown	11 (20.0)	12 (30.8)	2 (9.1)	7 (46.7)	9 (27.3)	6 (24.0)
Skin and soft tissue	18 (32.7)	7 (17.9)	7 (31.8)	3 (20.0)	11 (33.3)	4 (16.0)
Intra-vascular	15 (27.3)	13 (33.3)	7 (31.8)	4 (26.7)	8 (24.2)	9 (36.0)
Other	11 (20.0)	7 (17.9)	6 (27.3)	1 (6.7)	5 (15.2)	6 (24.0)
Risk Factors/Comorbidities						
Moderate/Severe renal impairment (<60 mL/min)[3]	40 (56.3)	17 (37.8)	13 (48.1)	6 (37.5)	27 (61.4)	12 (40.0)
Hemodialysis	21 (29.6)	8 (17.8)	9 (33.3)	1 (6.3)	12 (27.3)	7 (23.3)
Hyperglycemia/Diabetes[4]	51 (71.8)	24 (53.3)	18 (66.7)	11 (68.8)	33 (75.0)	14 (46.7)
Poorly controlled diabetes[5]	20 (28.2)	8 (17.8)	4 (14.8)	3 (18.8)	16 (36.4)	5 (16.7)
Controlled diabetes	31 (43.7)	16 (35.6)	14 (51.9)	8 (50.0)	17 (38.6)	9 (30.0)

	Total Population		MRSA[1]		MSSA[1]	
	Exebacase + Antibiotics (N=71) n (%)	Antibiotics Alone (N=45) n (%)	Exebacase + Antibiotics (N=27) n (%)	Antibiotics Alone (N=16) n (%)	Exebacase + Antibiotics (N=44) n (%)	Antibiotics Alone (N=30) n (%)
Recent injection drug use	6/62 (9.7)	5/39 (12.8)	4/23 (17.4)	2/13 (15.4)	2/39 (5.1)	3/27 (11.1)
Preexisting valvular heart disease	1/71 (1.4)	3/45 (6.7)	0	0	1/44 (2.3)	3/30 (10.0)
Surgery within previous 30 days	11/71 (15.5)	5/45 (11.1)	7/27 (25.9)	1/16 (6.3)	4/44 (9.1)	4/30 (13.3)
Extravascular foreign material	9/71 (12.7)	9/45 (20.0)	3/27 (22.1)	4/16 (25.0)	6/44 (13.6)	5/30 (16.7)
AIDS[6]	2/62 (3.2)	1/39 (2.6)	2/23 (8.7)	0	0	1/27 (3.7)
SIRS[6]	45/62 (72.6)	27/39 (69.2)	17/23 (73.9)	11/13 (84.6)	28/39 (71.8)	16/27 (59.3)
Cardiovascular[4]						
Hypertension	53 (74.7)	23 (51.1)	20 (74.1)	7 (43.8)	33 (75.0)	17 (56.7)
Any cardiac history[7]	41 (57.8)	26 (57.8)	14 (51.9)	10 (62.5)	27 (61.4)	17 (56.7)
More than one cardiac diagnosis[8]	27 (38.0)	17 (27.8)	9 (33.3)	6 (37.5)	18 (40.9)	12 (40.0)
Cardiac arrhythmias	23 (32.4)	16 (35.6)	6 (22.2)	7 (43.8)	17 (38.6)	10 (33.3)
Cardiac failure	23 (32.4)	12 (26.7)	8 (29.6)	5 (31.3)	15 (34.1)	8 (26.7)
Cardiomyopathy	29 (40.9)	17 (37.8)	8 (29.6)	7 (43.8)	21 (47.7)	11 (36.7)
Ischemic cardiac disease	14 (19.7)	10 (22.2)	4 (14.8)	3 (18.8)	10 (22.7)	8 (26.7)
Torsade de pointes	6 (8.5)	1 (2.2)	1 (3.7)	0	5 (11.4)	1 (3.3)
Dyslipidemia	24 (33.8)	14 (31.1)	10 (37.0)	6 (37.5)	14 (31.8)	8 (26.7)

Abbreviations: BSI=bloodstream infection.

1. One patient in the antibiotics alone group had both MRSA and MSSA and was counted in both subgroups.

2. Determined only for patients with BSI.

3. Creatinine clearance missing for 2 patients in the exebacase + antibiotics group and 1 patient in the antibiotics alone group.

4. Comorbidities are determined from medical history and grouped based on standardized MedDRA queries.

5. Poorly controlled diabetes as reported by the investigators.

6. Risk factor not included in protocol amendment #4.

7. Includes any medical history of cardiac arrhythmias, cardiac failure, cardiomyopathy, ischemic cardiac disease and torsade de pointes.

8. Defined as more than one cardiac medical history term.

Table 2. Standard-of-Care Antibiotics Received (mITT Population)

	Total Population		MRSA[1]		MSSA[1]	
	Exebacase + Antibiotics (N=71) n (%)	Antibiotics Alone (N=45) n (%)	Exebacase + Antibiotics (N=27) n (%)	Antibiotics Alone (N=16) n (%)	Exebacase + Antibiotics (N=44) n (%)	Antibiotics Alone (N=30) n (%)
Standard-of-Care Antibiotic Exposure Through Day 14[2]						
Daptomycin	5 (11.1)	5 (7.0)	5 (18.5)	3 (18.8)	0	3 (10.0)
Vancomycin	24 (33.8)	17 (37.8)	21 (77.8)	13 (81.3)	3 (6.8)	4 (13.3)
Beta-lactam antibiotics	42 (59.2)	23 (51.1)	1 (3.7)	0	41 (93.2)	23 (76.7)
Total Duration of Standard-of-Care Antibiotics (Days)[3]						
Mean (SD)	36.0 (24.88)	32.7 (17.07)	40.2 (33.38)	33.4 (17.84)	33.5 (18.16)	32.9 (17.38)
Median	31.0	30.0	31.0	35.0	30.5	30.0
Minimum, maximum	5, 184	4, 94	7, 184	2, 59	5, 91	4, 94
Duration of Standard-of-Care Antibiotics from Start of Study Drug (Days)[4]						
Mean (SD)	33.3 (24.92)	30.5 (17.01)	36.6 (33.62)	31.3 (17.98)	31.5 (18.20)	30.8 (17.16)
Median	29.0	29.0	29.0	32.5	29.5	28.5
Minimum, maximum	2, 181	2, 91	4, 181	2, 59	2, 88	3, 91

Abbreviations: BSI=bloodstream infection.

1. One patient in the antibiotics alone group had both MRSA and MSSA and was counted in both subgroups.

2. Defined as the standard-of-care antibiotic received for the majority of the time from study drug administration through Day 14.

3. Number of days from first antibiotic dose to last antibiotic dose, regardless of any changes in antibiotic agent and/or interruptions.

4. Number of days of antibiotic from start of study drug to last antibiotic dose, regardless of any changes in antibiotic agent and/or interruptions.

Table 3: Clinical Outcome Throughout the Study Assessed by Adjudication Committee by MRSA and MSSA Subgroup (mITT Population)

	Total Population		MRSA[1]		MSSA[1]	
	Exebacase + Antibiotics (N=71) n (%)	Antibiotics Alone (N=45) n (%)	Exebacase + Antibiotics (N=27) n (%)	Antibiotics Alone (N=16) n (%)	Exebacase + Antibiotics (N=44) n (%)	Antibiotics Alone (N=30) n (%)
Day 14 (Primary Outcome)						
Responder[2]	50 (70.4)	27 (60.0)	20 (74.1)	5 (31.3)	30 (68.2)	22 (73.3)
Difference (90% CI)[3]	10.4 [-6.3, 27.2]		42.8 [14.3, 71.4]		-5.2 [-25.6, 15.3]	
p-value[4]	0.31		0.01		0.80	
Non-response	18 (25.4)	13 (28.9)	4 (14.8)	8 (50.0)	14 (31.8)	6 (20.0)
Indeterminate	3 (4.2)	5 (11.1)	3 (11.1)	3 (18.8)	0	2 (6.7)
Secondary Outcomes						
Day 7						
Responder[2]	51 (71.8)	31 (68.9)	18 (66.7)	7 (43.8)	33 (75.0)	25 (83.3)
Non-response	17 (23.9)	11 (24.4)	7 (25.9)	8 (50.0)	10 (22.7)	2 (10.0)
Indeterminate	3 (4.2)	3 (6.7)	2 (7.4)	1 (6.3)	1 (2.3)	2 (6.7)
EOT						
Responder	44 (62.0)	28 (62.2)	14 (51.9)	7 (43.8)	30 (68.2)	21 (70.0)
Non-response	22 (31.0)	13 (28.9)	8 (29.6)	8 (50.0)	14 (31.8)	6 (20.0)
Indeterminate	5 (7.0)	4 (8.9)	5 (18.5)	1 (6.3)	0	3 (10.0)
TOC						
Responder	39 (54.9)	24 (53.3)	13 (48.1)	5 (31.3)	26 (59.1)	19 (63.3)
Non-response	25 (35.2)	15 (33.3)	8 (29.6)	9 (56.3)	17 (38.6)	7 (23.3)
Indeterminate	7 (9.9)	6 (13.3)	6 (22.2)	2 (12.5)	1 (2.3)	4 913.3)

Abbreviations: CI=confidence interval; EOT=end-of-treatment with antibiotics; TOC=test-of-cure.

1. One patient in the antibiotics alone group had both MRSA and MSSA and was counted in both subgroups.

2. Responder=clinical outcome of improvement or response.

3. CI for the difference in percentage improvement/response between exebacase + antibiotics and antibiotics alone groups calculated using a continuity corrected Z-statistic.

4. P-value is based on Fisher's exact test.

Table 4: Overview of Adverse Events (Safety Population)

	Exebacase + Antibiotics (N=72) n (%)	Antibiotics Alone (N=47) n (%)
Number of patients with:		
TEAE through Day 7	48 (66.7)	30 (63.8)
TEAE through TOC	64 (88.9)	40 (85.1)
Events occurring in ≥8% through TOC in either treatment group		
Urinary tract infection	8 (11.1)	6 (12.8)
Constipation	9 (12.5)	5 (10.6)
Diarrhea	8 (11.1)	3 (6.4)
Headache	7 (9.7)	4 (8.5)
Anemia	6 (8.3)	4 (8.5)
Cardiac murmur	6 (8.3)	1 (2.1)
Edema peripheral	6 (8.3)	4 (8.5)
Nausea	6 (8.3)	3 (6.4)
Death NOS	1 (1.4)	4 (8.5)
Abdominal pain	0	5 (10.6)
Serious TEAE through TOC	34 (47.2)	23 (48.9)
Serious TEAE through Day 180	45 (62.5)	28 (59.6)
TEAE related to study drug	8 (11.1)	4 (8.5)
Serious TEAE related to study drug	1 (1.4)	0
TEAE leading to study drug discontinuation/withdrawal	0	0
TEAE of hypersensitivity to exebacase	0	NA
Death through Day 30	7 (9.7)	6 (12.8)

	Exebacase + Antibiotics (N=72) n (%)	Antibiotics Alone (N=47) n (%)
Death through TOC[1]	14 (19.4)	7 (14.9)
Death through Day 180	17 (23.6)	9 (19.1)

Abbreviations: TEAE=treatment-emergent adverse event; TOC=test-of-cure; NA=not applicable; NOS=not otherwise specified.

Note: Denominator is all patients in the safety population within each treatment group.

1. All deaths through TOC occurred prior to Day 60, so this represents Day 60 mortality.

Table 5: Immunogenicity: Treatment-Emergent ADA and IgE (Safety Population)

Parameter	CF-301 (N=72) n (%)	Placebo (N=47) n (%)
CF-301 ADA-positive at baseline	15/72 (20.8%)	7/47 (14.9)
CF-301 ADA-negative at baseline	57/72 (79.2)	40/47 (85.1)
CF-301 ADA-negative at baseline and with NO post-dose sample	5	8
CF-301 ADA-negative at baseline and with at least 1 post-dose sample	52	32
No treatment-emergent ADA	15 (28.8)	24 (75.0)
Treatment-emergent positive ADA	37 (71.2)	8 (25.0)
Persistence[1]	15 (28.8)	3 (9.4)
Transient	3 (5.8)	4 (12.5)
Indeterminate (no Day 180 sample)	19 (36.5)	1 (3.1)
IgE-positive at baseline[2]	1/72 (1.4)	0/46 (0)
IgE-negative at baseline[2]	71/72 (98.6)	46/46 (100)
IgE-negative at baseline and with NO post-dose sample	6	9
IgE-negative at baseline and with at least 1 post-dose sample	65	37
No treatment-emergent IgE	56 (86.1)	36 (97.3)
Treatment-emergent IgE	9 (13.9)	1 (2.7)
Persistence (positive to Day 180)	3 (4.6)	0
Transient (negative result after positive result)	3 (4.6)	1 (2.7)
Indeterminate (no result after single positive result)	3 (4.6)	0

Abbreviations: ADA=antidrug antibody; IgE=immunoglobulin E.

Notes: Percentages are based on the number of patients with negative baseline and at least 1 post-baseline sample.

Treatment-emergent ADA/IgE was defined as negative ADA/IgE at baseline and emergence of positive ADA/IgE after dosing.

1. One patient had treatment-emergent ADA that emerged on Day 65 and persisted through Day 187. One patient had treatment-emergent ADA that emerged on Day 62 and persisted through Day 176.

2. One patient in the placebo group was missing the baseline IgE sample.

Table 6: Health Resource Utilization in US Patients (mITT Population)

	All US Patients		MRSA[1]		MSSA[1]	
	Exebacase + Antibiotics (N=57) n (%)	Antibiotics Alone (N=37) n (%)	Exebacase + Antibiotics (N=26) n (%)	Antibiotics Alone (N=15) n (%)	Exebacase + Antibiotics (N=31) n (%)	Antibiotics Alone (N=23) n (%)
In-hospital mortality	3 (5.3)	2 (5.4)	1 (3.9)	2 (13.3)	2 (6.5)	0
Patients discharged alive	54	35	25	13	29	23
Number of hospital days from dose of study drug to hospital discharge						
n	54	34	25	13	29	22
Median	7.0	7.0	6.0	10.0	8.0	7.0
Minimum, maximum	2, 69	2, 51	2, 69	5, 51	3, 66	2, 46
30-day all-cause readmission[2]	12 (22.2)	13 (37.1)	4 (16.0)	4 (30.8)	8 (27.6)	10 (43.5)
30-day *S. aureus* readmission[2]	3 (5.6)	2 (5.7)	2 (8.0)	2 (15.4)	1 (3.4)	0

1. One patient in the antibiotics alone group had both MRSA and MSSA and was counted in both subgroups.

2. Denominator is number of patients discharged alive.