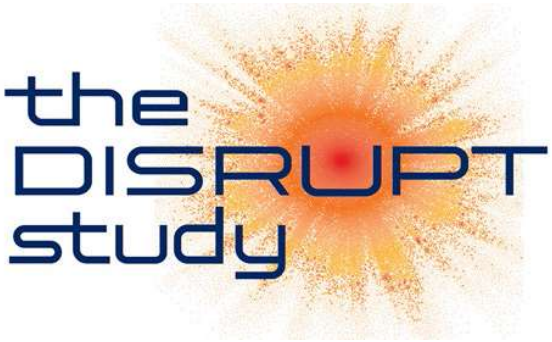
# Clinical Trial Protocol




## The DISRUPT Study

**Di**rect Lysis of ***S****taphylococcus aureus* **R**esistant **P**athogen **T**rial

## Exebacase (CF-301)

A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of a Single Dose of Exebacase in Patients Receiving Standard-of-Care Antibiotics for the Treatment of *Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Right-Sided Infective Endocarditis

**Protocol Number CF-301-105**
**Protocol Amendment 5 (CF-301-105-5)**

Sponsor:
ContraFect Corporation
28 Wells Ave
Yonkers, NY 10701

Original Protocol Date: October 18, 2019
Protocol Amendment 1 Date: May 21, 2020
Protocol Amendment 2 Date: October 15, 2020
Protocol Amendment 3 Date: January 29, 2021
Protocol Amendment 4 Date: July 22, 2021
Protocol Amendment 5 Date: February 10, 2022

IND Number: 113473
clinicaltrials.gov NCT04160468

**CONFIDENTIALITY STATEMENT**

# SUMMARY OF CHANGES

The primary purpose of this Protocol Amendment is to further clarify and refine the inclusion and exclusion criteria and streamline the study procedures to facilitate patient identification and enrollment. Daily assessment of signs and symptoms is removed in this Protocol Amendment to reduce the number of study-related patient encounters as a result of COVID-19-related restrictions and staffing challenges. The signs and symptoms will continue to be assessed at screening and on Day 7 and at the endpoint-determining study visits on Days 14, 30, and 60 to support the objectives of the study.

The table below describes the changes that were made from the prior version of the protocol:

| Section(s) | Brief Description of Changes |
|---|---|
| 1 | • Revised contact information. |
| 2, 4, 9.1, 11.5, 12.10, 12.11, 12.12, 12.13 | • Removed daily assessment of signs/symptoms, vital signs, and metastatic foci/septic emboli. Signs/symptoms, vital signs, and metastatic foci/septic emboli will continue to be assessed at screening and on Days 7, 14, 30, and 60. Additionally, if SoCA is changed after study drug dosing due to lack of clinical response, signs and symptoms will be assessed on the day of the SoCA change. |
| 2, 4, 9.1, 11.5, 12.10, 12.11, 12.12, 12.13 | • As previously communicated in Protocol Clarification Letter #8, clarified that in rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records alone may be used for physical examinations, signs/symptoms, and metastatic foci/septic emboli assessments after contacting the Medical Monitor or designee.<br>• Clarified that when medical records are used alone or to supplement information collected during the telephone/telehealth visit, the physical examinations, signs/symptoms, and metastatic foci/septic emboli assessments extracted from the medical record will be recorded in the site's source documents and entered in the relevant eCRFs. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) is expected to review, sign, and date the assessments extracted from the medical record and recorded in the site's source documents. The eCRFs will be verified by the site monitor using these source documents.<br>• For symptoms (Section 12.13), provided guidelines for assessing symptoms that are not specifically documented as "absent" in the medical record. |
| 2, 4, 11.3, 12.13 | • Clarified that pre-BSI/IE is the patient's "usual state of health" before the BSI/IE started. Pre-BSI/IE is established by asking the patient or legally acceptable representative about symptoms and severity (using Table 9) prior to onset of the BSI/IE. The medical record may also be used. |
| 4, 11.3, 12.8.2.5, 12.8.2.6 | • As already stated in the protocol, clarified the wording that the results of all blood cultures/other cultures from the initial *S. aureus*-positive blood culture 'collected pre-study' through the Day 60 visit will be entered in the eCRF, and the *S. aureus* isolates from the initial *S. aureus*-positive blood culture/other cultures 'collected pre-study' through the Day 60 visit should be sent to the central laboratory. |
| 2, 4, 9.1, 11.5, 12.14 | • Removed the follow-up TTE or TEE between 7 to 14 days after the initial echocardiogram or up to the Day 30 visit. Clarified that follow-up echocardiograms will be performed as clinically indicated. |

| Section(s) | Brief Description of Changes |
|---|---|
| 2, 4, 9.1, 11.3, 11.4, 11.5, 12.2.8.5, 12.8.1, 12.8.2.1 | • For adolescents, added that the results of local clinical laboratory testing during the screening window and at all other timepoints corresponding to the protocol can substitute for central safety laboratory tests and will be entered into the eCRF; samples for ADA and IgE must be collected at the timepoints specified in the protocol and sent to the central laboratory.<br>• Added that the Day 14 safety laboratory sample does not need to be collected for adolescents; if results from local clinical laboratory testing are available within the Day 14 visit window, these results should be entered into the eCRF, if feasible.<br>• Added that blood cultures may be collected 'every other day' for adolescents. |
| 2, 4, 11.3, 11.4, 12.8.2.1, 12.8.2.3, 12.8.2.4, 12.9 | • Clarified that the pre-dose/screening timepoint for ECGs, safety laboratory tests, blood cultures, ADA, IgE, and PK samples can be performed during screening or 'after randomization and before dosing'. |
| 2, 10.1, 10.2 | • Inclusion criterion #2 and exclusion criterion #3: Added text to indicate that there is an approximately +1-hour window to randomize the patient after the 72-hour window (i.e., approximately 73 hours) to account for any technical issues with randomization. If the patient is randomized within the approximately +1-hour window, please inform the Medical Monitor or designee. |
| 2, 4, 9.1, 10.1, 11.4, 11.5, 12.5 | • Inclusion criterion #4.b.ii: As previously communicated in Protocol Clarification Letter #7, added text to clarify that clots in the vein at the catheter site may be identified on ultrasound or other method (e.g., MRI, echocardiogram, surgery). Also clarified that the clots may be at 'or near' the catheter site. |
| 2, 10.1, 12.5 | • Inclusion criterion #4.b.iii: Clarified that patients who present with acute osteomyelitis as the first manifestation of *S. aureus* BSI (e.g., adolescents) may be enrolled even if original source of infection is not known. |
| 2, 10.1, 12.5 | • Inclusion criterion 4.b.vi.: As previously communicated in Protocol Clarification Letter #7, added text to clarify that in order for post-organ transplant patients to meet the protocol definition of 'significantly immunocompromised', the patient needs to be on immunosuppressant therapy for the organ transplant around the time of presentation with the *S. aureus* BSI/IE. |
| 2, 10.1, 12.5, 23.4 (Appendix 4) | • Inclusion criterion 4.b.vi.: As previously communicated in Protocol Clarification Letter #7, the dose of prednisone considered to be immunosuppressive therapy was decreased from ≥15 mg to ≥10 mg. Clarified that this includes 'patients who have taken ≥10 mg of prednisone or equivalent for 5 days or more'.<br>• A list of immunosuppressive therapy was added to Section 23.4 (Appendix 4). |
| 2, 10.1, 12.5 | • Inclusion criterion 4.b.vi.: Clarified that the criterion for complicated BSI of AIDS includes HIV positive with an AIDS-defining condition or a CD4 count of approximately ≤200 cells/mm³ 'within approximately 90 days'. |
| 2, 10.1, 12.5 | • Inclusion criterion 4.b.vi.: Clarified that the criterion for complicated BSI of severe leukopenia is defined as absolute neutrophil count (ANC) of approximately ≤500 cells/mL in the 7 days prior to the qualifying blood culture or 'during the screening window'. |
| 2, 10.1, 12.5 | • Inclusion criterion 4.b.vi.: Added 'advanced cirrhosis' to the list of criteria for significantly immunocompromised. |

| Section(s) | Brief Description of Changes |
|---|---|
| 2, 4, 9.1, 10.2, 11.4, 12.14 | • Exclusion criterion #2: As already stated in other sections of the protocol, clarified the situations in which a TEE is required. Added that, in cases where there is an alternative cause of new heart failure or cerebral emboli, a patient with a negative TTE for L-IE may be discussed with the Medical Monitor for potential enrollment. |
| 2, 9.4.2, 10.2, 13.7 | • Exclusion criterion #4: Clarified the note to indicate that patients with persistent *S. aureus* bacteremia for which treatment with ceftaroline fosamil or other non-protocol-recommended antibiotic (e.g., rifampin, gentamicin, other beta lactam) was instituted prior to randomization due to lack of response or intolerance may remain on the non-protocol-recommended antibiotic after randomization, if approved by the Medical Monitor. |
| 2, 10.2 | • Exclusion criterion #7: Added that patients with planned surgery for known or suspected infected non-cardiac hardware or prosthetic joint may be enrolled if surgical removal is planned within 5 days after randomization, with approval of the Medical Monitor. |
| 2, 10.2 | • Exclusion criterion #8 was removed. Patients with known or suspected brain abscess or meningitis due to *S. aureus* are no longer excluded from the study. |
| 2. 10.2 | • Exclusion criterion #14: added a note that patients who have received agents under FDA Emergency Use Authorization (EUA) for COVID-19 prevention (e.g., vaccines or Evusheld or similar agents) or for COVID-19 treatment under FDA EAU are <u>not</u> excluded. |
| 2, 12.18, 15.5 | • For the clinical outcome definitions, clarified the timing of SoCA change due to persistence, worsening, or recurrence or new signs/symptoms of *S. aureus* BSI/IE as 'after study drug dosing'.<br>• As previously communicated in Protocol Clarification Letter #9, clarified that new septic emboli are defined as an acute presentation of septic emboli after dosing and are a reason for failure for clinical outcome; septic emboli that are incidentally found on imaging are considered part of the patient's baseline *S. aureus* BSI/IE if found before Day 7. |
| 7.1.6 | • Added a summary of 30-day all-cause mortality and time to symptom resolution in the Phase 2 study. |
| 7.1.7 | • Added a summary of patients treated with exebacase under compassionate use/expanded access. |
| 9.4.2 | • Reduced the timeframe between vancomycin and study drug dosing from 2 hours to 1 hour, as follows: Study drug should be administered either prior to the start of vancomycin infusion or a minimum of '1 hour' after vancomycin infusion is complete. |
| 14.12 | • Clarified that AEs and SAEs will be followed to resolution, or until an outcome is reached, or until 'deemed to be stable.' |
| 23.4 (Appendix 4) | • New section added with list of immunosuppressive and myelosuppressive therapy, as previously communicated in Protocol Clarification Letter #7. |
| Various | • Made minor administrative and editorial changes throughout the document for clarity and consistency. |

# SPONSOR SIGNATURE PAGE

Protocol CF-301-105
Protocol Amendment 5 (CF-301-105-5)

A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of a Single Dose of Exebacase in Patients Receiving Standard-of-Care Antibiotics for the Treatment of *Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Right-Sided Infective Endocarditis

Sponsor's Approval

Cara Cassino

Digitally signed by member: 9DE54994-F817-4CB1-B437-8AB862CA5EB2
4EEE552B-4BCE-4CE5-84D4-71DCF96301B3
Date: 2022.02.15 09:48:44 -05'00'

Cara Cassino, MD
Chief Medical Officer / Executive Vice President of Research and Development
ContraFect Corporation

Date

# INVESTIGATOR'S AGREEMENT

Protocol CF-301-105
Protocol Amendment 5 (CF-301-105-5)

A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of a Single Dose of Exebacase in Patients Receiving Standard-of-Care Antibiotics for the Treatment of *Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Right-Sided Infective Endocarditis

I, the undersigned, have received and reviewed the CF-301-105 protocol and I agree to conduct this study as outlined in this protocol and in accordance with the ethical principles set forth in the Declaration of Helsinki, current Good Clinical Practice, and all applicable local laws and requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

# 1. CONTACT INFORMATION

**Table 1: Contact Information**

| Role in Study | Name | Contact Information |
|---|---|---|
| Sponsor Responsible Physician / Medical Lead / Primary Medical Monitor | Cara Cassino, MD<br>Chief Medical Officer / Executive Vice President of Research and Development | ContraFect Corporation<br>28 Wells Ave, Yonkers, NY 10701<br>Telephone: 914-330-2983<br>Email: Ccassino@contrafect.com |
| Sponsor Project Manager / Development Operations | Nancy Capra<br>Vice President, Project Management and Development Operations | ContraFect Corporation<br>28 Wells Ave, Yonkers, NY 10701<br>Telephone: 215-760-3490<br>Email: Ncapra@contrafect.com |
| Sponsor Clinical Operations | Kerry McConie<br>Director, Clinical Operations | ContraFect Corporation<br>28 Wells Ave, Yonkers, NY 10701<br>Telephone: 516-721-6653<br>Email: Kmcconie@contrafect.com |
| Sponsor Clinical Operations | Francine Pisana<br>Director, Clinical Operations | ContraFect Corporation<br>28 Wells Ave, Yonkers, NY 10701<br>Telephone: 917-833-2610<br>Email: Fpisana@contrafect.com |
| Sponsor Clinical Operations | Jill Steely<br>CRA Manager | ContraFect Corporation<br>28 Wells Ave, Yonkers, NY 10701<br>Telephone: 845-656-5681<br>Email: Jsteely@contrafect.com |
| Sponsor Clinical Operations | Beth Soffer<br>Clinical Operations | ContraFect Corporation<br>28 Wells Ave, Yonkers, NY 10701<br>Telephone: 215-738-6285<br>Email: Bsoffer@contrafect.com |
| Sponsor Protocol Author | Joy Lipka-Diamond<br>Clinical Operations | ContraFect Corporation<br>28 Wells Ave, Yonkers, NY 10701<br>Telephone: 215-872-3791<br>Email: Jlipka@contrafect.com |
| Labcorp Project Lead | Lee Anna Loehr<br>Senior Project Manager | Labcorp Drug Development<br>210 Carnegie Center Drive, Princeton, NJ 08540<br>Telephone: 713-204-4442<br>Email: lee.loehr@labcorp.com |

# 2. SYNOPSIS

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|---|
| **Name of Sponsor/Company:** ContraFect Corporation |
| **Investigational Product:** Exebacase (CF-301) |
| **Active Ingredient:** Exebacase |
| **Title of Study:** A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of a Single Dose of Exebacase in Patients Receiving Standard-of-Care Antibiotics for the Treatment of *Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Right-Sided Infective Endocarditis |
| **Study Name:** The DISRUPT Study **(Di**rect Lysis of ***S****taphylococcus aureus* **R**esistant **P**athogen **T**rial) |
| **Protocol Number:** CF-301-105 Protocol Amendment 5 (CF-301-105-5) |
| **Phase of Development:** 3 |
| **Study Centers:** Up to approximately 100 study centers, predominantly in the United States (US), will participate in this study. Site selection will take into account the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) at the study center. |
| **Objectives:**<br><u>*Primary*</u>:<br>• Efficacy: To determine if exebacase in addition to standard-of-care antibiotics (SoCA) is superior to SoCA alone for clinical responder rate at Day 14 in patients with MRSA bloodstream infections (BSI), including infective endocarditis (IE) (i.e., the MRSA population) in the microbiological intent-to-treat (mITT) analysis set<br>• Safety: To determine the safety and tolerability of exebacase in addition to SoCA compared with SoCA alone in the safety analysis set<br><u>*Secondary*</u>:<br>• To determine if exebacase in addition to SoCA is superior to SoCA alone for clinical responder rate at Day 14 in all patients with *S. aureus* (i.e., the overall population) in the mITT analysis set<br>• To determine if exebacase in addition to SoCA is superior to SoCA alone for 30-day survival in the MRSA population in the mITT analysis set<br>• To determine if exebacase in addition to SoCA is superior to SoCA alone for clinical responder rate at Day 60 in the MRSA population in the mITT analysis set<br>• To determine if exebacase in addition to SoCA is superior to SoCA alone for clinical responder rate at Day 60 in the overall population in the mITT analysis set<br>• To determine clinical responder rate at Day 60 in the overall right-sided IE (R-IE) and MRSA R-IE populations in the mITT analysis set |

*Additional*:

- To determine the survival time through Day 60 in the overall and MRSA populations in the mITT analysis set
- To determine clinical responder rate at Day 14 in the overall R-IE and MRSA R-IE populations in the mITT analysis set
- To determine clinical responder rate at Day 30 in the overall and MRSA populations, and overall R-IE and MRSA R-IE populations in the mITT analysis set
- To determine clinical responder rate at Day 14 by source of *S. aureus* infection in the overall and MRSA populations in the mITT analysis set
- To evaluate bacteremia clearance rate at Days 4 and 7 in the overall and MRSA populations in the mITT analysis set
- To describe post-dose immunologic response (anti-drug antibody to exebacase) in the safety analysis set
- To describe the relationship between baseline and post-dose immunologic parameters and efficacy and safety endpoints in the mITT and safety analysis sets, respectively
- To evaluate impact of exebacase on health resource utilization in the mITT analysis set
- To characterize the PK parameters of exebacase in the study population in the PK analysis set

**Study Design:**

This is a randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and safety of exebacase in addition to SoCA compared with SoCA alone for the treatment of adult and adolescent patients with *S. aureus* BSI including R-IE (excluding patients with left-sided endocarditis [L-IE]). Patients who meet all screening criteria and have a blood culture positive for *S. aureus* determined by rapid diagnostic or conventional methods, or Gram stain showing Gram-positive cocci in clusters plus either positive tube coagulase test or positive latex slide agglutination test from blood culture specimens collected within approximately 72 hours before randomization are eligible for the study.

Approximately 348 patients will be randomly assigned in a 2:1 ratio to receive a single dose of exebacase (232 patients) or placebo (116 patients). Patients will receive exebacase or placebo as soon as possible after randomization. The randomization will be stratified by poorly controlled diabetes (yes or no) as defined below and susceptibility of the *S. aureus* isolate (MRSA, methicillin susceptible *S. aureus* [MSSA], or unknown). For stratification, poorly controlled diabetes is defined as a hemoglobin A1C (HgA1C) ≥8% within approximately 90 days before randomization. A HgA1C test is not required for patients with no medical history of diabetes and no suspicion of diabetes during the screening period. These patients will be stratified to "no" for poorly controlled diabetes. A HgA1C test should be performed in patients with medical history of diabetes of suspicion of diabetes during screening for whom a HgA1C test result within approximately 90 days prior to randomization is not available. If a HgA1C is unavailable and testing cannot be performed for these patients prior to randomization, contact the Medical Monitor to determine how the patient should be stratified based on available clinical information. All efforts will be made to obtain susceptibility results from blood cultures before randomization to enable stratification by MRSA or MSSA. If a blood culture was

performed for the current *S. aureus* infection prior to the qualifying blood culture, susceptibility results from the prior blood culture may be used. If the patient has a concomitant *S. aureus* infection at another body site from which susceptibility results are available (e.g., skin, abscess), the susceptibility results from this other culture may be used. If the patient is known to be colonized with MRSA, MRSA may be selected for the stratification factor.

Patients will receive SoCA selected by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the US Food and Drug Administration (FDA) Form 1572 and trained on the protocol) based on recommendations in the protocol. These are based on authoritative treatment guidelines [Liu 2011, Baddour 2015] and include daptomycin or vancomycin for MRSA and semi-synthetic penicillins (e.g., nafcillin, oxacillin, cloxacillin, flucloxacillin) and first-generation cephalosporins (e.g., cefazolin) for MSSA. Daptomycin or vancomycin may be used for patients with MSSA with a known history of beta-lactam allergy or other reason that a beta-lactam cannot be used. The duration of SoCA will generally be from 2 to 8 weeks (14 to 56 days). If a longer duration of treatment with SoCA is anticipated, this must be discussed prior to randomization with the Medical Monitor. Long-term oral antibiotic suppression therapy (e.g., for osteomyelitis), is not considered to be SoCA for *S. aureus* BSI/IE and would be considered a "concomitant medication". Treatment with oral step-down antibiotics is not permitted, except in adolescents. The SoCA will be administered as specified in the manufacturer's prescribing information.

All efforts will be made to determine the source of *S. aureus* BSI/IE (e.g., full physical examination, imaging as needed, cultures of other infected body sites or catheters that may be considered the source), preferably during screening or within 1 week after randomization. The resolution of the source of *S. aureus* BSI/IE will be evaluated at Days 7, 14, 30, and 60.

Patients will be evaluated for signs and symptoms attributable to *S. aureus* BSI/IE and metastatic foci (e.g., deep tissue abscess, septic arthritis, etc.) and septic emboli (e.g., to the brain, lung, etc.) during screening and at the Day 7, 14, 30, and 60 visits. Additionally, if SoCA is changed after study drug dosing due to lack of clinical response, signs and symptoms will be assessed on the day of the SoCA change. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will assess whether each sign or symptom is attributable to *S. aureus* BSI/IE or provide an alternative attribution and will assess the symptom severity per the definitions described in Table 1. Some symptoms may be considered 'medically not evaluable' due to certain medical circumstances or treatments, such as a patient in a medically induced coma or after surgery to remove a metastatic focus.

Every effort should be made to perform study visits "in person", including physical examinations, assessment of signs and symptoms, and evaluation of metastatic foci/septic emboli, by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol), and preferably by the same person at all visits. If it is not feasible to evaluate the patient "in person" at study visits, the signs and symptoms should be evaluated during the telephone/telehealth visits by detailed questioning and a complete medical review of systems. Medical records may be used to supplement the telephone/telehealth evaluation for physical examination, signs and symptoms, and metastatic foci/septic emboli (see Sections 12.10, 12.13, and 12.12, respectively). In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records alone may be used for evaluation of signs and symptoms and presence of new or worsening metastatic foci after contacting the Medical Monitor or designee. The Investigator/

Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) must review, sign, and date the physical exam, sign and symptom, and metastatic foci/septic emboli data extracted from the medical record and recorded in the site's source documents.

Diagnostic testing will be performed as clinically indicated to assess metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures). Metastatic foci identified through Day 7 are considered part of the patient's baseline *S. aureus* BSI/IE; new metastatic foci identified after Day 7 or new septic emboli after study drug dosing are considered complications of *S. aureus* BSI/IE for the purpose of assessing clinical outcome. New septic emboli are defined as an acute presentation of septic emboli after dosing and are a reason for failure for clinical outcome; septic emboli that are incidentally found on imaging are considered part of the patient's baseline *S. aureus* BSI/IE if found before Day 7.

Intravenous catheters known or suspected to be infected must be removed, and as clinically needed replaced, preferably at a different site, as soon as possible within approximately 72 hours after randomization. Other hemodialysis access types (i.e., arteriovenous [AV] fistulas or AV grafts) and surgically managed infection sources that are known or suspected to be infected will be evaluated for removal/replacement, if clinically feasible. If removal/debridement is not feasible based on standard medical practice, the patient should be discussed with the Medical Monitor for potential enrollment. In patients with central venous catheters (CVC), ultrasounds to evaluate clots in the vein should be performed within approximately 48 hours after randomization, unless the clot in the vein has been detected within this timeframe via other method (e.g., imaging such as CT scan or MRI or direct visualization during surgery).

In addition to the study-qualifying blood culture from specimens collected within approximately 72 hours before randomization (described earlier in this section), 1 aerobic blood culture will be collected during screening (or after randomization and before dosing), collected via peripheral venipuncture when possible. One aerobic blood culture will be collected daily during the study until 2 consecutive negative cultures followed out to negative for at least 48 hours on 2 different days are obtained after exebacase/placebo administration (Note: blood cultures may be collected every other day for adolescents). Additional blood cultures will be performed as clinically indicated. Other (non-blood) cultures should be performed to determine the source of *S. aureus* BSI/IE and evaluate metastatic foci, and as clinically indicated during the study. All *S. aureus* isolates from blood and other (non-blood) cultures will be sent to a central laboratory.

Complete physical examinations and review of body systems will be performed during screening and on Days 7, 14, 30, and 60 for visits performed "in person" by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol). A physical examination is not required for visits performed remotely by telephone/telehealth; however, a complete medical review of body systems will be performed during the telephone/telehealth visit and medical record data may be used to supplement these visits (e.g., sign and symptom evaluation and physical exam findings) to assess the patient's clinical status, primary source of infection, and the status of any pre-existing or presence of new metastatic foci. The physical examinations will include a close evaluation for any new areas of pain or other signs or symptoms of metastatic foci of infection or septic emboli; new signs or symptoms (e.g., pain, shortness of breath) will trigger diagnostic testing for metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures). The physical examination will also include an evaluation of the primary source of *S. aureus* BSI/IE.

All adult patients (≥18 years of age) will have a transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) within 3 days before or after randomization. All efforts will be made to perform the TTE or TEE before randomization. Where possible, a TEE will be performed [Baddour 2015, Habib 2010, Habib 2015] and is recommended in patients with body mass index (BMI) >30 kg/m$^2$; the TEE may be performed within 3 days before or after randomization unless the TEE is performed due to clinical suspicion of L-IE. In patients that have clinical findings suggestive of L-IE (new murmur, worsening cardiac function, and/or peripheral or central nervous embolic phenomenon), a TEE will be performed before randomization to rule out mitral and/or aortic valve vegetation(s) or the patient will be excluded from the study per exclusion criterion #2. In cases where there is an alternative cause of new heart failure or cerebral emboli, a patient with a negative TTE for L-IE may be discussed with the Medical Monitor for potential enrollment. In patients with persistent bacteremia for ≥3 days (i.e., blood cultures positive for *S. aureus* for ≥3 days), an echocardiogram will be performed before randomization to rule out L-IE. A TTE may be performed with permission from the Medical Monitor. If this echocardiogram is not performed or L-IE is not ruled out by this echocardiogram, the patient should not be randomized. In adolescents (12 to <18 years of age), echocardiograms (TTE or TEE) will be performed as clinically indicated taking into consideration risk factors for endocarditis (e.g., structurally abnormal heart [including pacemakers]), clinical features suggestive of endocarditis (e.g., new murmur), or persistent bacteremia [McMullan 2020], described in Section 12.14. If the patient had an echocardiogram performed prior to the study that was intended to evaluate the current infection, an additional TTE or TEE is not required unless as indicated above, but should be discussed with the Medical Monitor if obtained ≥3 days prior to randomization. Follow-up echocardiograms will be performed as clinically indicated. Images from all echocardiograms through the Day 60 visit will be provided to the central echocardiography laboratory as directed by the Sponsor.

Safety monitoring will include adverse event (AE) monitoring, physical examinations, clinical safety laboratory tests, vital sign measurements, and 12-lead electrocardiograms (ECG). Safety monitoring will be performed from screening through the last follow-up visit (Day 60). An independent Data Safety Monitoring Board (DSMB) will review unblinded safety data throughout the study as defined in the DSMB charter. All fatal serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSARs) will be provided to the DSMB on an ongoing basis allowing the DSMB to monitor fatal and unexpected serious events in a timely manner.

Blood samples for PK and immunogenicity (exebacase-specific anti-drug antibody [ADA] and immunoglobulin E [IgE]) will be collected. Samples for ADA testing will be collected during screening and on any day between the Day 30 and Day 60 visit windows (i.e., between Day 26 and Day 67). The sample for IgE testing will be collected during screening and will be stored at the site unless the patient later develops clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug. If a patient has clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug, a blood sample for IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample at screening will be sent to a central laboratory for testing.

Clinical outcome will be assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol). An independent blinded clinical endpoint Adjudication Committee (AC) will determine study eligibility, final diagnosis, primary

source of BSI/IE, adequacy of source control, and clinical outcome on Days 14, 30, and 60. The adjudicated diagnosis, source, and clinical outcomes will be used for the analysis.

***Visits Performed Remotely by Telephone/Telehealth, Use of Medical Records, and Use of Mobile Health Services:***

Telephone/telehealth visits may be performed under the circumstances described in Section 11.5.1 of the protocol. During the telephone/telehealth visit, information on the following will be collected: any AEs that may have occurred since the last visit and outcome of any ongoing AEs, thorough medical review of body systems to assess signs and symptoms of *S. aureus* BSI/IE, outcome of pre-existing or presence of new metastatic foci, outcome of primary source of infection, SoCA and reasons for any changes in SoCA, concomitant medications, surgeries/procedures, vital status, and clinical outcome. Medical records* may be used to supplement information obtained during the telephone/telehealth visit.

In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records* alone may be used for assessments after contacting the Medical Monitor or designee.

* When medical records are used alone or to supplement information collected during the telephone/telehealth visit, the signs/symptoms, vital signs, and metastatic foci/septic emboli assessments extracted from the medical record will be recorded in the site's source documents and entered in the relevant eCRFs. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) is expected to review, sign, and date the assessments extracted from the medical record and recorded in the site's source documents. Symptom severity assessments must be made in accordance with Table 1. The eCRFs will be verified by the site monitor using these source documents.

Local laboratory, vital signs, and ECG data obtained in conjunction with the Day 7, 14, 30, or 60 visits may be used for the study if available (including using data from medical records of another hospital, skilled nursing facility or other similar institution).

Mobile health services, specifically contracted for the study, may be used to supplement telephone/telehealth visits to perform study visit procedures, such as collecting laboratory samples, evaluating vital signs, and/or obtaining a 12-lead ECG, after approval by the Medical Monitor or designee, as described in Section 11.5.1.

**Number of Patients (planned):** Approximately 348 patients will be randomized (2:1) to receive a single dose of exebacase or placebo.

**Inclusion Criteria**:

The following inclusion criteria must be met at the time of screening (i.e., within approximately 24 hours before randomization), unless otherwise noted below, in order for the patient to be eligible for enrollment:

1. Male or female, 12 years of age or older.
2. Within 72 hours* before randomization, blood culture positive for *S. aureus* determined by rapid diagnostic test or conventional method, or Gram stain showing Gram-positive cocci in clusters and either positive tube coagulase test or positive latex slide agglutination test from blood culture specimens.

Note: The 72-hour* time period starts at the time the specimen is collected for blood culture. Any *S. aureus*-positive blood culture collected within the 72 hours* before randomization can be used to support enrollment of the patient.

*There is an approximately +1-hour window to randomize the patient after the 72-hour window (i.e., approximately 73 hours) to account for any technical issues with randomization. If the patient is randomized within the approximately +1-hour window, please inform the Medical Monitor or designee.

3. At least two of the following signs or symptoms attributable to *S. aureus* BSI/IE within approximately 24 hours before randomization. If more than one measurement is taken within the approximately 24 hours before randomization, the most abnormal value is used for inclusion.
   a. Shortness of breath
   b. Sweating
   c. Chills and/or rigors
   d. Fatigue
   e. Confusion
   f. Pain associated with metastatic foci
   g. Fever (oral temperature equivalent ≥38.0°C [≥100.4°F]) or hypothermia (oral temperature equivalent <35°C [<95°F])
   h. Leukocytosis (white blood cell [WBC] count >10,000/µL) [CTCAE 2017], leukopenia (WBC <4000/µL), or bandemia (>10% immature neutrophils [bands] regardless of total peripheral WBC)
   i. Tachycardia (heart rate >100 bpm)
   j. Tachypnea (respiratory rate >20 breaths/min)
   k. Hypotension (systolic blood pressure <90 mmHg)
4. Patient must have:
   a. Known or suspected R-IE (involvement of pulmonic and/or tricuspid valve[s]) based on Modified Duke Criteria (defined in protocol)

      **or**

   b. Known or suspected complicated *S. aureus* BSI, demonstrated as one or more of the following:
      i. Blood culture positive for *S. aureus* on more than one day
      ii. Clots in the vein at or near the catheter site seen on ultrasound or other method (e.g., MRI, echocardiogram, surgery)
      iii. Signs or symptoms of metastatic foci of *S. aureus* infection (e.g., splenic abscess, deep tissue abscess not associated with open wound or other local source of infection, septic pulmonary emboli) or hematogenous seeding (e.g., of the renal system evidenced by *S. aureus* bacteriuria [in absence of other source such as indwelling ureteral catheter], septic arthritis, osteomyelitis) confirmed by physical examination, imaging, and/or culture (as described in the study procedures sections of the protocol)
      Note: Patients who present with acute osteomyelitis as the first manifestation of *S aureus* BSI (e.g., adolescents) may be enrolled even if original source of infection is not known.
      iv. Persistent fever (oral temperature equivalent ≥38.0°C [≥100.4°F]) for 72 hours or more

v. Met criteria for sepsis or septic shock using the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score (definition in protocol [adapted from Singer 2016]) during the time of diagnosis/presumptive diagnosis of BSI. If the SOFA score is the only criteria for complicated *S. aureus* BSI that is met, contact the Medical Monitor prior to randomization.

vi. Significantly immunocompromised:

- AIDS (HIV positive with an AIDS-defining condition or a CD4 count of approximately ≤200 cells/mm³ within approximately 90 days)
- Severe leukopenia defined as absolute neutrophil count (ANC) of approximately ≤500 cells/mL in the 7 days prior to the qualifying blood culture or during the screening window
- Post organ transplantation including autologous bone marrow or stem cell transplantation and on immunosuppressive therapy for the organ transplant around the time of presentation with the *S. aureus* BSI/IE
- On treatment for active graft vs. host disease
- On immunosuppressive therapy such as:
  - Biologics such as infliximab, monoclonal antibodies such as daclizumab, methotrexate, cyclophosphamide, or similar agents. A list of similar agents is in Appendix 4 in Section 23.4.
  - Patients who have taken ≥10 mg of prednisone or equivalent for 5 days or more.
- On myelosuppressive chemotherapy or immunotherapy
- Advanced cirrhosis

**or**

c. At least one of the following risk factors for complicated *S. aureus* BSI:

i. Preexisting right-sided valvular heart disease
ii. Surgery (e.g., orthopedic, cardiothoracic, or intraabdominal surgery) within the previous 30 days that puts the patient at risk for nosocomial bacteremia
iii. Extravascular foreign material. Note: Catheters including ports, AV fistulas and related dialysis access points are considered intravascular foreign material.
iv. Hemodialysis

5. Patient is not pregnant or breastfeeding and meets one of the following criteria:

a. A female patient who is not of childbearing potential is eligible without requiring the use of contraception. This includes female patients who have not undergone menarche or who are documented to be surgically sterile (e.g., hysterectomy, or removal of both ovaries, or tubal ligation) or postmenopausal (i.e., amenorrhea >1 year and follicle stimulating hormone [FSH] >40 mIU/mL) with a negative pregnancy test. FSH and pregnancy testing is not required in postmenopausal females with amenorrhea for >2 years.

b. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to remain abstinent* or use 2 methods of contraception and refrain from donating sperm (male patients) from screening through 30 days after receiving the study drug.

*Abstinence is defined as refraining from heterosexual intercourse from screening through 30 days after receiving the study drug; the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will consider whether abstinence is consistent with the preferred and usual lifestyle of the patient.

Acceptable methods of contraception include either:

- Hormonal contraception (injection, implant, pill, patch, or vaginal ring) and a condom or diaphragm with spermicide, or
- Intrauterine device (IUD) and a condom or diaphragm

c. A male patient who is not of reproductive potential is eligible without requiring the use of contraception. This includes males who have undergone a successful vasectomy, defined as (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.

6. Willing and able to provide written informed consent or assent. If the patient is not able to provide written informed consent or assent, written informed consent may be provided by the patient's legally acceptable representative as permissible based on local laws and regulations. For patients 12 to <18 years of age, written informed consent from the patient's parent/guardian or other legally acceptable representative will be obtained according to the site's IRB requirements. For emancipated minors, written informed consent will be obtained according to the site's IRB requirements.

**Exclusion Criteria:**

1. Patient previously received exebacase.
2. Known or suspected left-sided IE (involvement of mitral and/or aortic valve[s]) based on Modified Duke Criteria (defined in protocol).
   Note: In adult patients that have clinical findings suggestive of L-IE (new murmur, worsening cardiac function, and/or peripheral or central nervous embolic phenomenon), a TEE will be performed before randomization to rule out mitral and/or aortic valve vegetation(s) or the patient will be excluded from the study. In cases where there is an alternative cause of new heart failure or cerebral emboli, a patient with a negative TTE for L-IE may be discussed with the Medical Monitor for potential enrollment. In patients with persistent bacteremia for ≥3 days (i.e., blood cultures positive for *S. aureus* for ≥3 days), an echocardiogram will be performed before randomization to rule out L-IE. A TTE may be performed with permission from the Medical Monitor. If this echocardiogram is not performed or L-IE is not ruled out by this echocardiogram, the patient should not be randomized. In adolescents (12 to <18 years of age), echocardiograms (TTE or TEE) will be performed as clinically indicated taking into consideration risk factors for endocarditis (e.g., structurally abnormal heart [including pacemakers]), clinical features suggestive of endocarditis (e.g., new murmur), or persistent bacteremia [McMullan 2020].
3. Treatment with any potentially effective systemic anti-staphylococcal antibiotic for more than 72 hours* within 7 days before randomization.
   Exception: Documented *S. aureus* resistance to the prior systemic antibiotics and/or persistent *S. aureus*-positive blood cultures while on the systemic antibiotics.

*There is an approximately +1-hour window to randomize the patient after the 72-hour window (i.e., approximately 73 hours) to account for any technical issues with randomization. If the patient is randomized within the approximately +1-hour window, please inform the Medical Monitor or designee.

4. Current or planned treatment within the 14 days after randomization with dalbavancin or oritavancin.
   Notes:
   - Patients who are receiving teicoplanin, linezolid, telavancin, beta-lactam/beta-lactam inhibitors (e.g., piperacillin-tazobactam), carbapenems, fourth- or fifth-generation cephalosporins (e.g., cefepime, ceftaroline fosamil), and/or sulfamethoxazole/trimethoprim are eligible for the study provided that treatment is switched to a protocol-specified appropriate SoCA (appropriate SoCA includes daptomycin and vancomycin for MRSA and semi-synthetic penicillins [e.g., nafcillin, oxacillin, cloxacillin, flucloxacillin] and first-generation cephalosporins [e.g., cefazolin] for MSSA.
   - Daptomycin or vancomycin may be used for patients with MSSA with a known history of beta-lactam allergy or other reason that beta-lactam cannot be used.
   - Patients with persistent *S. aureus* bacteremia for which treatment with ceftaroline fosamil or other non-protocol-recommended antibiotic (e.g., rifampin, gentamicin, other beta lactam) was instituted prior to randomization due to lack of response or intolerance (i.e., added to or switched from a protocol-recommended SoCA) may remain on the non-protocol-recommended antibiotic after randomization, if approved by the Medical Monitor.
   - Vancomycin or daptomycin used in combination with beta-lactams has not been shown to offer benefit and may increase the risk of kidney injury [Tong 2020]; therefore, this combination should not routinely be used as first-line therapy.
5. Removed (Protocol Amendment 4).
6. Presence of any removable or surgically managed infection source (e.g., intravascular catheter, abscess) that will not be removed or debrided based upon standard medical practice within approximately 72 hours after randomization.

   Note: Other hemodialysis access types (i.e., AV fistulas or AV grafts) and surgically managed infection sources that are known or suspected to be infected will be evaluated for removal/replacement if clinically feasible. If removal/debridement is not feasible based on standard medical practice, the patient should be discussed with the Medical Monitor for potential enrollment.
7. Presence of prosthetic valve or cardiac valve support ring, or presence of known or suspected infected hardware* (e.g., orthopedic), prosthetic joint*, or cardiac device (e.g., implantable cardioverter defibrillator [ICD], permanent pacemaker). Note: Patients who have *S. aureus* bacteremia after the removal of infected hardware or cardiac device may be included in the study.
   *Patients with planned surgery for known or suspected infected non-cardiac hardware or prosthetic joint may be enrolled if surgical removal is planned within 5 days after randomization, with approval of the Medical Monitor.
8. Removed (Protocol Amendment 5)

9. Patient with **BOTH** asplenia and creatinine clearance (CrCl) <60 mL/min including those on dialysis (risk for reduced ability to catabolize exebacase). Note: CrCl will be calculated by Cockcroft-Gault formula (provided in protocol) using ideal body weight in patients with BMI ≥30 kg/m$^2$ and serum creatinine result obtained locally.
10. Patient receiving continuous renal replacement therapy (CRRT) within 4 hours prior to dosing and/or within 8 hours after dosing.
11. Known polymicrobial BSI (i.e., more than one pathogen in the blood). Note: Culture results that include organisms that are considered contaminants do not exclude the patient.
12. Patient with known, ongoing systemic infection caused by other bacterial pathogen(s) (i.e., other than *S. aureus*) and/or fungal pathogen(s) and/or patient who has a known positive coronavirus disease 2019 (COVID-19) diagnostic test at the time of screening. Patients who previously had COVID-19 and are COVID-19-negative by diagnostic test are eligible for enrollment. Note: COVID-19 testing should be performed as clinically indicated in accordance with local standard medical practice.
13. Patient is not expected to survive through Day 14 of the study due to underlying comorbidity (e.g., terminal end-stage cancer) and/or patient has an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of >30.
14. Patient participated or plans to participate in another interventional investigational drug, device, or diagnostic trial involving administration of an investigational agent within 30 days or 5 half-lives of investigational drug, whichever is longer, prior to or during the study.
    Note: Patients who have received agents under FDA Emergency Use Authorization (EUA) for COVID-19 prevention (e.g., vaccines or Evusheld or similar agents) or for COVID-19 treatment under FDA EAU are not excluded.
15. Other comorbid condition or laboratory abnormality that would, in the opinion of the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol), pose a safety risk for the patient to participate or pose a risk to the patient's ability to complete the study.
16. Patient is employed by the Sponsor or a member of the investigational site study team (i.e., on the Delegation of Authority Log) or is a first degree relative of a person employed by the Sponsor or a member of the investigational site study team (i.e., on the Delegation of Authority Log). Patient is institutionalized by administrative or court order.
17. Patient is not willing or able to comply with the protocol requirements.

**Investigational Product, Dosage and Mode of Administration:**

Exebacase will be provided as frozen, sterile, injectable solution for dilution. Exebacase will be diluted and administered as approximately a 2-hour IV infusion, as specified in the Pharmacy Manual.

The dosing scheme is as follows:

- Patients with normal renal function or mild renal impairment (CrCl* ≥60 mL/min) will be administered a dose of **18 mg** of exebacase.
- Patients with moderate or severe renal impairment (CrCl* of 15 to <60 mL/min) will be administered a dose of **12 mg** of exebacase.

- Patients with end-stage renal disease (ESRD; CrCl* <15 mL/min), including those on hemodialysis, will be administered a dose of **8 mg** of exebacase. In patients receiving hemodialysis, study drug will be administered either ≥8 hours before the start of hemodialysis or ≥4 hours after the end of hemodialysis.

*Note: CrCl will be calculated by Cockcroft-Gault formula (provided in protocol) using ideal body weight in patients with BMI ≥30 kg/m$^2$ and serum creatinine result obtained locally as close to the start of study drug dosing as possible (but not more than approximately 24 hours before the start of study drug dosing).

**Reference Therapy, Dosage and Mode of Administration:**

Placebo will be provided as frozen, sterile, injectable solution for dilution. Placebo is similar in appearance to exebacase. Placebo will be diluted and administered as approximately a 2-hour IV infusion, as specified in the Pharmacy Manual.

**Duration of Treatment:** Patients will receive a single dose of exebacase or placebo in addition to SoCA. The duration of SoCA will generally be from 2 to 8 weeks (14 to 56 days). If a longer duration of treatment with SoCA is anticipated, this must be discussed prior to randomization with the Medical Monitor. Long-term oral antibiotic suppression therapy (e.g., for osteomyelitis), is not considered to be SoCA for *S. aureus* BSI/IE and would be considered a "concomitant medication".

**Duration of Study (for each patient):** The duration of the study for each patient will be approximately 60 days (±7 days).

**Criteria for Evaluation:**

*Efficacy*:

Metastatic foci, septic emboli, signs and symptoms attributable to *S. aureus* BSI/IE, blood cultures and other (non-blood) cultures, physical examinations (including a close evaluation for any new areas of pain or other signs or symptoms of metastatic foci or septic emboli), imaging (as needed for determining diagnosis and assessing metastatic foci or septic emboli), and echocardiography will be assessed or performed at the timepoints described previously in this Synopsis.

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will assess whether each sign or symptom is attributable to *S. aureus* BSI/IE or provide an alternative causality. The signs and symptoms attributable to *S. aureus* BSI/IE that will be assessed are described in the inclusion criteria earlier in this Synopsis. Each patient is required to have at least 2 signs or symptoms attributable to *S. aureus* BSI/IE at screening (within approximately 24 hours before randomization) in order to be enrolled in the study. Signs and symptoms will be assessed during screening and at the Day 7, 14, 30, and 60 visits. Additionally, if SoCA is changed after study drug dosing due to lack of clinical response, signs and symptoms will be assessed on the day of the SoCA change. Select symptoms (shortness of breath, fatigue, confusion) will also be evaluated at pre-BSI/IE. Pre-BSI/IE is the patient's "usual state of health" before the BSI/IE started. Pre-BSI/IE is established by asking the patient or legally acceptable representative about these symptoms and severity (using Table 1) prior to onset of the BSI/IE. The medical record may also be used.

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will assess the severity of specific symptoms attributable to *S. aureus* as absent, mild, moderate, or severe, as defined in Table 1. Symptoms of sweating and chills/rigors and signs attributable to *S. aureus* will be assessed as present or absent. The Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) and the AC will assess the resolution of or persistence, worsening, or recurrence of signs and symptoms attributable to *S. aureus* BSI/IE which were present at screening, or any new signs or symptoms attributable to *S. aureus* BSI/IE, when evaluating clinical outcome, according to the clinical outcome definitions in Table 2. All signs and symptoms attributable to *S. aureus* that were present at screening must be absent or improve by 2 grades (i.e., from severe to mild) in order to be considered as resolved. Symptoms attributable to *S. aureus* that were present at screening and only improve by 1 grade (i.e., from severe to moderate or from moderate to mild) are considered persistence.

**Table 1: Severity Definitions for Symptoms Attributable to *S. aureus***

| Symptom | Absent | Mild | Moderate | Severe |
|---|---|---|---|---|
| Shortness of breath (SOB)[1] | Resolution (to pre-BSI/IE) or absence of SOB | SOB with moderate exertion (e.g., climbing stairs) | SOB with minimal exertion (e.g., normal/ routine activities (e.g., walking on flat surface, performing usual daily activities [i.e., instrumental ADL]) | SOB at rest and/or requiring oxygen (or increase in oxygen requirement in patients who required oxygen pre-BSI/IE); limits ability to perform self-care ADL |
| Fatigue[1] | Resolution (to pre-BSI/IE) or absence of fatigue | Transient, relieved by rest; does not interfere with usual activities | Frequent, interferes with usual daily activities (i.e., instrumental ADL) | Fatigue not relieved by rest; limits ability to perform self-care ADL |
| Confusion[1,2] | Resolution (to pre-BSI/IE) or absence of confusion (e.g., disorientation) | Transient confusion (e.g., mild disorientation that does not interfere with usual activities). | Moderate disorientation; interferes with ability to do usual activities (i.e., instrumental ADL) | Severe, continuous confusion state (e.g., delirium) disorientation limiting ability to perform self-care ADL |
| Pain assoc. with metastatic foci | Absence of pain from metastatic foci | Transient mild pain; does not interfere with usual activities or sleep | Frequent pain; interferes with usual activities or sleep | Constant pain interferes with usual activities or sleep and/or ability to perform self-care ADL |

Reference: Adapted from NIH Common Terminology Criteria for Adverse Events (CTCAE)
Abbreviation: ADL=activities of daily living; assoc.=associated; SOB=shortness of breath
Note: Some symptoms may be considered 'medically not evaluable' due to certain medical circumstances or treatments, such as a patient in a medically induced coma or after surgery to remove a metastatic focus.

1. A pre-BSI/IE assessment will be done for shortness of breath, fatigue, and confusion. Pre-BSI/IE is the patient's "usual state of health" before the BSI/IE started.
2. Confusion is defined as a disorder characterized by a lack of clear and orderly thought and behavior. Confusion may include disorientation, illusions, movement changes, inattentiveness, agitation, and/or hallucinations

Clinical outcome will be assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) and the AC at Days 14, 30, and 60 according to the definitions in Table 2.

**Table 2: Clinical Outcome Definitions at Days 14, 30, and 60**

| Clinical Outcome | Definition |
|---|---|
| Responder | All of the following criteria are met:<br>• Resolution of signs and symptoms attributable to *S. aureus* BSI/IE which were present at screening[1],<br>• No new signs or symptoms attributable to *S. aureus* BSI/IE,<br>• No complications of *S. aureus* BSI/IE, including:<br>▪ No development of a new metastatic focus of *S. aureus* infection (e.g., deep tissue abscess, septic arthritis) after Day 7[2],<br>▪ No development of new septic emboli (e.g., to the brain, lung, etc.) after study drug dosing[3],<br>• No change in the SoCA after study drug dosing due to persistence, worsening, or recurrence or new signs/symptoms of *S. aureus* BSI/IE[4],<br>• Blood culture(s) negative for *S. aureus* by Day14[5], **and**<br>• The patient is alive. |
| Failure | At least 1 of the following criteria is met:<br>• Persistence, worsening, or recurrence of signs or symptoms attributable to *S. aureus* BSI/IE which were present at screening,[1]<br>• New signs or symptoms attributable to *S. aureus* BSI/IE,<br>• Complications of *S. aureus* BSI/IE, including:<br>▪ Development of a new metastatic focus of *S. aureus* infection (e.g., deep tissue abscess, septic arthritis) after Day 7[2],<br>▪ Development of new septic emboli (e.g., to the brain, lung, etc.) after study drug dosing[3],<br>• SoCA was changed after study drug dosing due to persistence, worsening, or recurrence or new signs/symptoms of *S. aureus* BSI/IE[4],<br>• Failure to clear blood cultures by Day14[5], **or**<br>• Death due to any cause. |
| Indeterminate | The patient is not available for the evaluation of clinical outcome for any reason including:<br>• Lost to follow-up<br>• Withdrawal of consent/assent<br>• Other reason for not performing assessment |

Note: Visit windows are as follows: Day 14 (±1 day), Day 30 (±4 days), Day 60 (±7 days).

1. Specific symptoms attributable to *S. aureus* will be assessed as absent, mild, moderate, and severe according to the definitions in Table 1 Sweating and chills/rigors and signs attributable to *S. aureus* will be assessed as present or absent. All signs and symptoms attributable to *S. aureus* that were present at screening must be absent or improve by 2 grades (i.e., from severe to mild) in order to be considered as resolved. Symptoms attributable to *S. aureus* that were present at screening and only improve by 1 grade (i.e., from severe to moderate or from moderate to mild) are considered persistence.
2. Metastatic foci identified through Day 7 are considered part of the patient's baseline *S. aureus* BSI/IE; new metastatic foci identified after Day 7 are considered complications of *S. aureus* BSI/IE for the purpose of assessing clinical outcome.
3. New septic emboli are defined as an acute presentation of septic emboli after dosing and are a reason for failure for clinical outcome; septic emboli that are incidentally found on imaging are considered part of the patient's baseline *S. aureus* BSI/IE if found before Day 7.
4. Patients may be treated empirically and SoCA may be changed after susceptibility data become available. A change in SoCA based on susceptibility data from the blood culture collected within approximately 72 hours before randomization does not count as "failure".
5. Failure to attain negative blood cultures on or before Day 14. Only applies to Day 14 assessment.

Microbiological outcome will be determined programmatically at Days 4 and 7 according to the definitions in Table 3.

**Table 3: Microbiological Outcome Definitions at Days 4 and 7**

| Microbiological Outcome | Definitions |
|---|---|
| Clearance of bacteremia[1] | Two consecutive blood cultures collected on 2 different days on or prior to assessment were negative for *S. aureus*. |
| Ongoing bacteremia[1] | Blood culture on the day of assessment or the most recent blood culture prior to the day of assessment was positive for *S. aureus*. |
| If the patient does not meet the criteria for clearance or ongoing bacteremia, including because follow-up blood cultures were not done, microbiological outcome is presumed from clinical outcome as follows: | |
| Presumed clearance of bacteremia[1] | The patient is a responder at Day 14 (per the adjudicated clinical outcome, as defined in Table 2. |
| Presumed ongoing bacteremia[1] | The patient is a failure at Day 14 (per the adjudicated clinical outcome, as defined in Table 2). |
| Indeterminate | The patient is indeterminate for clinical outcome at Day 14 (per the adjudicated clinical outcome, as defined in Table 2. |

1. For the analysis, clearance of bacteremia will include both clearance and presumed clearance of bacteremia, and ongoing bacteremia will include both ongoing and presumed ongoing bacteremia.

*Safety*:

Adverse events will be monitored from the time of consent/assent through the last follow-up visit (Day 60).

Patients must be observed during exebacase/placebo infusion by someone from the clinical care team or research team with patient care experience. Vital signs (blood pressure, respiratory rate, heart rate, and temperature) will be performed approximately 30 to 40 minutes after the start of infusion and as clinically indicated during the infusion and at the Day 7, 14, 30, and 60 visits for visits performed "in person" or may be obtained via the study-specific mobile health service.

While not observed in the Phase 2 study (Study CF-301-102), if a patient has clinical signs and symptoms of a potential allergic reaction that may be attributed to study drug, the infusion must be stopped immediately and vital signs checked; if hypotension or oxygen desaturation are present with or without skin flushing, hives, or rash, epinephrine should be administered immediately intramuscularly. Additional treatments for sequelae of suspected anaphylactic reaction should be provided in accordance with standard medical practice. A blood sample for exebacase-specific IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample at screening will be sent to a central laboratory for testing.

Blood and urine samples for safety laboratory tests (biochemistry, hematology, coagulation, and urinalysis) will be collected during screening, approximately 24 hours after study drug administration (Day 2), on Day 14 for adults*, and Day 30; the samples will be sent to a central laboratory for testing. *The collection of Day 14 samples is not required for adolescents. Results from local clinical laboratory testing completed within the Day 14 visit window should be entered into the eCRF if available and feasible. For all patients, if a blood or urine sample for safety laboratory testing by the central laboratory is not able to be obtained at a given timepoint/visit, the local laboratory results may be collected for that timepoint/visit, if feasible. If a blood or urine sample for safety laboratory testing by the central laboratory or local laboratory results are not able to be obtained at the Day 30 visit, samples may be on

any day between the Day 30 and 60 visit windows (i.e., between Day 26 and Day 67) when collecting the blood sample(s) for exebacase-specific ADA and pregnancy test (if applicable). For adolescents, the results of local clinical laboratory testing during the screening window and at all other timepoints corresponding to the protocol can substitute for central safety laboratory tests and will be entered into the eCRF; samples for ADA and IgE must be collected at the timepoints specified in the protocol and sent to the central laboratory.

A 12-lead ECG will be performed during screening (or after randomization and before dosing) and on Day 14. Additional ECGs will be performed as clinically indicated.

Complete physical examinations and review of body systems will be performed during screening and on Days 7, 14, 30, and 60 for visits performed "in person" by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol). A physical examination/vital signs are not required for visits performed remotely by telephone/telehealth; however, a complete medical review of body systems will be performed during the telephone/telehealth visit and medical record data may be used to supplement these visits (e.g., sign and symptom evaluation and physical exam findings) to assess the patient's clinical status, primary source of infection, and the status of any pre-existing or presence of new metastatic foci. The complete physical examinations/medical review of symptoms will include evaluation of general, head, eye, ear, nose, and throat (HEENT), cardiovascular, skin for any evidence of emboli, musculoskeletal, respiratory, gastrointestinal, neurological systems, and signs of pain. The physical examinations/medical review of symptoms will include a close evaluation for any new or worsening signs or symptoms (e.g., pain, shortness of breath) of suspected new metastatic foci of infection or suspected septic emboli. Diagnostic testing (e.g., imaging, aspiration, and/or cultures) will be performed to confirm suspected new metastatic foci or septic emboli. The physical examination/medical review of symptoms will also include an evaluation of the primary source of *S. aureus* BSI/IE. Additional physical examinations will be performed as clinically indicated.

Vital status (whether the patient is alive or dead, or last known date alive if vital status is unknown) will be obtained at Days 14, 30, and 60 for all patients, including patients that discontinue the study or withdraw consent/assent (as described in the informed consent/assent form). The patient's vital status will be determined using available sources (e.g., the patient, patient's contacts, hospital and other medical records, and public records, such as social media, obituaries, social security death index) as described in the informed consent/assent form and FDA guidance (described in Section 12.17 of the protocol).

An independent DSMB will review accruing safety and tolerability data in an unblinded manner throughout the study. All fatal SAEs and SUSARs will be provided to the DSMB on an ongoing basis. The DSMB will also review results from a futility analysis of the primary efficacy parameter in the MRSA population when approximately 60% of patients in the MRSA population in the mITT analysis set have primary (Day 14) adjudicated clinical outcome data available. Details of the roles and responsibilities of the DSMB, timing of data reviews, and the futility stopping threshold will be documented in the DSMB charter. The Sponsor and study staff will remain blinded throughout the study. The DSMB will monitor the overall safety of patients in order to minimize unacceptable risk to patients. As a result, the DSMB may recommend changes to study conduct on the basis of emerging safety information to protect the safety and welfare of clinical study patients. Enrollment will continue during the DSMB reviews.

*Immunogenicity:*

Blood samples will be collected for exebacase-specific ADA during screening and on any day between the Day 30 and Day 60 visit windows (i.e., between Day 26 and Day 67); ADA samples will be sent to a central laboratory for testing. A blood sample for IgE will be collected during screening and retained at the site. If a patient has clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug, a blood sample for IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample at screening will be sent to a central laboratory for testing.

*Health Resource Utilization:*

The following health resource utilization information will be collected through Day 60: in-hospital mortality, hospital length-of-stay, intensive care unit (ICU) length-of-stay, discharge location (e.g., home, nursing home and skilled nursing facility/long-term acute care, rehabilitation, palliative care/hospice), outpatient SoCA administration by outpatient facility or home health care, 30-day all-cause readmission, and 30-day readmission for *S. aureus* BSI/IE or complication of *S. aureus* BSI/IE (e.g., metastatic foci, septic emboli).

*Pharmacokinetics:*

All patients will be assigned to one of two PK sampling schemes and blood samples will be collected at 3 timepoints as listed below, and sent to a central laboratory for measurement of exebacase:

- PK Group 1: pre-dose (collected during screening), within 5 to 25 minutes after the end of infusion, and between 3 to 5 hours after the end of infusion
- PK Group 2: pre-dose (collected during screening), within 5 to 25 minutes after the end of infusion, and between 8 to 12 hours after the end of infusion.

The actual time of PK sample collection, actual time of start and end of infusion, actual rate of volume and rate of infusion, and dosing information will be recorded.

**Statistical Methods:**

A Statistical Analysis Plan (SAP) will be prepared and finalized before database lock and analyses of unblinded data. Summary data will be tabulated and presented by treatment group. Treatment groups will be referred to as "exebacase + SoCA" and "SoCA alone" for patients randomly assigned to exebacase and placebo, respectively.

*Analysis Sets*:

- Intent-to-treat (ITT) analysis set: all randomized patients
- Safety analysis set: all randomized patients who receive any amount of study drug
- Microbiological ITT (mITT) analysis set: all randomized patients who receive any amount of study drug and had documented *S. aureus* BSI/IE based on a blood culture prior to administration of study drug. Determination of *S. aureus* is based on the central laboratory determination of genus and species unless no central result is available. In this case, the local laboratory result will be used.
- Per-Protocol (PP) analysis set: all randomized patients who have no confounding factors (as defined in the SAP) potentially affecting the evaluation of efficacy
- PK analysis set: all randomized patients receiving exebacase with PK samples valid for exebacase assay

*Sample Size*:

The study is designed to have sufficient power for the primary efficacy outcome in patients with MRSA (clinical outcome at Day 14 in the mITT analysis set) and the first two secondary efficacy outcomes (clinical outcome at Day 14 in the overall population in the mITT analysis set and 30-day all-cause mortality in the MRSA population in the mITT analysis set). Based on data from the Phase 2 study, assuming a 7% (exebacase + SoCA group) and 24% (SoCA alone group) 30-day all-cause mortality rate in the MRSA population with no censoring (i.e., all patients are followed until 30 days), 80% power, 2:1 randomization ratio, and a 2-sided alpha of 0.05, a total of 135 patients are required in the mITT analysis set in the MRSA population (90 and 45 patients in the exebacase + SoCA and SoCA alone groups, respectively) based on the log rank test. A total of 135 patients in the MRSA population results in 86% power to detect a significant difference between treatment groups assuming a 68% clinical responder rate in the exebacase + SoCA group at Day 14 and 40% in the SoCA alone group, using a 2-sided alpha of 0.05, and a Fisher's exact test. In the overall population (MRSA and MSSA), if 40% of patients have MRSA, a sample size of 339 patients (226 and 113 patients in the exebacase + SoCA and SoCA alone groups, respectively) in the mITT analysis set provides 83% power to show a significant treatment difference based on a 77% clinical responder rate in the exebacase + SoCA group at Day 14 and 61% in the SoCA alone group using a 2-sided alpha of 0.05 and a Fisher's exact test.

Table 4 provides a summary of the sample size calculations. If approximately 97% of randomized patients are in the overall population mITT analysis set, a total of 348 patients will be required.

**Table 4: Sample Size Calculations (2:1 Randomization Ratio, 2-sided Alpha=0.05)**

| | **Primary Outcome Clinical Responder Day 14 (MRSA Population)** | | **Secondary Outcome Clinical Responder Day 14 (Overall Population)** | | **Secondary Outcome 30-Day All-Cause Mortality (MRSA Population)** | |
|---|---|---|---|---|---|---|
| | **Exebacase + SoCA** | **SoCA Alone** | **Exebacase + SoCA** | **SoCA Alone** | **Exebacase + SoCA** | **SoCA Alone** |
| Outcome Rate | 68% | 40% | 77% | 61% | 7% | 24% |
| Power | 86% | | 83% | | 80% | |
| Sample Size (mITT analysis set) | 90 | 45 | 226 | 113 | 90 | 45 |

*Efficacy*:

The primary efficacy outcome is clinical responder rate at Day 14 in patients with MRSA in the mITT analysis set. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group. The clinical responder rate will be compared between the treatment groups using Fisher's exact test.

To control for the inflation of the overall type I error rate, a hierarchical testing procedure will be used. If statistical significance is declared for the primary efficacy outcome, testing will be done for the secondary efficacy outcomes in the order listed below. Testing will proceed to the next secondary outcome only if statistical significance (2-sided alpha=0.05) is declared for the preceding secondary outcome being tested.

- Clinical responder rate at Day 14 in the overall population (MRSA and MSSA) in the mITT analysis set. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group. The clinical responder rate will be compared between the treatment groups using Fisher's exact test.

- 30-day survival in the MRSA population in the mITT analysis set. Time to death through Day 30 will be analyzed using the Kaplan-Meier method. Differences between treatment groups will be determined using the log-rank test.
- Clinical responder rate at Day 60 in the MRSA population in the mITT analysis set. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group. The clinical responder rate will be compared between the treatment groups using Fisher's exact test.
- Clinical responder rate at Day 60 in the overall population (MRSA and MSSA) in the mITT analysis set. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group. The clinical responder rate will be compared between the treatment groups using Fisher's exact test.

Analyses of other secondary and additional efficacy outcomes will be conducted to support the findings of the primary efficacy outcome and secondary efficacy outcomes in the hierarchical testing procedure. Clinical response at Day 14, Day 30 and Day 60 and survival through Day 60 will be evaluated in the MSSA population (mITT analysis set) as an additional efficacy analysis.

Analyses of the primary efficacy outcome and key secondary efficacy outcomes will also be conducted in the PP analysis set.

*Safety*:

Safety will be evaluated by presenting summaries of treatment-emergent AEs (TEAEs), clinical laboratory evaluations (biochemistry, hematology, and coagulation), vital signs (blood pressure, respiratory rate, heart rate, and temperature), and ECG parameters. A TEAE is one that occurs on or after the administration of study drug through the Day 60 visit (Day 60 ± 7 days).

Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). An overall summary of AEs will be provided by treatment group. The incidence of TEAEs will be presented by system organ class (SOC) and preferred term (PT) through Day 7 and Day 60, by SOC, PT and relationship to study drug, and by SOC, PT and severity. Serious adverse events, SAEs with an outcome of death, and TEAEs that lead to discontinuation of the study drug will also be presented by SOC and PT. Descriptive statistics for clinical laboratory results, vital signs, and ECG parameters, including change from baseline, will be presented by timepoint collected and for the overall most abnormal post-baseline value (clinical laboratory results and vital signs only). Incidences of potentially clinically significant clinical laboratory results, vital signs, and ECG parameters, as defined in the SAP, will also be summarized by timepoint collected and the overall most abnormal post-baseline value (clinical laboratory results and vital signs only). Urinalysis results will be presented in a listing.

*Interim Analysis*:

Interim analyses of safety data (unblinded) will be provided to the DSMB throughout the study as defined in the DSMB charter. A futility analysis of the primary efficacy outcome in the MRSA population based on Day 14 clinical outcome data from approximately 60% of patients in the MRSA population in the mITT analysis set will also be reviewed by the DSMB. The futility analysis will be based on conditional power and the threshold for stopping the study due to futility will be provided in the SAP and DSMB charter. The futility boundary is non-binding.

*Immunogenicity:*

ADA results will be defined as positive and negative. ADA-positive samples will be further classified as neutralizing or non-neutralizing. Baseline and Day 30-60 ADA results will be summarized by result and in a shift table. For ADA positive patients, the number and percentage with neutralizing or

non-neutralizing ADA will be provided. The number and percentage of patients who had treatment-emergent ADA (defined as ADA-negative at baseline and ADA-positive at Day 30-60) will be summarized. The number and percentage of patients who had treatment-boosted ADA (defined as increased ADA titers in patients who were positive at baseline) will be summarized. TEAEs by baseline ADA result and clinical outcome at Day 14 by baseline ADA result will also be summarized. IgE results will be presented in a listing.

*Health Resource Utilization:*

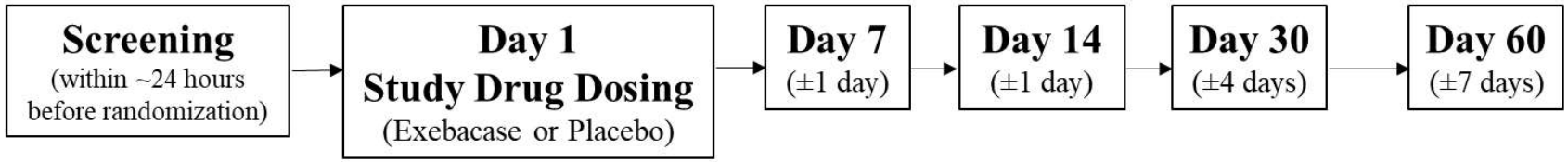
The following with be evaluated in the exebacase + SoCA and SoCA alone treatment groups (mITT analysis set) for patients enrolled in the US for both the overall population and the MRSA population: in-hospital mortality, hospital length-of-stay and ICU length-of-stay (post-study drug administration), discharge location, outpatient SoCA administration by outpatient facility or home health care, 30-day all-cause readmission, 30-day readmission for *S. aureus* BSI/IE or complication of *S. aureus* BSI/IE (e.g., metastatic foci, septic emboli), and insurance type.

*Pharmacokinetics*:

All PK data, dosing, and covariate information collected in this study will be pooled with the data collected from the prior studies to update the previously developed population PK model. The population PK analysis will be described in a separate SAP.

The relationship between PK parameters of exebacase (area under the plasma concentration versus time curve [AUC] and maximum plasma drug concentration [$C_{max}$]), derivative parameters (such as parameter over minimum inhibitory concentration [MIC]), and the clinical outcome and ADA will be explored. The relationship between PK parameters and most frequent or most clinically significant AEs may be explored.

## 3. STUDY SCHEMATIC




**Standard-of-Care Antibiotics (SoCA)**
~14 to 56 days

Notes:
Screening: Patients will be randomized as soon as possible after confirmation of study eligibility. However, to provide flexibility, screening assessments may be performed within approximately 24 hours before randomization, unless otherwise noted in the protocol.
Day 1: Study drug dosing will occur as soon as possible after randomization.
When a specific "Day" is noted (e.g., Day 14), the day is relative to exebacase/placebo administration (Day 1).

# 4. SCHEDULE OF ASSESSMENTS

| Study Procedures (Protocol Section) | Screening[1] | Day 1: Dosing[1,2] | Day 7 (±1)[2] | Day 14 (±1)[2] | Day 30 (±4)[2] | Day 60 (±7)[2] |
|---|---|---|---|---|---|---|
| Informed consent/assent (12.1) | X | | | | | |
| Inclusion/exclusion criteria (12.2) | X | | | | | |
| SOFA/APACHE II (12.2.2/12.2.3)[3] | X | | | | | |
| Medical history (12.4)[4] | X | | | | | |
| Diagnosis (12.5) | X | | X | | | |
| Risk factors (12.6) | X | | | | | |
| Source of infection (12.7)[5] | X | | X | X | X | X |
| Safety labs (12.8.1, 12.8.2.1)[6] | X | 24 hr post-dose (Day 2) | | X (adults) | X | |
| Pregnancy test (12.8.1, 12.8.2.2)[7] | X | | | | X (between Day 30 to Day 60) | |
| ADA (12.8.2.3)[8] | X | | | | X (between Day 30 to Day 60) | |
| IgE (12.8.2.3)[9] | X | | | | | |
| PK (12.8.2.4)[10] | X | X | | | | |
| Blood cultures (12.8.2.5)[11] | X | Daily until 2 consecutive negatives on 2 different days post-dose & as clinically indicated | | | | |
| Other cultures (12.8.2.6)[12] | To determine source of infection (at screening or within 1 week)[5], evaluate metastatic foci[15], & as clinically indicated thru Day 60 | | | | | |
| 12-Lead ECG (12.9) | X | | | X | | |
| Physical exam (12.10)[13] | X | | X | X | X | X |
| Weight and height (12.10) | X | | | | | |
| Vital signs (12.11)[14] | X | 30-40 min post-study drug start[14] | X | X | X | X |
| Metastatic foci/septic emboli (12.12)[15] | X | X | X | X | X | X |
| Signs/symptoms of infection (12.13)[16] | X | X | X | X | X | X |
| Echocardiography (12.14)[17] | ±3 days of rand (before rand preferred/required for some patients); and as clinically indicated[17] | | | | | |
| Randomization (12.3)[1,18] | | X | | | | |
| Remove infected IV catheter (12.15)[19] | | Within 72 hr after randomization | | | | |
| Ultrasound of CVC site (12.16)[20] | | Within 48 hr after randomization | | | | |
| Vital status (12.17)[21] | | | | X | X | X |
| Clinical outcome (12.18) | | | | X | X | X |
| Microbiological outcome (12.19) | | | Days 4 & 7 | | | |
| Health resource utilization (12.20) | | Through Day 60 visit | | | | |
| Study drug dosing (9.4.1, 13)[22] | | X | | | | |
| SoCA dosing (9.4.2) | Approximately 14 to 56 days | | | | | |
| Medications (13.6, 13.7) | Prior/concomitant medications from 28 days before randomization through Day 60 visit | | | | | |
| Adverse event assessment (14) | From time of consent/assent through Day 60 visit | | | | | |

**Abbreviations and Footnotes:**
Abbreviations: ADA=anti-drug antibody; APACHE II = Acute Physiology and Chronic Health Evaluation II; AV= arteriovenous; BSI=bloodstream infection; CVC=central venous catheter; ECG=electrocardiogram; eCRF=electronic case report form; hr=hour; IE=infective endocarditis; IgE=immunoglobulin E; IRT=interactive response technology; IV=intravenous; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-sensitive *S. aureus*; PK=pharmacokinetic; rand=randomization; (q)SOFA=(quick) sequential (sepsis-related) organ failure assessment; SoCA=standard-of-care antibiotics; TEE=transesophageal echocardiogram; TTE=transthoracic echocardiogram.

1. Patients will be randomized as soon as possible after confirmation of study eligibility. To provide flexibility, screening assessments may be performed within approximately 24 hours before randomization, unless otherwise noted. Study drug dosing will occur as soon as possible after randomization.
2. When a specific "Day" is noted (e.g., Day 14), the day is relative to exebacase/placebo administration (Day 1). Visit windows are as follows: Day 7 (±1 day), Day 14 (±1 day), Day 30 (±4 days), Day 60 (±7 days).
3. During screening, the qSOFA score will be determined for all patients (Section 12.2.2). In patients that have at least 2 criteria of qSOFA, a SOFA score will be performed (Section 23.1) to determine whether the patient has sepsis and/or septic shock per the inclusion criteria and the diagnosis definition. Baseline APACHE II score will be calculated for all patients (Sections 12.2.3 and 23.2). Patients with APACHE II score of >30 are excluded from the study.
4. Medical history for 1 year prior to screening, including relevant previous and current medical diagnoses and major surgical procedures.
5. All efforts will be made to determine the source of *S. aureus* BSI/IE (e.g., full physical examination, imaging as needed, cultures of other infected body sites or catheters that may be considered the source) preferably during screening or within 1 week after randomization. The resolution of the source of *S. aureus* BSI/IE will be evaluated at Days 7, 14, 30, and 60.
6. *Local Laboratory*: Limited laboratory tests may need to be performed by the site's local laboratory during screening for study eligibility determination, and to determine the dose of study drug (based on CrCl using ideal body weight and serum creatinine result obtained as close to the start of study drug dosing as possible (but not more than approximately 24 hours before the start of study drug dosing) (Section 9.4.1). The specific laboratory tests that are required to be available locally are described in Section 12.8.1.
   *Central Laboratory*: Blood and urine samples for safety laboratory tests (biochemistry, hematology, coagulation, and urinalysis) will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) or after randomization and before dosing, approximately 24 hours after study drug administration (Day 2), on Day 14 for adults*, and Day 30; samples will be sent to a central laboratory for testing. The collection of Day 14 samples is not required for adolescents. Results from local clinical laboratory testing completed within the Day 14 visit window should be entered into the eCRF if available and feasible. For all patients, if a blood or urine sample for safety laboratory testing by the central laboratory is not able to be obtained at a given timepoint/visit, the local laboratory results may be entered into the eCRF for that timepoint/visit, if feasible. If a blood or urine sample for safety laboratory testing by the central laboratory or local laboratory results are not able to be obtained at the Day 30 visit, samples may be collected on any day between the Day 30 and 60 visit windows (i.e., between Day 26 and Day 67) when collecting the blood sample(s) for exebacase-specific ADA and pregnancy test (if applicable). For adolescents, the results of local clinical laboratory testing during the screening window and at all other timepoints corresponding to the protocol can substitute for central safety laboratory tests and will be entered into the eCRF; samples for ADA and IgE must be collected at the timepoints specified in the protocol and sent to the central laboratory.
7. For females of childbearing potential only: Urine or serum pregnancy test performed locally during screening for eligibility determination; blood samples for serum pregnancy test will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) and between the Day 30 and 60 visits and samples are sent to the central laboratory for testing.
8. Blood samples for exebacase-specific ADA will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) or after randomization and before dosing and on any day between the Day 30 and Day 60 visit windows (i.e., between Day 26 and Day 67); samples are sent to the central laboratory.
9. Blood samples for exebacase-specific IgE testing will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) or after randomization and before dosing and retained at the site. If a patient has clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug (Section 9.4.1.1), a blood sample for exebacase-specific IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample at screening will be sent to a central laboratory for testing.
10. All patients will be assigned to a PK sampling scheme and blood samples will be collected at 3 timepoints as follows: PK Group 1: pre-dose (collected during screening for patients who meet eligibility criteria and are expected to be randomized or after randomization and before dosing), within 5 to 25 minutes after the end of infusion, and between 3 to 5 hours after the end of infusion. PK Group 2: pre-dose (collected during screening for patients who meet eligibility criteria and are expected to be randomized or after randomization and before dosing), within 5 to 25 minutes after the end of infusion, and between 8 to 12 hours after the end of infusion.

11. Blood cultures will be collected from a peripheral venipuncture site when possible. Results of all blood cultures performed (from the initial *S. aureus*-positive blood culture collected pre-study through the Day 60 visit) will be entered in the eCRF (whether positive or negative for *S. aureus*). All *S. aureus* isolates (from the initial *S. aureus*-positive blood culture collected pre-study through the Day 60 visit) should be sent to the central lab. Blood cultures will be performed as follows:
    - Qualifying blood culture: The "qualifying" blood culture from specimens collected within approximately 72 hours before randomization (per the inclusion criteria in Section 10.1) will be recorded in the eCRF and the *S. aureus* isolate should be sent to the central laboratory. The site will make all efforts to work with the local microbiology laboratory to ensure that, wherever possible, the *S. aureus* isolate from the qualifying blood culture is retained and sent to the central laboratory. Note: Since susceptibility of the *S. aureus* isolate is a stratification factor (Section 12.3), the site will make all efforts to work with the local microbiology laboratory to ensure that susceptibility results from blood cultures are obtained before randomization to enable stratification by MRSA or MSSA. If a blood culture was performed for the current *S. aureus* infection prior to the qualifying blood culture, susceptibility results from the prior blood culture may be used. If the patient has a concomitant *S. aureus* infection at another body site from which susceptibility results are available (e.g., skin, abscess), the susceptibility results from this other culture may be used. If the patient is known to be colonized with MRSA, MRSA may be selected for the stratification factor.
    - Screening: One aerobic blood culture will be collected during screening (or after randomization and before dosing).
    - Daily: One aerobic blood culture will be collected daily during the study until 2 consecutive negative cultures followed out to negative for at least 48 hours on 2 different days are obtained after exebacase/placebo administration. Note: blood cultures may be collected every other day for adolescents.
    - Additional blood cultures will be performed as clinically indicated.
12. "Other" (non-blood) cultures, which are cultures from catheter tips or body sites or body fluids other than blood, should be performed to determine the source of *S. aureus* BSI/IE (Section 12.7) and evaluate metastatic foci (Section 12.12), and as clinically indicated during the study. Results of all other (non-blood) cultures (whether positive or negative for *S. aureus*) collected pre-study through the Day 60 visit will be recorded in the eCRF. *S. aureus* isolates from all other (non-blood) cultures collected pre-study through the Day 60 visit should be sent to the central laboratory.
13. Complete physical examinations and review of body systems will be performed during screening and at the Days 7, 14, 30, and 60 visits. Additional physical examinations will be performed as clinically indicated. The physical examinations will include a close evaluation for any new areas of pain or other signs or symptoms of metastatic foci of infection or septic emboli; new signs or symptoms (e.g., pain, shortness of breath) will trigger diagnostic testing for metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures). The physical examination will also include an evaluation of the primary source of *S. aureus* BSI/IE. Every effort should be made to perform study visits "in person" by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol). If it is not feasible to evaluate the patient "in person" at study visits, telephone/telehealth visits may be performed under the circumstances described in Section 11.5.1. A physical examination is not required for visits performed remotely by telephone/telehealth; however, a complete medical review of body systems will be performed during the telephone/telehealth visit and medical record data may be used to supplement these visits (e.g., sign and symptom evaluation and physical exam findings) to assess the patient's clinical status, primary source of infection, and the status or any pre-existing or presence of new metastatic foci. In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records alone may be used for physical examinations after contacting the Medical Monitor or designee as described in Section 12.10.
14. Vital signs (blood pressure, respiratory rate, heart rate, and temperature) will be performed during screening, approximately 30 to 40 minutes after the start of exebacase/placebo infusion and as clinically indicated during the infusion and at the Day 7, 14, 30, and 60 visits for visits performed "in person" or may be obtained via the study-specific mobile health service (Section 11.5.1). If it is not possible to perform vital signs "in person" or via the study-specific mobile health service, medical records may be used as described in Section 12.11. At screening, if more than one measurement is taken within the approximately 24 hours before randomization, the most abnormal value is recorded in the eCRF. At Days 7, 14, 30, and 60, if more than one measurement is taken on a given day, the most abnormal value is recorded in the eCRF.
15. Patients will be evaluated for existing and new metastatic foci (e.g., deep tissue abscess, septic arthritis, etc.) and septic emboli (e.g., to the brain, lung, etc.) during screening and at the Day 7, 14, 30, and 60 visits. Diagnostic testing will be performed as clinically indicated to assess metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures). For non-blood sites of *S. aureus* infection that are present at screening, the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will determine whether this is the source of *S. aureus* BSI/IE (Section 12.7) or a metastatic focus (Section 12.12). The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will consider the development of new metastatic foci or septic emboli, and timing for metastatic foci (i.e., before or after Day 7), when evaluating clinical outcome (Section 12.18). Metastatic foci identified through Day 7 are considered part of the patient's

baseline *S. aureus* BSI/IE; new metastatic foci identified after Day 7 or new septic emboli after study drug dosing are considered complications of *S. aureus* BSI/IE for the purpose of assessing clinical outcome. New septic emboli are defined as an acute presentation of septic emboli after dosing and are a reason for failure for clinical outcome; septic emboli that are incidentally found on imaging are considered part of the patient's baseline *S. aureus* BSI/IE if found before Day 7. Every effort should be made to perform study visits "in person" by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol), and preferably by the same person at all visits. If it is not feasible to evaluate the patient "in person" at study visits, telephone/telehealth visits may be performed under the circumstances described in Section 11.5.1. Metastatic foci/septic emboli should be evaluated during the telephone/telehealth visit by detailed questioning and a complete review of systems. Medical records may be used to supplement the telehealth/telephone evaluation. In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records alone may be used alone after contacting the Medical Monitor or designee as described in Section 12.12.

16. Signs and symptoms attributable to *S. aureus* BSI/IE will be evaluated during screening and at the Day 7, 14, 30, and 60 visits. Additionally, if SoCA is changed after study drug dosing due to lack of clinical response, signs and symptoms will be assessed on the day of the SoCA change and entered into the eCRF. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the 1572 and trained on the protocol) will assess whether each sign or symptom is attributable to *S. aureus* BSI/IE or provide an alternative attribution and will assess the symptom severity per the definitions in Table 9. Select symptoms will also be evaluated at pre-BSI/IE, which is the patient's "usual state of health" before the BSI/IE started. Specific symptoms attributable to *S. aureus* will be assessed as absent, mild, moderate, and severe according to the definitions in Table 9. Sweating and chill/rigors and signs attributable to *S. aureus* will be assessed as present or absent. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will assess the severity (see Section 12.12) and consider the progression of attributable signs and symptoms when evaluating clinical outcome (Section 12.18). Some symptoms may be considered 'medically not evaluable' due to certain medical circumstances or treatments, such as a patient in a medically induced coma or after surgery to remove a metastatic focus. Every effort should be made to perform study visits "in person" by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol), and preferably by the same person at all visits. If it is not feasible to evaluate the patient "in person" at study visits, telephone/telehealth visits may be performed under the circumstances described in Section 11.5.1. Signs and symptoms should be evaluated during the telephone/telehealth visits by detailed questioning and a complete medical review of systems. Medical records may be used to supplement the telehealth/telephone evaluation of signs and symptoms. In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records may be used alone after contacting the Medical Monitor or designee as described in Section 12.13.

17. Images from all echocardiograms from the initial echocardiogram performed to evaluate the current infection through the Day 60 visit will be provided to the central echocardiography laboratory, as directed by the Sponsor, and recorded in the eCRF. The results of any prior echocardiograms that are part of the patient's medical history (i.e., from the 1 year prior to screening) will be recorded in the eCRF. Echocardiograms will be performed as follows:

- All adult patients (≥18 years of age) will have a TTE or TEE within 3 days before or after randomization. All efforts will be made to perform the TTE or TEE before randomization.
  - Where possible, a TEE will be performed [Baddour 2015, Habib 2010, Habib 2015] and is recommended in patients with BMI >30 kg/m$^2$; the TEE may be performed within 3 days before or after randomization unless the TEE is performed due to clinical suspicion of L-IE (see below).
  - In patients that have clinical findings suggestive of L-IE (new murmur, worsening cardiac function, and/or peripheral or central nervous embolic phenomenon), a TEE will be performed before randomization to rule out mitral and/or aortic valve vegetation(s) or the patient will be excluded from the study per exclusion criterion #2 (Section 10.2). In cases where there is an alternative cause of new heart failure or cerebral emboli, a patient with a negative TTE for L-IE may be discussed with the Medical Monitor for potential enrollment.
  - In patients with persistent bacteremia for ≥3 days (i.e., blood cultures positive for *S. aureus* for ≥3 days), an echocardiogram will be performed before randomization to rule out L-IE. A TTE may be performed with permission of the Medical Monitor. If this echocardiogram is not performed or L-IE is not ruled out by this echocardiogram, the patient should not be randomized.
- In adolescents (12 to <18 years of age), echocardiograms (TTE or TEE) will be performed as clinically indicated taking into consideration risk factors for endocarditis (e.g., structurally abnormal heart [including pacemakers]), clinical features suggestive of endocarditis (e.g., new murmur), or persistent bacteremia [McMullan 2020], described in Section 12.14.

- If the patient had an echocardiogram performed prior to the study that was intended to evaluate the current infection, it will be sent to the central echocardiography laboratory, as directed by the Sponsor, and an additional TTE or TEE is not required unless as indicated above but should be discussed with the Medical Monitor if obtained ≥3 days prior to randomization.
- Follow-up echocardiograms will be performed as clinically indicated.

18. Patients will be randomized via the IRT system. The randomization will be stratified by poorly controlled diabetes (yes or no) as defined as a HgA1C ≥8% within approximately 90 days before randomization and susceptibility of the *S. aureus* isolate (MRSA, MSSA, or unknown). A HgA1C test is not required for patients with no medical history of diabetes and no suspicion of diabetes during the screening period. These patients will be stratified to "no" for poorly controlled diabetes. A HgA1C test should be performed in patients with medical history of diabetes or suspicion of diabetes during screening for whom a HgA1C test result within the approximately 90 days prior to randomization is not available. If a HgA1C is unavailable and testing cannot be performed for these patients prior to randomization, contact the Medical Monitor to determine how the patient should be stratified based on available clinical information. All efforts will be made to obtain susceptibility results before randomization to enable stratification by MRSA or MSSA (see Section 12.8.2.5). Creatinine clearance value will be entered into the IRT system and the system will provide the dose of study drug based on the CrCl value (Section 9.4.1). The Cockcroft-Gault formula for calculating CrCl using ideal body weight in patients with BMI ≥30 kg/m$^2$ and serum creatinine result obtained locally is provided in Section 12.8.1.1. The IRT system will also provide the PK group (Section 12.8.2.4).
19. If not already done prior to the study, intravenous catheters known or suspected to be infected must be removed, and as clinically needed replaced, preferably at a different site, as soon as possible within approximately 72 hours after randomization. Other hemodialysis access types (i.e., AV fistulas or AV grafts) and surgically managed infection sources that are known or suspected to be infected will be evaluated for removal/replacement, if clinically feasible. If removal/debridement is not feasible based on standard medical practice, the patient should be discussed with the Medical Monitor for potential enrollment.
20. In patients with CVCs, ultrasounds to evaluate clots in the vein should be performed within approximately 48 hours after randomization, unless the clot in the vein has been detected within this timeframe via other method (e.g., imaging such as CT scan or MRI or direct visualization during surgery).
21. Vital status (whether the patient is alive or dead, or last known date alive if vital status is unknown) will be obtained at Days 14, 30, and 60 for all patients, including patients that discontinue the study or withdraw consent/assent (as described in the informed consent/assent form). Vital status will be determined using available sources (e.g., the patient, patient's contacts, hospital and other medical records, and public records, such as social media, obituaries, social security death index), as described in the informed consent/assent form and FDA guidance (see Section 12.17).
22. Study drug (exebacase or placebo) dosing will occur as soon as possible after randomization. The dose is based on CrCl as described in Section 9.4.1. Study drug will be infused over approximately 2 hours as described in the Pharmacy Manual. Patients must be observed during study drug infusion by a medically qualified person from the clinical care team or research team with patient care experience (Section 9.4.1.1).

# 5. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

## TABLE OF CONTENTS

# LIST OF TABLES

# 6. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 2: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ABG | arterial blood gas |
| AC | Adjudication Committee |
| ADA | anti-drug antibody |
| AE | adverse event |
| AECI | adverse event of clinical interest |
| ANSM | Agence Nationale de Sécurité du Médicament et des Produits de Santé |
| APACHE II | Acute Physiology and Chronic Health Evaluation II |
| ATU | Autorisation Temporaire D'utilisation |
| AUC | area under the plasma concentration versus time curve |
| $AUC_{0-24}$ | area under the plasma concentration versus time curve from time 0 to 24 hours |
| $AUC_{0-\infty}$ | area under the plasma concentration versus time curve from time 0 to infinity |
| AUC/MIC | area under the plasma concentration versus time curve/minimum inhibitory concentration |
| AV | arteriovenous |
| BAT | basophil activation test |
| BMI | body mass index |
| BSI | bloodstream infection |
| CDC | Centers for Disease Control |
| CL | clearance |
| $C_{max}$ | maximum plasma drug concentration |
| CoNS | coagulase negative *Staphylococci* |
| COVID-19 | coronavirus disease 2019 |
| CVC | central venous catheter |
| DAIR | Debridement, antibiotics, irrigation, and retention |
| DSMB | Data Safety Monitoring Board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EOT | end-of-treatment with standard-of-care antibiotics |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ESRD | end-stage renal disease |
| EUA | Emergency Use Authorization |
| FDA | Food and Drug Administration |
| FiO2 | fraction of inspired oxygen |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| HgA1C | hemoglobin A1C |
| HIV | human immunodeficiency virus |
| hVISA | heterogeneous vancomycin-intermediate *S. aureus* |
| ICD | implantable cardioverter defibrillator |
| ICH | International Conference on Harmonization |
| ICU | intensive care unit |
| IA | intraarticular |
| IE | infective endocarditis |
| IEC | Independent Ethics Committee |
| IgE | immunoglobulin E |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| ITT | intent-to-treat |
| L-IE | left-sided infective endocarditis |
| MedDRA | Medical Dictionary of Regulatory Activities |
| MIC | minimum inhibitory concentration |
| mITT | microbiological intent-to-treat |
| MRSA | methicillin-resistant *S. aureus* |
| MSSA | methicillin-susceptible *S. aureus* |
| NOAEL | no observed adverse effect level |
| NOEL | no observed effect level |
| PaO2 | partial pressure of oxygen |
| PJI | prosthetic joint infection |
| PK | pharmacokinetic(s) |
| PK-PD | pharmacokinetic-pharmacodynamic |

| **Abbreviation or Specialist Term** | **Explanation** |
|---|---|
| PP | per protocol |
| PT | preferred term |
| qSOFA | quick Sequential (sepsis-related) Organ Failure Assessment |
| R-IE | right-sided infective endocarditis |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SoCA | standard-of-care antibiotics |
| SOC | system organ class |
| SOFA | Sequential (sepsis-related) Organ Failure Assessment |
| SpO2 | oxygen saturation |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TEE | transesophageal echocardiogram |
| $t_{1/2}$ | elimination half-life |
| TK | toxicokinetic |
| $T_{max}$ | time to maximum plasma concentrations |
| TOC | test-of-cure |
| TTE | transthoracic echocardiogram |
| US | United States |
| Vz | volume of distribution |
| VISA | vancomycin intermediate *S. aureus* |
| VRSA | vancomycin resistant *S. aureus* |
| WBC | white blood cell |
| WHO | World Health Organization |

# 7. INTRODUCTION

## 7.1. Background

### 7.1.1. Summary

Exebacase, a direct lytic agent, is an entirely new treatment modality against *Staphylococcus aureus*. Exebacase is a recombinantly-produced, purified cell wall hydrolase enzyme that results in rapid bacteriolysis, potent biofilm eradication, synergy with antibiotics, low propensity for resistance, and the potential to suppress antibiotic resistance when used together with antibiotics [Schuch 2014, Schuch 2017]. Exebacase represents a first-in-field, first-in-class treatment with the potential to improve clinical outcome when used in addition to standard-of-care antibiotics (SoCA) to treat *S. aureus* bloodstream infections (BSI) including infective endocarditis (IE). In 2015, the United States (US) Food and Drug Administration (FDA) granted Fast Track designation for the development of an intravenous (IV) formulation of CF-301 (exebacase) to treat *S. aureus* bacteremia/endocarditis. In 2020, the FDA granted Breakthrough Therapy designation for exebacase in 2020 for the indication of treatment of methicillin-resistant *S. aureus* (MRSA) BSI (bacteremia), including right-sided endocarditis (R-IE), when used in addition to standard-of-care anti-staphylococcal antibiotics in adult patients.

*S. aureus*, a virulent pathogen in humans, is a leading cause of BSI including IE, which are associated with substantial morbidity and mortality. In 2017, the US Centers for Disease Control (CDC) estimated that there were approximately 119,000 episodes of *S. aureus* BSI in the US, and approximately 20,000 patients died of these infections [Kourtis 2019]. *S. aureus* BSI is often associated with complications, including metastatic bone and soft tissue infections, IE, and recurrent infections. Complicated *S. aureus* BSI requires extended duration treatment with SoCA, often accompanied by surgical intervention (e.g., in the setting of prosthetic devices, or metastatic soft tissue infections). *S. aureus* BSI associated with prosthetic devices can be particularly difficult to treat due to the presence of biofilms, which conventional SoCA are unable to penetrate. The availability of a new, highly effective treatment for *S. aureus* BSI remains an area of high unmet medical need due to the high degree of morbidity and mortality, potentially lengthy treatment, and the increasing prevalence of multidrug resistant strains.

In *in vitro* experiments, exebacase exhibited potent activity against all strains of *S. aureus*, including methicillin-resistant strains and those that demonstrated resistance to vancomycin, daptomycin, and linezolid. *In vitro* and *in vivo* studies have demonstrated exebacase has a rapid onset of bactericidal action and synergistic effect when administered in combination with SoCA for *S. aureus* BSI (e.g., daptomycin). More recently, *in vitro* studies have demonstrated synergy when exebacase was used together with daptomycin against vancomycin-intermediate (VISA), heterogeneous vancomycin-intermediate (hVISA), and vancomycin-resistant (VRSA) strains of *S. aureus*. Importantly, while biofilm formation limits the efficacy of SoCA in the treatment of complicated *S. aureus* BSI including IE, exebacase demonstrates potent ability to clear biofilms in *in vivo* and *in vitro* models. *In vitro*, exebacase exhibits low potential to develop resistance and can reduce the propensity for the development of resistance to SoCA when co-administered.

Exebacase has been evaluated in a Phase 1 randomized, double-blind, placebo-controlled, dose-escalating study in 20 healthy subjects, and a Phase 2 multinational, randomized, double-blind, placebo-controlled, superiority-design, proof-of-concept study in 121 patients with complicated *S. aureus* BSI including IE being treated with standard-of-care antibiotics (SoCA). In the Phase 1 and Phase 2 studies, exebacase was generally safe and well tolerated, with no adverse clinical safety signals. There were no treatment-emergent adverse events (TEAEs) of hypersensitivity to exebacase or immune-related events in either study. The Phase 2 study established proof-of-concept for exebacase as a potential therapeutic used in addition to SoCA to treat patients with *S. aureus* BSI including R-IE, with a focus on MRSA. Amongst all patients with *S. aureus*, the study showed that 70.4% of patients in the exebacase + SoCA group and 60.0% of patients in the SoCA alone (placebo) group were clinical responders at Day 14 (p-value=0.3137). In the prespecified MRSA subgroup, the clinical responder rate at Day 14 was 42.8 percentage points higher in the exebacase + SoCA group compared with the SoCA alone group (ad hoc p-value=0.0101). In patients with BSI/R-IE, 80.0% and 59.5% of patients in the exebacase + SoCA and SoCA alone groups, respectively, were responders at Day 14 (ad hoc p-value=0.0280). In the Phase 2 study, the TEAEs were consistent with the patient population with severe, potentially life-threatening *S. aureus* BSI including right- and left-sided IE (R-IE and L-IE) and underlying comorbid conditions and the incidence was similar between treatment groups. The clinical studies are described in more detail in Section 7.1.6.

Full details of the background and development of exebacase are described in the Investigator's Brochure.

### 7.1.2. Overview of *S. aureus* Bloodstream Infections

*S. aureus* is a leading cause of BSI and is associated with substantial morbidity including a range of potentially serious and life-threatening complications that may be difficult to recognize and manage (e.g., IE) [Fowler 2003]. Intravenous drug users and patients with human immunodeficiency virus (HIV) and renal insufficiency, especially those requiring hemodialysis, are particularly at risk for developing *S. aureus* infections. Approximately 20% of patients with *S. aureus* BSI develop metastatic complications such as IE. The incidence of IE in the setting of *S. aureus* BSI has been estimated to be 10% to 15% [Fowler 2003, Chang 2003, Valente 2005], although incidence as high as 21% has been reported [Chang 2003]. Risk factors for IE in the setting of *S. aureus* BSI include presence of prosthetic heart valve, predisposing cardiac abnormalities, injection drug use, intravascular catheter infection, bacteremia of unclear origin, and persistent bacteremia [Chang 2003, El-Ahdhab 2005, Hill 2007].

Infective endocarditis due to *S. aureus* BSI is associated with substantial morbidity and mortality and is associated with complications more frequently than other causative pathogens (stroke, 21% versus 14%; systemic emboli, 27% versus 18%; persistent bacteremia, 17% versus 5%; and in-hospital mortality, 22% versus 14%, respectively) [Fowler 2005a]. The likelihood of developing complications depends on several factors including the infecting pathogen, duration of illness prior to therapy, and underlying comorbidities. Symptomatic cerebrovascular

complications occur in up to 35% of patients [Ruttman 2006, Snygg-Martin 2008, García-Cabrera 2013]. Silent cerebrovascular complications (including ischemia and microhemorrhage) may occur in up to 80% of patients [Snygg-Martin 2008, Cooper 2009]. The in-hospital mortality rate for IE is estimated to be 18% to 23% and the 6-month mortality rate has been estimated to be between 22% to 27% [Wallace 2002, Chu 2004, Hasbun 2003, Hill 2007, Wang 2007].

### 7.1.3. Current Treatments and Drug Resistance

Current treatment of *S. aureus* BSI includes prompt control or removal of the source of infection (e.g., removal of implicated catheters and/or drainage of abscess, if present) [López-Cortès 2013] and early initiation of effective antibiotic therapy. Antibiotic resistance, toxicity related to high dose/long duration therapy, and biofilm formation that cannot be cleared by SoCA contribute to treatment failure. Despite the availability of conventional antibiotic treatments, the 30-day all-cause mortality of *S. aureus* BSI has been estimated to be between 20% to 40% [Anantha 2014, Van Hal 2012] and mortality rates have not improved over recent decades [Souli 2019, Turner 2019, Tong 2015].

The antibiotic resistance among bloodstream *S. aureus* isolates, including methicillin resistance and the emergence of resistance to vancomycin, daptomycin, and linezolid is of concern. Mortality associated with MRSA bacteremia has been reported to be higher than mortality associated with methicillin-sensitive *S. aureus* (MSSA) bacteremia [Shurland 2007, Cosgrove 2003]. Treatment failure is fairly common in patients with *S. aureus* BSI, particularly among those patients with infection due to MRSA [Lodise 2008]. Both the CDC and the World Health Organization (WHO) regard antibiotic resistance as one of the greatest threats to human health worldwide, with MRSA, categorized as a "serious threat" by the CDC and a "high priority" by the WHO [CDC 2019, WHO 2017]. MRSA infections occurred in an estimated 323,700 hospitalized patients in the Untied Statues (US) in 2017, and approximately 10,600 patients died [Jernigan 2020, CDC 2019].

The treatment of *S. aureus* BSI, particularly drug-resistant strains, is challenging due to the limited number of treatment options, and the requirements for longer duration, high-dose treatment regimens. Both vancomycin and daptomycin, the only antibiotics indicated for the treatment of MRSA, are associated with dose-limiting toxicities. Evidence suggests that emerging resistance to current therapies for MRSA (e.g., vancomycin minimum inhibitory concentration [MIC] >1.5 µg/mL), VISA, and high-level VRSA are associated with worse clinical outcomes [Bayer 2013].

Daptomycin, the newest drug developed for MRSA BSI, is over 10 years old and was approved based on noninferiority to older comparator antibiotics (e.g., vancomycin) with clinical cure rates of approximately 40% in both groups [Fowler 2006]. Despite the availability of antibiotics with activity against MRSA, attempts to develop new antibiotic treatments for *S. aureus* BSI have been unsuccessful [Geriak 2019]. While a number of clinical trials have evaluated the utility of

adjunct agents for treatment of *S. aureus* BSI, none have shown a significant impact on efficacy. Immunotherapeutic agents all failed to advance to confirmatory clinical trials [Weems 2006, Rupp 2007, Weisman 2011, Otto 2010]. The addition of adjunct conventional antibiotics such as gentamicin [Cosgrove 2009], rifampin [Thwaites 2018] or a beta-lactam antibiotic [Tong 2020] to conventional therapy for *S. aureus* or MRSA BSI were similarly unsuccessful.

While the introduction of penicillin to treat *S. aureus* BSI drastically decreased the case fatality rate of *S. aureus* BSI from approximately 80% in the pre-antibiotic era, case fatality rates reported over recent decades have plateaued to the approximately 15% to 50% range [Fowler 2005b]. This continued high mortality rate may be, at least in part, reflective of a relative plateau in antibiotic efficacy. The last major advance in the treatment of MRSA bacteremia was the introduction of vancomycin, over 60 years ago. Thus, there is an urgent need for novel treatments for *S. aureus* BSI in general, and MRSA BSI in particular.

Exebacase, a targeted treatment for *S. aureus* BSI, with limited propensity for resistance, potent antibiofilm activity, and the potential for synergistic efficacy and reduced resistance when used in combination with existing agents has the potential to address this need.

The Phase 2 study of exebacase (CF-301-102) is the first to show promising improvement in clinical outcome among patients who receive adjunctive therapy for *S. aureus* BSI. This improvement was particularly marked in the pre-specified MRSA subgroup. The results of the Phase 2 study of exebacase are described in Section 7.1.6.

### 7.1.4. Exebacase for the Treatment of *S. aureus*

Exebacase, a direct lytic agent, is an entirely new treatment modality for *S. aureus* and a member of a new class of antimicrobials known as lysins (cell wall hydrolase enzymes). In nature, lysins are one of the most potent killing agents produced by bacteriophages to digest the bacterial cell wall to allow phage progeny release. Lysin technology has enabled the production of lysins as purified biologic therapeutics for human medicinal use, completely devoid of bacteriophage. Exebacase is a recombinantly-produced, purified protein that represents a first-in-field, first-in-class treatment with the potential to improve clinical outcome when used in addition to SoCA to treat *S. aureus* BSI including IE. Exebacase is new treatment modality, fundamentally distinct from conventional antibiotics. When added externally to *S. aureus* bacteria, exebacase creates immediate lysis upon contact with the cell wall, causing log-fold death of the target bacterium. Whereas most conventional antibiotics typically target a broad spectrum of bacteria, including normal flora, lysins are highly targeted to specific bacterial species. Exebacase specifically targets staphylococci, including MSSA and MRSA as well as strains that are non-susceptible to vancomycin and daptomycin. The highly targeted nature of exebacase reduces the potential for biological toxicity associated with negative effects of broad-spectrum antibiotics on the human gastrointestinal microbiome (e.g., killing of beneficial normal flora).

Exebacase is distinct from current SoCA due to: (1) its novel mechanism of action; (2) rapid, potent bactericidal activity against antibiotic-resistant *S. aureus*; (3) potent ability to eradicate biofilms; (4) synergy with SoCA; (5) narrow spectrum of lytic action; (6) low propensity to develop bacterial resistance; and (7) ability to protect against the emergence of resistance to SoCA when used in combination. Exebacase activity has been extensively evaluated *in vitro* and *in vivo*, in animal models of infection. These studies indicate that exebacase is complimentary to and synergistic with conventional antibiotics, and thereby has the ability to address the limitations of the current standard-of-care antibiotics against *S. aureus.*

Full details of the background and development of exebacase are available in the Investigator's Brochure.

### 7.1.5. Preclinical Studies

*Nonclinical Efficacy Studies*

The efficacy of exebacase administered as a single dose or multiple doses, either alone or in addition to anti-staphylococcal antibiotics (daptomycin, vancomycin, or oxacillin) was demonstrated in two murine *S. aureus* bacteremia models. The results from these studies demonstrated that: (1) exebacase as single-agent significantly enhanced 24-hour survival in MRSA infections; (2) In a higher inoculum infection model, exebacase in addition to daptomycin, vancomycin, or oxacillin, was effective against *S. aureus*, including MSSA and MSRA, whereas monotherapy with human equivalent therapeutic doses of antibiotics was ineffective; (3) Single and repeat doses of exebacase administered in addition to 7 daily doses of daptomycin significantly improved survival when compared to either exebacase alone or daptomycin alone.

The efficacy of exebacase in addition to daptomycin or vancomycin was also demonstrated in the rat and rabbit IE models. In both animal models of IE, the addition of exebacase to daptomycin or vancomycin resulted in a substantially reduced bacterial density in all tissues compared to vehicle control, a single dose of exebacase alone or daptomycin or vancomycin administered alone for 4 days. Using the murine neutropenic thigh infection model, area under the plasma concentration versus time curve/ minimum inhibitory concentration ratio (AUC/MIC) ratio was determined to be the pharmacokinetic-pharmacodynamic (PK-PD) index most predictive of exebacase efficacy. An AUC/MIC ratio of ≥1.5 was associated with maximal efficacy for exebacase alone. An AUC/MIC ratio of ≥0.5 was associated with maximal efficacy of exebacase administered in addition to daptomycin, vancomycin, or oxacillin. In the murine neutropenic thigh infection model with a catheter biofilm implant, an AUC/MIC index of ≥0.2 was associated with efficacy of exebacase administered in addition to daptomycin.

In an *in vitro* and *in vivo* study in mice, exebacase synergized with daptomycin at sub-MIC levels to kill a range of MSSA and MRSA isolates in the presence of pulmonary surfactant (an inhibitor of daptomycin alone) [Schuch 2015].

*Nonclinical Safety Studies*

The PK/toxicokinetic (TK), safety pharmacology, and toxicity of exebacase have been investigated in the rat and the dog. Key findings by study type are summarized below.

Safety Pharmacology, PK, and Toxicology:

- In both species, exposure (AUC) and maximum plasma drug concentration ($C_{max}$) generally increased with increasing dose in an approximately dose proportionate fashion. Following a single dose and repeat doses, the terminal half-life ($t_{1/2}$) was short: For a single dose, $t_{1/2}$ was <1 hour in rats and 1.2 to 1.4 hours in dogs.
- Exebacase has no direct pharmacological effects on the central nervous system (CNS) in rats or on cardiovascular or respiration function in dogs. In dogs, evidence of a hypersensitivity or anaphylactoid-like response was observed in some animals, but this required the administration of at least 3 doses administered 1 week apart. A similar response was not observed after a single administration, even at a high dose.

The immunological response to exebacase in the rat and the dog following single and repeat doses:

- Following single exebacase doses in the rat up to 25 mg/kg, exebacase-specific ADA was detected 14 days after dosing, with increasing numbers of positive samples identified with increasing doses.
- Following 7 daily repeat doses of up to 50 mg/kg/day in the rat and the dog, titers of exebacase-specific ADA were detected in most animals by Day 8 (following last dose) and increased in incidence and titer by days 15 and 29 post-dose.
- The presence of exebacase-specific ADA did not affect the clearance of or exposure to exebacase. These results were consistent with a typical immune response of animals to a foreign protein with regard to the timeline of appearance of ADA.

A Good Laboratory Practice (GLP) extended single-dose toxicity study in the rat and repeat-dose toxicity studies in the rat and the dog characterized the dose-limiting toxicity following exebacase dosing:

- Following a single-dose of exebacase administered as a 2-hour infusion in the rat, microscopic observations of perivascular/adventitial inflammation surrounding the pulmonary arteries were the primary toxicological observation. These adventitial findings occurred at low incidence and minimal severity at single doses of 10 and 25 mg/kg at the Day 3 necropsy and resolved during a 14-day recovery period. No adventitial findings were observed at the 2.5 mg/kg dose and therefore it was reported as the no observed effect level (NOEL) for the study. Based on exebacase-specific ADA, that was not associated with adventitial findings or adverse immunological effects, the 2.5 mg/kg dose could be considered a no observed adverse effect level (NOAEL).

  - A subsequent review of the study results by a Pathology Working Group determined that, based on a lack of adventitial findings at the 5.0 mg/kg dose, the Pathology Working Group considered the 5.0 mg/kg dose as the NOEL for the study. This review is described in detail in the Investigator's Brochure.

- In the GLP 7-day, repeat-dose toxicity studies, adventitial findings in both the rat and the dog were the dose-limiting toxicity findings. However, compared to a single dose of exebacase where the adventitial finding was of low incidence, minimal severity, and reversible at dose of ≤25 mg/kg, following repeat doses of exebacase, the adventitial finding increased in incidence, severity, and tissue distribution in medium to larger blood vessels of multiple tissues.

A series of special toxicity studies were conducted in the rat:

- Enzymatically-active exebacase was associated with the development of the adventitial vascular findings whereas enzymatically-inactive exebacase was not.
- Exebacase produced signs and symptoms of hypersensitization response in specialized rat models of hypersensitivity of the Brown Norway and Lewis rats. However, the precise nature of the hypersensitivity response (Type I or Type III) was not definitively identified; studies in rodents may not necessarily be predictive for humans in terms of the nature of hypersensitivity reactions [Finkelman 2007]. Of note, in the Phase 1 and 2 clinical studies, exebacase did not appear to be sensitizing for allergic hypersensitivity; further information on clinical immunogenicity is in Section 7.1.6.

A series of exploratory studies in the rat were performed to identify the PK parameter most predictive of adventitial/perivascular findings in the great vessels of the cardio-pulmonary circulation and to more accurately predict the exposures associated with this finding. Overall, the exploratory studies and Neural Network analyses concluded that AUC is the PK parameter most associated with an observation of adventitial/perivascular findings in the pulmonary arteries.

From cross-species population PK modeling of all PK/TK data sets from 9 studies that included 270 rats and 78 dogs, an accurate estimate of the exposure levels associated with the 2.5 mg/kg was obtained. Based on this collective analysis, the predicted mean area under the concentration versus time curve from time 0 to 24 hours ($AUC_{0-24}$) was 3,596 ng*hr/mL and the predicted mean $C_{max}$ was 1,754 ng/mL following a single 2.5 mg/kg 2-hour infusion of exebacase in the rat. The predicated mean $AUC_{0-24}$ and $C_{max}$ were 7,192 ng*hr/mL and 3,508 ng/mL following a single 5.0 mg/kg 2-hour infusion of exebacase in the rat.

Additional detail on the preclinical studies can be found in the Investigator's Brochure.

### 7.1.6. Clinical Studies

Exebacase has been evaluated in two clinical studies:

- Study CF-301-101, entitled "A Phase 1, Placebo-Controlled, Dose-Escalating Study to Examine the Safety and Tolerability of Single Intravenous Doses of CF-301 in Healthy Male and Female Subjects"
- Study CF-301-102, a Phase 2 study, entitled "A Multicenter, Double-Blind, Randomized, Comparative Study of the Safety, Tolerability, Efficacy, and Pharmacokinetics of CF-301 vs. Placebo in Addition to Standard-of-Care Antibacterial Therapy for the Treatment of Adult Patients with *Staphylococcus aureus* Bloodstream Infections (Bacteremia) Including Endocarditis"

***Study CF-301-101:***

The Phase 1 clinical study, CF-301-101, was a double-blind, randomized, study to evaluate the safety, tolerability, and PK of single, escalating IV doses of exebacase in healthy male and female subjects. Pre-defined stopping rules were included in the protocol and an independent Data Safety Monitoring Board (DSMB) reviewed unblinded safety and PK data at pre-specified timepoints throughout the study and rendered a recommendation to the Sponsor as to whether or not dosing should progress as planned.

A total of 143 males and females were screened for participation in the study and 97 of those potential subjects were screened for the presence of exebacase-specific ADA, exebacase-specific immunoglobulin E (IgE), and *ex vivo* exebacase-specific basophil activation test (BAT). Thirteen potential subjects were excluded due to positive ADA, 5 were excluded due to positive BAT, and 1 was excluded due to positive BAT and IgE. A total of 20 healthy male and female subjects were enrolled in the study. Thirteen subjects received exebacase (4 subjects at the 0.04 mg/kg dose level; 4 subjects at the 0.12 mg/kg dose level; 4 subjects at the 0.25 mg/kg dose level; and 1 subject at the 0.4 mg/kg dose level) and 7 subjects received placebo.

Exebacase was generally safe and well tolerated during study CF-301-101. There were no deaths, no serious adverse events (SAE), and no discontinuations due to AEs during the study. There were no infusion reactions or AEs of hypersensitivity related to exebacase. A total of 5 non-serious TEAEs were reported by 4 subjects: 2 subjects who received exebacase reported headache, contact dermatitis, and allergic rhinitis and 2 subjects who received placebo reported viral upper respiratory tract infection and viral infection. All TEAEs were mild in intensity and resolved. Only 1 TEAE (headache in the exebacase group) was considered related to study drug. The number of TEAEs observed in the placebo and exebacase groups was similar and the incidence of TEAEs among subjects who received exebacase was not dose dependent.

Pharmacokinetic parameters of exebacase are summarized in Table 3. After infusion of exebacase, plasma concentrations and PK parameters ($C_{max}$ and AUC) increased in a linear and dose proportional manner with a slope less than 1 (i.e., for a 2-fold increase in dose, AUC or $C_{max}$ increased by 1.75-fold). However, there was no evidence of a plateau in exposures by increasing dose within the range studied in healthy volunteers. The geometric mean terminal elimination half-life ($t_{1/2}$) ranged from 4.37 to 6.58 hours for subjects that received 0.04 mg/kg, 0.12 mg/kg, and 0.25 mg/kg of exebacase, independent of dose, and was 11.3 hours for the 1 subject that received 0.4 mg/kg of exebacase, with individual subject values ranging from 4.33 to 14.7 hours across the 4 dose levels with no apparent relationship to dose.

**Table 3: Phase 1 Study: Pharmacokinetic Parameters for Exebacase**

| Parameter* | Cohort 1 0.04 mg/kg | Cohort 2 0.12 mg/kg | Cohort 3 0.25 mg/kg | Cohort 4 0.4 mg/kg |
|---|---|---|---|---|
| Cmax (ng/mL) | 205 (14.2) (4) | 489 (16.1) (4) | 731 (25.4) (4) | 1,212 (1) |
| Tmax (hr) | 1.75 (4) | 2.00 (4) | 2.00 (4) | 2.00 (1) |
| | [1.00 – 2.00] | [1.88 – 2.02] | [1.48 – 2.00] | [2.00 – 2.00] |
| AUC(0-t) (hr×ng/mL) | 498 (12.8) (4) | 1,121 (16.0) (4) | 1,749 (25.0) (4) | 3,311 (1) |
| AUC(inf) (hr×ng/mL) | 503 (12.6) (4) | 1,126 (16.0) (4) | 1,758 (24.8) (4) | 3,316 (1) |
| λz (1/hr) | 0.1054 (52.6) (4) | 0.1585 (6.79) (4) | 0.1145 (64.9) (4) | 0.0613 (1) |
| t½ (hr) | 6.58 (52.6) (4) | 4.37 (6.79) (4) | 6.05 (64.9) (4) | 11.3 (1) |
| CL (L/hr) | 5.98 (24.6) (4) | 6.72 (25.1) (4) | 10.3 (17.5) (4) | 9.86 (1) |
| Vz (L) | 56.7 (31.9) (4) | 42.4 (24.4) (4) | 90.3 (73.5) (4) | 161 (1) |

Abbreviations: λz = elimination rate constant; $AUC_{(0-t)}$ = area under the curve from zero to the time of the last quantifiable concentration; $AUC_{(inf)}$ = area under the curve to infinity; CL = clearance; $C_{max}$ = maximum plasma concentration; CV = coefficient of variation; hr = hour; IV = intravenous; $T_{max}$ = time to $C_{max}$; $t_{1/2}$ = half-life; $V_z$ = volume of distribution.
*Geometric mean (geometric CV) (N) except $T_{max}$ for which the median (N) [Range] is reported.

Results of immunogenicity testing showed that a total of 9 of 13 subjects (69.2%) dosed with exebacase developed exebacase-specific ADA (7 subjects by Day 28 and 2 subjects by Day 90). The ADA titers at Day 28 were variable and ranged from 1:10 to 1:2560 and were waning or absent by Day 180. Only 1 subject developed a low-level treatment-emergent IgE signal that resolved by Day 90 and remained resolved at Day 180. No AEs related to hypersensitivity to exebacase were reported. No subjects tested positive for exebacase-specific BAT. Consideration of this single, transient low-level signal for exebacase-reactive IgE, along with the lack of any signal from the CF-301-specific BAT, suggests a low risk for allergic-type hypersensitivity.

In conclusion, exebacase was generally well tolerated at doses of 0.04, 0.12, 0.25, and 0.4 mg/kg/dose, and no clinical adverse safety signals were observed. The increase in plasma AUC and $C_{max}$ of exebacase across the dose range of 0.04 to 0.4 mg/kg/dose was less than dose-proportional with no evidence of a plateau in exposures. While 69.2% of subjects developed exebacase-specific ADA, no correlation between ADA titers and either IgE or BAT was observed. ADA response signals were decreasing or absent by Day 180. There was no detectable exebacase in urine.

***Study CF-301-102*:**

The Phase 2 study, CF-301-102, was a multinational, randomized, double-blind, placebo-controlled, superiority-design, proof-of-concept study to evaluate the safety, tolerability, efficacy, and PK of exebacase in addition to SoCA versus SoCA alone for the treatment of adult patients with *S. aureus* BSIs including IE.

Patients received a single dose of exebacase or placebo in addition to appropriate SoCA, which included vancomycin, daptomycin, semi-synthetic penicillins, and first generation cephalosporins. The dose of exebacase was 0.25 mg/kg based on target attainment, with a dose adjustment to 0.12 mg/kg for patients with CrCl <60 mL/min and patients >50 years of age.

An independent DSMB reviewed unblinded safety and PK data throughout the core study. An independent blinded Adjudication Committee (AC) determined the final diagnosis and clinical response based on clinical response definitions in the protocol and centralized echocardiographic readings.

A total of 121 patients were randomized in a 3:2 ratio to exebacase (73 patients) or placebo (48 patients). The safety population included 119 patients who received study drug, and the microbiological intent-to-treat (mITT) population included 116 patients, consisting of 71 patients in the exebacase + SoCA group and 45 patients in the SoCA alone (placebo) group with documented *S. aureus* from blood cultures who received study drug.

The majority of patients (79.3%) were enrolled in the US. In general, the treatment groups were well balanced with respect to demographics. There was a greater percentage of patients with poorly controlled diabetes, severe renal impairment, and on dialysis in the exebacase + SoCA group. In the mITT population, 27 of 71 patients (38.0%) in the exebacase + SoCA group and 16 of 45 patients (35.6%) in the SoCA alone group had MRSA.

The majority of patients in both treatment groups had a final adjudicated diagnosis of *S. aureus* BSI (77.5% and 86.7% in the exebacase + SoCA and SoCA alone groups, respectively). There was a higher rate of L-IE in the exebacase + SoCA group (11 patients; 15.5%) compared with the SoCA alone group (3 patients; 6.7%).

*Efficacy:*

The primary efficacy outcome was clinical outcome at Day 14 in the mITT population, as assessed by the AC. As shown in Table 4, 70.4% of patients in the exebacase + SoCA group and 60.0% of patients in the SoCA alone group were clinical responders at Day 14 (p-value=0.3137). In the prespecified analysis in the MRSA subgroup, the clinical responder rate at Day 14 was 42.8 percentage points higher in the exebacase + SoCA group compared with the SoCA alone group; 74.1% and 31.3% of patients in the exebacase + SoCA and SoCA alone groups, respectively, were responders at Day 14 (ad hoc p-value=0.0101). Responder rates in the MSSA subgroup were similar between treatment groups, 68.2% in the exebacase + SoCA group and 73.3% in the SoCA alone group, but results were affected by a difference in the number of

patients with left-sided endocarditis between treatment groups, as discussed in the paragraphs that follow the table.

**Table 4: Phase 2 Study: Clinical Outcome at Day 14 Assessed by Adjudication Committee by MRSA and MSSA Subgroup (mITT Population)**

| | Total Population | | MRSA[1] | | MSSA[1] | |
|---|---|---|---|---|---|---|
| | Exebacase + SoCA (N=71) n (%) | SoCA Alone (N=45) n (%) | Exebacase + SoCA (N=27) n (%) | SoCA Alone (N=16) n (%) | Exebacase + SoCA (N=44) n (%) | SoCA Alone (N=30) n (%) |
| Responder[2] | 50 (70.4) | 27 (60.0) | 20 (74.1) | 5 (31.3) | 30 (68.2) | 22 (73.3) |
| 95% CI[3] | [58.4, 80.7] | [44.3 74.3] | [53.7, 88.9] | [11.0, 58.7] | [52.4, 81.4] | [54.1, 87.7] |
| Difference (90% CI)[4] | 10.4 [-6.3, 27.2] | | 42.8 [14.3, 71.4] | | -5.2 [-25.6, 15.3] | |
| p-value[4] | 0.3137 | | 0.0101 | | 0.7964 | |
| Improvement | 44 (62.0) | 25 (55.6) | 19 (70.4) | 4 (25.0) | 25 (56.8) | 21 (70.0) |
| Response | 6 (8.5) | 2 (4.4) | 1 (3.7) | 1 (6.3) | 5 (11.4) | 1 (3.3) |
| 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) |

Abbreviations: MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-sensitive *S. aureus*; SoCA=standard-of-care antibiotics.
Note: Denominator is all patients in the mITT population with noted infection, within each treatment group.
One patient in the SoCA alone group had both MRSA and MSSA and was counted in both subgroups.
1. Responder=clinical outcome of improvement or response.
2. Confidence intervals (CIs) calculated using Clopper-Pearson method.
3. CI for the difference in percentage improvement/response between exebacase + SoCA and SoCA alone groups calculated using a continuity corrected Z-statistic.
4. P-value is based on Fisher's exact test.

In patients with L-IE, 2 of 11 patients (18.2%) in the exebacase + SoCA group and 2 of 3 patients (66.7%) in the SoCA alone group were responders at Day 14. The difference in the number of patients with L-IE between treatment groups (11 and 3 patients in the exebacase + SoCA and SoCA alone groups, respectively) was unexpected. Due to the inherent differences in clinical severity, SoCA treatment modalities, and outcome rates for patients with L-IE, this difference between treatment groups affected the efficacy analysis, and an ad hoc analysis excluding patients with L-IE was conducted. As shown in Table 5, in patients with BSI/R-IE (excluding L-IE), 80.0% and 59.5% of patients in the exebacase + SoCA and SoCA alone groups, respectively, were responders at Day 14 (ad hoc p-value=0.0280).

The ad hoc analysis of clinical outcome by diagnosis was also analyzed by MRSA and MSSA subgroups, given the difference in the number of patients with left-sided endocarditis in the MSSA subgroup (8 and 3 patients in the exebacase + SoCA and SoCA alone groups, respectively). In patients with MRSA BSI/R-IE, 19 of 24 patients (79.2%) in the exebacase + SoCA group were responders at Day 14 compared with 5 of 16 patients (31.3%) in the SoCA alone group (ad hoc p-value=0.0036). The analysis of MSSA patients excluding patients with left-sided endocarditis indicated that in the subpopulation of patients with MSSA BSI/R-IE, 29 of 36 patients (80.6%) in the exebacase + SoCA group were responders at Day 14 compared with 20 of 27 patients (74.1%) in the SoCA alone group (ad hoc p-value=0.5571).

**Table 5: Phase 2 Study: Clinical Responders at Day 14 Assessed by Adjudication Committee by Diagnosis (mITT Population)**

| | Total Population | | MRSA[1] | | MSSA[1] | |
|---|---|---|---|---|---|---|
| | Exebacase + SoCA (N=71) n/N (%) | SoCA Alone (N=45) n/N (%) | Exebacase + SoCA (N=27) n/N (%) | SoCA Alone (N=16) n/N (%) | Exebacase + SoCA (N=44) n/N (%) | SoCA Alone (N=30) n/N (%) |
| IE | 5/16 (31.3) | 3/6 (50.0) | 2/5 (40.0) | 0/1 (0) | 3/11 (27.3) | 3/5 (60.0) |
| R-IE | 3/5 (60.0) | 1/3 (33.3) | 1/2 (50.0) | 0/1 (0) | 2/3 (66.7) | 1/2 (50.0) |
| L-IE[2] | 2/11 (18.2) | 2/3 (66.7) | 1/3 (33.3) | 0 | 1/8 (12.5) | 2/3 (66.7) |
| BSI | 45/55 (81.8) | 24/39 (61.5) | 18/22 (81.8) | 5/15 (33.3) | 27/33 (81.8) | 19/25 (76.0) |
| Complicated | 33/42 (78.6) | 21/36 (58.3) | 13/17 (76.5) | 3/13 (23.1) | 20/25 (80.0) | 18/24 (75.0) |
| Uncomplicated | 12/13 (92.3) | 3/3 (100) | 5/5 (100) | 2/2 (100) | 7/8 (87.5) | 1/1 (100) |
| BSI/R-IE | 48/60 (80.0) | 25/42 (59.5) | 19/24 (79.2) | 5/16 (31.3) | 29/36 (80.6) | 20/27 (74.1) |
| p-value[3] | 0.0280 | | 0.0036 | | 0.5571 | |
| Complicated BSI/R-IE | 36/47 (76.6) | 22/39 (56.4) | 14/19 (73.7) | 3/14 (21.4) | 22/28 (78.6) | 19/26 (73.1) |
| p-value[3] | 0.0646 | | 0.0049 | | 0.7540 | |

Abbreviations: BSI= blood stream infection; IE=infective endocarditis; L-IE=left-sided infective endocarditis; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-sensitive *S. aureus*; R-IE=right-sided infective endocarditis; SoCA=standard-of-care antibiotics.
Notes: Clinical responder=clinical outcome of improvement or response.
Denominator is all patients in the mITT population with noted diagnosis at time point within each treatment group.
1. One patient in the SoCA alone group had both MRSA and MSSA and was counted in both subgroups.
2. One patient in the exebacase + SoCA group with MRSA had both R-IE and L-IE and is counted under L-IE.
3. P-value is based on Fisher's exact test.

Secondary efficacy analyses included clinical outcome at Day 7, at the end of treatment with SoCA (EOT), and at test-of-cure (TOC) (28 days after EOT). Responder rates at Day 7, EOT, and TOC were similar between treatment groups, but when patients with L-IE were excluded, results for the secondary efficacy endpoints were supportive of the primary efficacy endpoint. In patients with BSI/R-IE (excluding L-IE), responder rates at Day 7, EOT, and TOC were 76.7%, 71.7%, and 63.3% in the exebacase + SoCA group, respectively, and 69.0%, 64.3%, and 57.1% in the SoCA alone group, respectively.

In the MRSA subgroup, 66.7%, 51.9%, and 48.1% of patients in the exebacase + SoCA group were responders at Day 7, EOT, and TOC, respectively, compared with 43.8%, 43.8%, and 31.3% in the SoCA alone group, respectively. The trend observed at Day 7, EOT, and TOC was supportive of the 42.8 percentage point higher clinical responder rate at Day 14 among MRSA patients in the exebacase + SoCA group compared with the SoCA alone group. In the MSSA subgroup, the responder rates at Day 7, EOT, and TOC were similar between treatment groups; as described above, the MSSA results were affected by the difference in the number of patients with left-sided endocarditis between treatment groups.

An exploratory analysis of health resource utilization in patients with MRSA enrolled in the US showed that, in patients who were alive at the time of discharge, the median length of stay was lower in the exebacase + SoCA group compared with the SoCA alone group (6 days and 10 days, respectively), and the 30-day all-cause readmission rate was 16.0% and 30.8% for the exebacase + SoCA and SoCA alone groups, respectively.

An exploratory analysis of 30-day all-cause mortality was performed. The 30-day all-cause mortality rate was 9.7% (7 of 72 patients) in the exebacase + SoCA group and 12.8% (6 of 47 patients) in the SoCA alone group. In the MRSA subgroup, the 30-day all-cause mortality rate was 3.7% (1 of 27 patients) in the exebacase + SoCA group and 25.0% (4 of 16 patients) in the SoCA alone group (ad hoc p value=0.0556) [Fowler 2020].

An ad hoc analysis of time to resolution of symptoms was performed. A total of 86 patients (53 in the exebacase + SoCA group and 33 in SoCA alone group) had at least one symptom attributable to *S. aureus* BSI/IE present at screening. Of these, symptoms resolved in 94.3% in the exebacase + SoCA group and 87.9% in the SoCA alone group. The median time to symptom resolution was 3 days in the exebacase + SoCA group and 6 days in SoCA alone group. Median time to symptom resolution in the MRSA subgroup was 3 and 7 days in the exebacase + SoCA group and SoCA alone group, respectively, and 3 and 5 days in the exebacase + SoCA group and SoCA alone group in the MSSA subgroup, respectively [Cassino 2021].

*Pharmacokinetics:*

Based on a population PK model of the 72 patients that received exebacase, the median $C_{max}$ and $AUC_{0-24}$ were estimated to be 1056 ng/mL and 3108 ng*hr/mL, respectively. All patients achieved the efficacy target of AUC/MIC $\geq$0.5.

*Safety:*

As expected in a critically ill, hospitalized study population, a similarly high percentage of patients in both treatment groups had at least 1 TEAE through TOC (88.9% and 85.1% in the exebacase + SoCA and SoCA alone groups, respectively) and through Day 180 (93.1% and 85.1% in the exebacase + SoCA and SoCA alone groups, respectively), as shown in Table 6. The incidence of TEAEs within approximately 7 days of administration of the single dose of study drug (on Day 1) was similar between treatment groups (66.7% and 63.8% of patients in the exebacase + SoCA and SoCA alone groups, respectively).

There were no TEAEs of hypersensitivity related to exebacase, and no patients had an AE of clinical interest defined as a TEAE that resulted in stopping of the study drug infusion (i.e., withdrawal of study drug).

Treatment-emergent AEs that the Investigator considered to be related to study drug occurred in 8 patients (11.1%) in the exebacase + SoCA group and 4 patients (8.5%) in the SoCA alone group. All of these TEAEs were non-serious, except for 1 SAE of splenic artery thrombosis, which occurred 30 days after exebacase dosing and was not considered related to study drug by the Sponsor.

Serious TEAEs also occurred in a similar percentage of patients in the exebacase + SoCA and SoCA alone groups through TOC (47.2% and 48.9%, respectively) and through Day 180 (62.5% and 59.6%, respectively).

A total of 7 patients (9.7%) in the exebacase + SoCA group and 6 patients (12.8%) in the SoCA alone group died through Day 30. In the MRSA subgroup, 1 of 27 patients (3.7%) in the exebacase + SoCA group and 4 of 16 patients (25.0%) in the SoCA alone group died through Day 30 (ad hoc p-value=0.0556). A total of 14 patients (19.4%) in the exebacase + SoCA group and 7 patients (14.9%) in the SoCA alone group died through TOC, which is equivalent to 60-day mortality since the last death occurred on Day 58. A total of 17 patients (23.6%) and 9 patients (19.1%) in the exebacase + SoCA and SoCA alone groups, respectively, died through Day 180. The higher number of patients with L-IE and comorbidities (diabetes, renal impairment, hemodialysis, hypertension, and >1 baseline cardiac diagnosis) in the exebacase + SoCA group may have contributed to the higher percentage of deaths in the exebacase + SoCA group through TOC and Day 180. In patients with BSI/R-IE (excluding L-IE), a similar percentage of patients died in the exebacase + SoCA and SoCA alone groups through TOC (14.8% and 13.6%, respectively) and through Day 180 (19.7% and 18.2%, respectively).

A population PK model was developed from the data collected in the Phase 2 study to assess the probabilities of a relationship between exebacase exposures and safety parameters. The model showed no significant relationship between the exposures of exebacase ($C_{max}$ and $AUC_{0-24}$) and death, any SAE, SAE in cardiac disorders system organ class (SOC), or TEAEs in key SOCs of interest (cardiac disorders, infections and infestations, gastrointestinal disorders, or respiratory, thoracic and mediastinal disorders).

**Table 6: Phase 2 Study: Overview of Adverse Events (Safety Population)**

| Parameter | Exebacase+ SoCA (N=72) n (%) | SoCA 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) |
| TEAE through Day 180 | 67 (93.1) | 40 (85.1) |
| 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 interruption or withdrawal[1] | 1 (1.4) | 0 |
| Serious TEAE leading to study drug interruption or withdrawal | 0 | 0 |
| Death through Day 30 | 7 (9.7) | 6 (12.8) |
| Death through TOC[2] | 14 (19.4) | 7 (14.9) |
| Death through Day 180 | 17 (23.6) | 9 (19.1) |

Abbreviations: eCRF=electronic case report form; SoCA=standard-of-care antibiotics; TEAE=treatment-emergent adverse event; TOC=test-of-cure.
Note: Denominator is all patients in the safety population within each treatment group.
1. There were no TEAEs leading to study drug discontinuation/withdrawal. One patient in the exebacase + SoCA group had non-serious TEAEs (arterial hypertension and shakiness) that resulted in study drug interruption; the study drug infusion was subsequently resumed, both TEAEs resolved, and the patient received the full dose.
2. The last death through TOC occurred on Day 58; thus, death through TOC is equivalent to 60-day mortality.

*Immunogenicity:*

At baseline, 20.8% and 14.9% of patients in the exebacase + SoCA and SoCA alone groups, respectively, were positive for exebacase-specific ADA. This is consistent with prior estimates of pre-existing ADA in the Phase 1 study, a validation study, and a study evaluating pre-existing ADA in the serum of patients with *S. aureus* bacteremia from an established repository.

Among patients dosed with exebacase, pre-existing exebacase-specific ADA did not appear to affect efficacy outcomes or the incidence of TEAEs: clinical responder rates at Day 14 were similar in patients who were ADA-positive and ADA-negative at baseline (73.3% and 69.6%, respectively), and the rates of TEAEs were similar in patients who were ADA-positive and ADA-negative at baseline (100.0% and 91.2%, respectively).

Of baseline ADA-negative patients with at least 1 post-dose ADA sample, 37 of 52 patients (71.2%) in the exebacase + SoCA group developed treatment-emergent ADA. These results are consistent with data from the Phase 1 study (Study CF-301-101) in which 69.3% of patients who received exebacase developed treatment-emergent ADA. In the SoCA alone group, 8 of 32 patients (25.0%) developed treatment-emergent exebacase-specific ADA. The etiology of this observation is unclear but suggests that something other than study drug triggers ADA (e.g., potentially related to exposure to phage material in the setting of *S. aureus* infection).

Only 1 patient (1.4%) in the exebacase + SoCA group was positive for exebacase-specific IgE at baseline. In this patient, IgE was not increased post-dose, and there were no TEAEs of hypersensitivity or immune-related TEAEs reported. Of baseline IgE-negative patients with at least 1 post-dose IgE sample, 6 of 65 patients (9.2%) in the exebacase + SoCA group developed treatment-emergent IgE compared with no patients in the SoCA alone group. The treatment-emergent IgE responses were generally of low magnitude and transient, which is consistent with Phase 1 (Study CF-301-101), suggesting that a single dose of exebacase is not sensitizing for Type I hypersensitivity.

In conclusion, the Phase 2 study established proof-of-concept for exebacase and the emerging new field of direct lytic agents as potential therapeutics. The results of the Phase 2 study support the further evaluation of exebacase in a definitive Phase 3 study designed to examine efficacy and safety in patients with BSI/R-IE including a focus on MRSA. Exebacase was generally safe and well tolerated, with AEs consistent with the critically ill patient population with severe, potentially life-threatening *S. aureus* BSI including R-IE and L-IE and underlying comorbid conditions. There were no TEAEs of hypersensitivity to exebacase or immune-related events reported during the study, despite the presence of exebacase-specific ADA at baseline in approximately 20% of the study population. Pre-existing ADA did not appear to affect efficacy or safety outcomes in the study. Importantly, exebacase did not appear to be sensitizing for allergic hypersensitivity given low incidence of treatment-emergent IgE, which was of low magnitude and transient. Additional detail on the clinical studies can be found in the Investigator's Brochure.

### 7.1.7. Compassionate Use/Expanded Access

Exebacase has also been administered to 15 patients with prosthetic joint infections and 7 patients under expanded access. The youngest patient dosed with exebacase was 5 months old [Moorthy 2021].

***Prosthetic Joint Infections***

Exebacase has been arthroscopically administered to a total of 15 successive individual named patients with coagulase negative *Staphylococci* (CoNS) prosthetic joint infections (PJIs) in the setting of a lysin-debridement, (systemic antistaphylococcal) antibiotics, and implant retention (DAIR) procedure at the reference regional center (CROIAc) at Hopital de la Croix-Rousse in Lyon, France under individual Autorisation Temporaire D'utilisation (ATU) from the French Health Authority, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM). Twelve of these patients had PJIs of the knee; three patients had a PJIs of the hip. All patients underwent the arthroscopic DAIR procedure performed with local arthroscopic administration of exebacase to the affected joint. Exebacase has been well tolerated after intraarticular (IA) administration with no local tissue effects seen at the joint and no systemic effects attributed to IA administration of exebacase. No serious adverse reactions to exebacase were reported for any of the patients treated under ATU.

Four of these patients with relapsing, multidrug-resistant *Staphylococcus epidermidis* PJI of the knee were recently described [Ferry 2021]. These patients with relapsing infections had experienced iterative relapses, in some cases while on suppressive antibiotic therapy, after open DAIR. The "Lysin-DAIR procedure" was proposed based on the potent bacteriolytic and anti-biofilm activity, as compassionate treatment, followed by suppressive tedizolid as salvage therapy. After >1 year of follow up (respectively 14 and 16 months), two of the four patients who had a septic arthritis picture at presentation had a favorable clinical response, whereas the other two patients who had a fistula at the time of presentation had a less favorable outcome.

***Compassionate Use/Expanded Access***

As of December 18, 2021, 7 patients have received exebacase under compassionate use. All 7 patients had *S. aureus* bacteremia, which the treating physicians were not able to clear with standard of care antistaphylococcal antibiotics. All patients received treatment with exebacase under Emergency IND requested by the treating physician and approved by the US FDA. Exebacase was intravenously administered using the same dosing paradigm as in the Phase 3 study. All patients tolerated exebacase well, and there were no serious adverse drug reactions reported for any of these patients who were dosed under compassionate use.

## 7.2. Benefits and Risks

The Phase 3 study will evaluate the efficacy and safety of exebacase in addition to SoCA compared with SoCA alone in adult and adolescent patients with complicated *S. aureus* BSI including R-IE (excluding patients with L-IE) with a focus on patients with MRSA. As previously described (Sections 7.1.2 and 7.1.3), *S. aureus* BSIs including IE are highly morbid conditions, which result in substantial morbidity and mortality despite currently available SoCA. The main objective of the Phase 3 study is to evaluate whether exebacase in addition to SoCA improves clinical outcomes in these patients compared to SoCA alone. As such, all patients in this study will be treated with SoCA therapy for *S. aureus* BSI or R-IE based on current guidelines. The therapeutic benefits and side effects of SoCA are well documented in the prescribing information and published literature.

Patients will be randomized to receive a single dose of exebacase or placebo in addition to SoCA. No patients in the study will be treated with the experimental therapy, exebacase, alone. Together with the efficacy results in Phase 2, and the favorable safety and tolerability profile in Phase 1 and Phase 2 (described in Section 7.1.6), a single dose of exebacase may provide additional clinical benefit over and above the benefit of SoCA alone, which allows for a positive benefit-to-risk ratio.

A rigorous safety monitoring plan has been put in place for the Phase 3 study. All patients will be dosed in a hospital setting and all patients will be closely monitored by repeated assessment of AEs, physical examinations, vital signs, and clinical safety laboratory tests. Although no patients in the Phase 1 or Phase 2 studies experienced hypersensitivity reactions to exebacase during or after infusion, and no patients discontinued study drug administration, patients must be observed

during exebacase/placebo infusion by someone from the clinical care team or research team with patient care experience as described in Section 9.4.1.1, and vital signs will be measured approximately 30 to 40 minutes after the start of infusion and as clinically indicated during the infusion. An independent DSMB will review accruing safety and tolerability data in an unblinded manner throughout the study, as described in the DSMB charter. All fatal SAEs and suspected unexpected serious adverse reactions (SUSARs) will be provided to the DSMB on an ongoing basis. The DSMB will also review results from a futility analysis of the primary efficacy parameter in the MRSA population in the mITT analysis set when approximately 60% of patients have primary (Day 14) adjudicated clinical outcome data available. The DSMB will monitor the overall safety of patients in order to minimize unacceptable risk to patients. As a result, the DSMB may recommend changes to study conduct on the basis of emerging safety information to protect the safety and welfare of clinical study patients. Enrollment will continue during the DSMB reviews.

Overall, based on the benefit-to-risk analysis, the Sponsor considers the current study to be appropriate in the planned study population.

## 7.3. Population to be Studied

Adult and adolescent patients with complicated *S. aureus* BSI including R-IE will be included in this study.

## 7.4. Rationale for Route and Dose

In the Phase 1 study (Study CF-301-101), single escalating doses of exebacase (0.04, 0.12, 0.25, or 0.4 mg/kg) were administered over 2-hour infusion. In the Phase 2 study (Study CF-301-102), a single dose of exebacase was administered over 2-hour infusion at a dose of 0.25 mg/kg based on target attainment, with a dose adjustment to 0.12 mg/kg for patients with CrCl <60 mL/min and patients >50 years of age.

A population PK model was developed using the data from the Phase 2 study in patients with complicated *S. aureus* BSI/IE. The population PK model showed that CrCl was a statistically significant and clinically relevant covariate affecting the PK of exebacase. Age was also statistically significant, but not a clinically meaningful predictor of exebacase exposures (≤4% effect on $AUC_{0\text{-}24}$ or $C_{max}$). For a given dose, compared with patients with normal renal function, patients with mild renal impairment are expected to have up to 20% higher $C_{max}$ and up to 30% higher $AUC_{0\text{-}24}$; patients with moderate renal impairment are expected to have up to 40% higher $C_{max}$ and up to 70% higher $AUC_{0\text{-}24}$; patients with severe renal impairment are expected to have up to 60% higher $C_{max}$ and up to 2-fold higher $AUC_{0\text{-}24}$; and patients with end-stage renal disease (ESRD) are expected to have up to 90% higher $C_{max}$ and up to 3-fold higher $AUC_{0\text{-}24}$.

The Phase 1 and Phase 2 studies of exebacase (Studies CF-301-101 and CF-301-102) were both performed with weight-based dosing (i.e., mg/kg) commonly used for IV dosing. Monte Carlo simulations performed on the population PK model showed that weight-based dosing would introduce a significant systematic bias in exposures, regardless of renal function group, and also increase the range of exposures. Weight-based dosing would result in a situation where patients with higher body weight would be expected to achieve significantly higher exposures than the target value and patients with lower body weight would be expected to achieve significantly lower exposures than the target value, rather than ensuring similar exposures across individuals, which is the intent of a weight-based dosing. A simulation of a scenario for administration of fixed dose that achieves the same average exposure as in Phase 2 resulted in no weight-dependent increase in exposure. Therefore, selection of the doses to be used in the Phase 3 study focused on the fixed dosing scenarios.

Modeling data identified 3 categories for dosing based on renal function: 1) patients with normal renal function (CrCl ≥90 mL/min) and mild renal impairment (CrCl ≥60 to <90 mL/min); 2) patients with moderate (CrCl ≥30 to <60 mL/min) and severe (CrCl ≥15 to <30 mL/min) renal impairment; 3) patients with ESRD (CrCl <15 mL/min) including patients who require dialysis. Simulations were performed for a series of fixed doses of exebacase ranging from 5 to 24 mg for each of the renal impairment groups described above. The doses for the Phase 3 study were selected to match the median $AUC_{0-24}$ of 3108 ng*hr/mL, which is the median exposure determined by population PK analysis of the 72 patients that received exebacase in the Phase 2 study.

Based on the simulations, the following dosing scheme was selected for the Phase 3 study:

- For patients with normal renal function or mild renal impairment (CrCl ≥60 mL/min), an exebacase dose of **18 mg** administered as approximately a 2-hour IV infusion would result in $C_{max}$ and $AUC_{0-24}$ values of 1254 ng/hr and 3026 ng*hr/mL, respectively.
- For patients with moderate or severe renal impairment (CrCl of 15 to <60 mL/min), an exebacase dose of **12 mg** administered as approximately a 2-hour IV infusion would result in $C_{max}$ and $AUC_{0-24}$ values of 1107 ng/hr and 3099 ng*hr/mL, respectively.
- For patients with ESRD (CrCl <15 mL/min), including those on dialysis, an exebacase dose of **8 mg** administered as approximately a 2-hour IV infusion would result in $C_{max}$ and $AUC_{0-24}$ values of 910 ng/hr and 3109 ng*hr/mL, respectively. In patients receiving hemodialysis, study drug will be administered either ≥8 hours before the start of hemodialysis or ≥4 hours after the end of hemodialysis.

For the dosing regimen described above, approximately all patients would be expected to achieve efficacy targets associated with AUC/MIC ≥0.5 for isolates that have an exebacase MIC ≤2 μg/mL. The fixed-dose scheme above is expected to result in similar exposures in patients regardless of their body weight or renal function status and achieve the average exposure target of approximately 3108 ng*hr/mL.

## 7.5. Rationale for Inclusion of Adolescent Patients

To date, exebacase has not been evaluated in adolescent patients. It is anticipated that, as with adults, adolescent patients with *S. aureus* BSI including R-IE may derive benefit from a new therapeutic agent that may provide additional benefit above SoCA alone. Therefore, adolescent patients are an important patient population in which to study the safety, efficacy, and PK of exebacase in addition to SoCA.

Literature specific to adolescents with *S. aureus* BSI is limited, since most literature summarizes data across all pediatric age groups (some of which also includes neonates), and many studies are at single hospitals or groups of hospitals within a specific country or region. Among different hospitals or regions, the incidence of *S. aureus* bacteremia among pediatrics, including adolescents, ranges from 3.7 to 14.4 per 100,000 population [Oestergaard 2018, McMullan 2016, Mejer 2012, Vanderkooi 2011]. The rate of *S. aureus* bacteremia among hospitalized pediatric patients, including adolescents, ranges from approximately 1.5 to 3.5 per 1000 hospital admissions [Klieger 2015, Cobos-Carrascosa 2015, Burke 2009]. In one study, definitive IE occurred in 12% of pediatric patients with *S. aureus* bacteremia, including adolescents [Valente 2004], which is similar to the incidence of IE in adult patients with *S. aureus* bacteremia [Fowler 2003, Chang 2003].

Risk factors for *S. aureus* bacteremia in pediatric patients, including adolescents, are similar to those of adults and include dialysis, plasmapheresis, organ transplantation, cancer, immunodeficiency, previous hospitalization, and presence of a central venous catheter (CVC) [Oestergaard 2018, Burke 2009]. Diabetes, a risk factor in adults, is increasingly diagnosed at younger ages, and adolescent obesity is likely to increase the incidence of diabetes in adolescents [Twig 2020]. Risk factors for *S. aureus* IE in pediatric patients, including adolescents, include presence of congenital heart disease and/or multiple positive blood cultures [Valente 2004].

Mortality due to *S. aureus* bacteremia in pediatric patients, including adolescents, ranges from approximately 6% to 9% for hospital-onset infections and 2% to 4% for community-onset infections [McMullan 2016, Klieger 2015].

Guidelines regarding selection of antibiotics for treatment of MRSA *S. aureus* bacteremia and IE in pediatrics include those antibiotics also recommended for adults, and the recommended duration of antibiotics is similar in adults and pediatric patients [Liu 2011].

Adult PK data for exebacase was assessed in a population PK model with a range of body weights in adults. Exposure in adults showed no significant effect of weight on the PK of exebacase. According to CDC Growth Charts, in an age range of 12.0 to 17.99 years, mean body weight ranges from 42.07 to 67.87 kg for males and 44.89 to 59.81 for females [CDC 2002]. Compared to a normal 75 kg adult, the weight difference on average is about 33% lower in the age range of 12.0 to 17.99 years. This difference, along with the knowledge that population PK in adults did not indicate any clinically relevant body weight effect on the PK of exebacase, suggests patients 12 to <18 years of age are likely to have exposures comparable to adults at a

given dose. In addition, the metabolism of exebacase (a peptide) in adults and adolescents is expected to be similar since adults and adolescents have similar capacity for catabolism of peptides. The collective data indicates adolescents receiving the same dose of exebacase as adults are not expected to have substantially different exposure than adults.

Adolescent patients with *S. aureus* BSI/R-IE may derive benefit from exebacase. A favorable benefit-to-risk ratio was demonstrated in adults with *S. aureus* BSI/R-IE in the Phase 2 study, and exposures are expected to be similar between adults and adolescents. Therefore, adolescents 12 to <18 years of age with *S. aureus* BSI/R-IE are being enrolled in this study to allow initial assessment of safety, PK, and efficacy in this age group.

## 7.6. Rationale for Inclusion of Patients with Renal Impairment

Patients with renal impairment, particularly those with ESRD receiving dialysis, are at high risk for infections with *S. aureus*, including complicated BSI/R-IE; therefore, it is anticipated that patients with renal impairment may derive benefit from a new therapeutic agent that may provide additional benefit above SoCA alone. Therefore, patients with renal insufficiency are an important patient population in which to study the safety, efficacy, and PK of exebacase in addition to SoCA.

Patients with renal impairment and on hemodialysis were included in the Phase 2 study (Study CF-301-102). Among patients that received exebacase in the Phase 2 study, there were 5 patients (7.0%), 13 patients (18.3%) and 27 patients (38.0%) that had mild, moderate, and severe renal impairment, respectively, and 21 patients (29.6%) that were on hemodialysis.

Exebacase is a therapeutic protein with a molecular mass of approximate 26 kDa. Measurement of exebacase levels in urine of healthy subjects in the Phase 1 study (Study CF-301-101) determined a negligible amount (<0.1% of the dose) of exebacase excreted in urine. The lack of urinary excretion of exebacase is consistent with the expected route of elimination of endogenous and biotechnology-derived proteins via tissue catabolism resulting in degradation to small peptides and individual amino acids (S6R1).

In a biodistribution study of Iodine-$^{131}$ radio-labeled exebacase in mice, IV administration of $^{131}$-I-exebacase resulted in detection of exebacase in multiple tissues. The kidneys had the highest level of exebacase, followed by the liver, spleen, stomach, lung, and blood. Over time there was a significant decrease in the level of exebacase in the majority of organs, including the kidney, suggesting rapid clearance of exebacase from the blood and catabolism by multiple tissues. This is consistent with normal catabolism of protein and peptides. Furthermore, literature reviews reveal that even in subjects with severe renal impairment, the capacity for catabolism of peptides and small proteins (e.g., <60 kDa), remains substantial (>50% remaining capacity) [Meibohm 2012, Czock 2012, Maack 1979, Meier 2004, Ishimitsu 1994]. Based on the collective nonclinical and clinical data for exebacase and published literature, the main route of elimination for exebacase is understood to be catabolism and not urinary excretion.

In view of the spleen's role as a major organ for exebacase catabolism, patients with both asplenia and CrCl <60 mL/min (including those on dialysis) are excluded due to the risk for reduced ability to catabolize exebacase.

As described in Section 7.4, the doses for the Phase 3 study were selected such that the exposures in the Phase 3 study are expected to match the exposures observed in the Phase 2 study regardless of patient renal status or body weight.

As described in Section 7.2, an independent DSMB will review accruing safety and tolerability data in an unblinded manner throughout the study. The DSMB will monitor the overall safety of patients in order to minimize unacceptable risk to patients. As a result, the DSMB may recommend changes to study conduct on the basis of emerging safety information to protect the safety and welfare of clinical study patients.

Patients with renal impairment, particularly those on hemodialysis, are at particular risk for *S. aureus* BSI with associated poor outcomes. As patients with renal impairment and *S. aureus* BSI may benefit from treatment with exebacase, this approach will allow for obtaining data in a patient population with renal impairment, safeguard the safety of patients in this study, and allow for continued evaluation of exebacase in this important population.

### 7.7. Statement of Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles of the Declaration of Helsinki, and applicable regulatory and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements.

## 8. TRIAL OBJECTIVES AND PURPOSE

### 8.1. Primary Objectives

- Efficacy: To determine if exebacase in addition to SoCA is superior to SoCA alone for clinical responder rate at Day 14 in patients with MRSA BSI, including IE (i.e., the MRSA population) in the microbiological intent-to-treat (mITT) analysis set
- Safety: To determine the safety and tolerability of exebacase in addition to SoCA compared with SoCA alone in the safety analysis set

### 8.2. Secondary Objectives

- To determine if exebacase in addition to SoCA is superior to SoCA alone for clinical responder rate at Day 14 in all patients with *S. aureus* (i.e., the overall population) in the mITT analysis set
- To determine if exebacase in addition to SoCA is superior to SoCA alone for 30-day survival in the MRSA population in the mITT analysis set

- To determine if exebacase in addition to SoCA is superior to SoCA alone for clinical responder rate at Day 60 in the MRSA population in the mITT analysis set
- To determine if exebacase in addition to SoCA is superior to SoCA alone for clinical responder rate at Day 60 in the overall population in the mITT analysis set
- To determine clinical responder rate at Day 60 in the overall R-IE and MRSA R-IE populations in the mITT analysis set

## 8.3. Additional Objectives

- To determine the survival time through Day 60 in the overall and MRSA populations in the mITT analysis set
- To determine clinical responder rate at Day 14 in the overall R-IE and MRSA R-IE populations in the mITT analysis set
- To determine clinical responder rate at Day 30 in the overall and MRSA populations, and overall R-IE and MRSA R-IE populations in the mITT analysis set
- To determine clinical responder rate at Day 14 by source of *S. aureus* infection in the overall and MRSA populations in the mITT analysis set
- To evaluate bacteremia clearance rate at Days 4 and 7 in the overall and MRSA populations in the mITT analysis set
- To describe post-dose immunologic response (anti-drug antibody to exebacase) in the safety analysis set.
- To describe the relationship between baseline and post-dose immunologic parameters and efficacy and safety endpoints in the mITT and safety analysis sets, respectively
- To evaluate impact of exebacase on health resource utilization in the mITT analysis set
- To characterize the PK parameters of exebacase in the study population in the PK analysis set

# 9. INVESTIGATIONAL PLAN

## 9.1. Overall Study Design

This is a randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and safety of exebacase in addition to SoCA compared with SoCA alone for the treatment of adult and adolescent patients with *S. aureus* BSI including R-IE (excluding patients with L-IE). Patients who meet all screening criteria and have blood culture positive for *S. aureus* determined by rapid diagnostic or conventional methods, or Gram stain showing Gram-positive cocci in clusters plus either positive tube coagulase test or positive latex slide agglutination test from

blood culture specimens collected within approximately 72 hours before randomization are eligible for the study.

Approximately 348 patients will be randomly assigned in a 2:1 ratio to receive a single dose of exebacase (232 patients) or placebo (116 patients). Patients will receive exebacase or placebo as soon as possible after randomization. The randomization will be stratified by poorly controlled diabetes (yes or no) as defined below and susceptibility of the *S. aureus* isolate (MRSA, MSSA, or unknown). For stratification, poorly controlled diabetes is defined as a hemoglobin A1C (HgA1C) ≥8% within approximately 90 days before randomization. A HgA1C test is not required for patients with no medical history of diabetes and no suspicion of diabetes during the screening period. These patients will be stratified to "no" for poorly controlled diabetes.
A HgA1C test should be performed in patients with medical history of diabetes or suspicion of diabetes during screening for whom a HgA1C test result within the approximately 90 days prior to randomization is not available. If a HgA1C is unavailable and testing cannot be performed for these patients prior to randomization, contact the Medical Monitor to determine how the patient should be stratified based on available clinical information. All efforts will be made to obtain susceptibility results from blood cultures before randomization to enable stratification by MRSA or MSSA. If a blood culture was performed for the current *S. aureus* infection prior to the qualifying blood culture, susceptibility results from the prior blood culture may be used. If the patient has a concomitant *S. aureus* infection at another body site from which susceptibility results are available (e.g., skin, abscess), the susceptibility results from this other culture may be used. If the patient is known to be colonized with MRSA, MRSA may be selected for the stratification factor.

Patients will receive SoCA selected by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) based on recommendations in the protocol. These are based on authoritative treatment guidelines [Liu 2011, Baddour 2015] and include daptomycin or vancomycin for MRSA and semi-synthetic penicillins (e.g., nafcillin, oxacillin, cloxacillin, flucloxacillin) and first-generation cephalosporins (e.g., cefazolin) for MSSA. Daptomycin or vancomycin may be used for patients with MSSA with a known history of beta-lactam allergy or other reason that beta-lactam cannot be used. The duration of SoCA will generally be from 2 to 8 weeks (14 to 56 days). If a longer duration of treatment with SoCA is anticipated, this must be discussed prior to randomization with the Medical Monitor. Long-term oral antibiotic suppression therapy (e.g., for osteomyelitis), is not considered to be SoCA for *S. aureus* BSI/IE and would be considered a "concomitant medication". Treatment with oral step-down antibiotics is not permitted, except in adolescents. The SoCA will be administered as specified in the manufacturer's prescribing information.

All efforts will be made to determine the source of *S. aureus* BSI/IE (e.g., full physical examination, imaging as needed, cultures of other infected body sites or catheters that may be considered the source), preferably during screening or within 1 week after randomization.
The resolution of the source of *S. aureus* BSI/IE will be evaluated at Days 7, 14, 30, and 60.

Patients will be evaluated for signs and symptoms attributable to *S. aureus* BSI/IE and metastatic foci (e.g., deep tissue abscess, septic arthritis, etc.) and septic emboli (e.g., to the brain, lung, etc.) during screening and at the Day 7, 14, 30, and 60 visits. Additionally, if SoCA is changed after study drug dosing due to lack of clinical response, signs and symptoms will be assessed on the day of the SoCA change. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will assess whether each sign or symptom is attributable to *S. aureus* BSI/IE or provide an alternative attribution and will assess the symptom severity per the definitions described in Table 9. Some symptoms may be considered 'medically not evaluable' due to certain medical circumstances or treatments, such as a patient in a medically induced coma or after surgery to remove a metastatic focus.

Every effort should be made to perform study visits "in person", including physical examinations, assessment of signs and symptoms, and evaluation of metastatic foci/septic emboli by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol), and preferably by the same person at all visits. If it is not feasible to evaluate the patient "in person" at study visits, the signs and symptoms should be evaluated during the telephone/telehealth visits by detailed questioning and a complete medical review of systems. Medical records may be used to supplement the telephone/telehealth evaluation for physical examination, signs and symptoms, and metastatic foci/septic emboli (see Sections 12.10, 12.13, and 12.12, respectively). In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records alone may be used after contacting the Medical Monitor or designee. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) must review, sign, and date the physical exam, sign and symptom, and metastatic foci/septic emboli data extracted from the medical record and recorded in the site's source documents.

Diagnostic testing will be performed as clinically indicated to assess metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures). Metastatic foci identified through Day 7 are considered part of the patient's baseline *S. aureus* BSI/IE; new metastatic foci identified after Day 7 or new septic emboli after study drug dosing are considered complications of *S. aureus* BSI/IE for the purpose of assessing clinical outcome. New septic emboli are defined as an acute presentation of septic emboli after dosing and are a reason for failure for clinical outcome; septic emboli that are incidentally found on imaging are considered part of the patient's baseline *S. aureus* BSI/IE if found before Day 7.

Intravenous catheters known or suspected to be infected must be removed, and as clinically needed replaced, preferably at a different site, as soon as possible within approximately 72 hours after randomization. Other hemodialysis access types (i.e., arteriovenous [AV] fistulas or AV grafts) that are known or suspected to be infected will be evaluated for removal/replacement, if clinically feasible. If removal is not feasible based on standard medical practice, the patient should be discussed with the Medical Monitor prior to enrollment. In patients with CVCs,

ultrasounds to evaluate clots in the vein should be performed within approximately 48 hours after randomization, unless the clot in the vein has been detected within this timeframe via other method (e.g., imaging such as CT scan or MRI or direct visualization during surgery).

In addition to the study-qualifying blood culture from specimens collected within approximately 72 hours before randomization (described earlier in this section), 1 aerobic blood culture will be collected during screening (or after randomization and before dosing), collected via peripheral venipuncture when possible. One aerobic blood culture will be collected daily during the study until 2 consecutive negative cultures followed out to negative for at least 48 hours on 2 different days are obtained after exebacase/placebo administration (Note: blood cultures may be collected every other day for adolescents). Additional blood cultures will be performed as clinically indicated. Other (non-blood) cultures should be performed to determine the source of *S. aureus* BSI/IE and evaluate metastatic foci, and as clinically indicated during the study.

Complete physical examinations and review of body systems will be performed during screening and on Days 7, 14, 30, and 60 for visits performed "in person" by the Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol). A physical examination is not required for visits performed remotely by telephone/telehealth; however, a complete medical review of body systems will be performed during the telephone/telehealth visit and medical record data may be used to supplement these visits (e.g., sign and symptom evaluation and physical exam findings) to assess the patient's clinical status, primary source of infection, and the status of any pre-existing or presence of new metastatic foci; the findings will be entered in the electronic case report forms (eCRF) (Section 11.5.1). The physical examinations will include a close evaluation for any new areas of pain or other signs or symptoms of metastatic foci of infection or septic emboli; new signs or symptoms (e.g., pain, shortness of breath) will trigger diagnostic testing for metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures). The physical examination will also include an evaluation of the primary source of *S. aureus* BSI/IE. Additional physical examinations will be performed as clinically indicated.

All adult patients (≥18 years of age) will have a transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) within 3 days before or after randomization. All efforts will be made to perform the TTE or TEE before randomization. Where possible, a TEE will be performed [Baddour 2015, Habib 2010, Habib 2015] and is recommended in patients with body mass index (BMI) >30 kg/m$^2$; the TEE may be performed within 3 days before or after randomization unless the TEE is performed due to clinical suspicion of L-IE. In patients that have clinical findings suggestive of L-IE (new murmur, worsening cardiac function, and/or peripheral or central nervous embolic phenomenon), a TEE will be performed before randomization to rule out mitral and/or aortic valve vegetation(s) or the patient will be excluded from the study per exclusion criterion #2 (Section 10.2). In cases where there is an alternative cause of new heart failure or cerebral emboli, a patient with a negative TTE for L-IE may be discussed with the Medical Monitor for potential enrollment. In patients with persistent

bacteremia for ≥3 days (i.e., blood cultures positive for *S. aureus* for ≥3 days), an echocardiogram will be performed before randomization to rule out L-IE. A TTE may be performed with permission of the Medical Monitor. If this echocardiogram is not performed or L-IE is not ruled out by this echocardiogram, the patient should **not** be randomized.
In adolescents (12 to <18 years of age), echocardiograms (TTE or TEE) will be performed as clinically indicated taking into consideration risk factors for endocarditis (e.g., structurally abnormal heart [including pacemakers]), clinical features suggestive of endocarditis (e.g., new murmur) or persistent bacteremia [McMullan 2020], described in Section 12.14. If the patient had an echocardiogram performed prior to the study that was intended to evaluate the current infection, an additional TTE or TEE is not required unless as indicated above, but should be discussed with the Medical Monitor if obtained ≥3 days prior to randomization. Follow-up echocardiograms will be performed as clinically indicated. Images from all echocardiograms through the Day 60 visit will be provided to the central echocardiography laboratory as directed by the Sponsor.

Safety monitoring will include AE monitoring, physical examinations, vital sign measurements, clinical safety laboratory tests, and 12-lead electrocardiograms (ECG). Safety monitoring will be performed from screening through the last follow-up visit (Day 60). An independent DSMB will review unblinded safety data throughout the study as defined in the DSMB charter. All fatal SAEs and SUSARs will be provided to the DSMB on an ongoing basis allowing the DSMB to monitor fatal and unexpected serious events in a timely manner.

Blood samples for PK and immunogenicity (exebacase-specific ADA and IgE) will be collected. Samples for ADA testing will be collected during screening and on any day between the Day 30 and Day 60 visit windows (i.e., between Day 26 and Day 67). The sample for IgE testing will be collected during screening and will be stored at the site unless the patient later develops clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug.
If a patient has clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug (Section 9.4.1.1), a blood sample for IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample at screening will be sent to a central laboratory for testing.

Clinical outcome will be assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol).
An independent blinded clinical endpoint AC will determine study eligibility, final diagnosis, primary source of BSI/IE, adequacy of source control, and clinical outcome on Days 14, 30, and 60. The adjudicated diagnosis, source, and clinical outcomes will be used for the analysis.

***Visits Performed Remotely by Telephone/Telehealth, Use of Medical Records, and Use of Mobile Health Nursing Services***

Telephone/telehealth visits may be performed under the circumstances described in Section 11.5.1. During the telephone/telehealth visit, information on the following will be collected: any AEs that may have occurred since the last visit and outcome of any ongoing AEs, thorough medical review of body systems to assess signs and symptoms of *S. aureus* BSI/IE, outcome of pre-existing or presence of new metastatic foci, outcome of primary source of infection, SoCA and reasons for any changes in SoCA, concomitant medications, surgeries/procedures, vital status, and clinical outcome. Medical records* may be used to supplement information obtained during the telephone/telehealth visit.

In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records* alone may be used for physical examinations, signs/symptoms, and metastatic foci/septic emboli assessments after contacting the Medical Monitor or designee.

* When medical records are used alone or to supplement information collected during the telephone/telehealth visit, the physical examinations, signs/symptoms, and metastatic foci/septic emboli assessments extracted from the medical record will be recorded in the site's source documents and entered in the relevant eCRFs. The Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) is expected to review, sign, and date the assessments extracted from the medical record and recorded in the site's source documents. Symptom severity assessments must be made in accordance with Table 9. The eCRFs will be verified by the site monitor using these source documents.

Local laboratory, vital signs, and ECG data obtained in conjunction with the Day 7, 14, 30, or 60 visits may be used for the study if available (including using data from medical records of another hospital, skilled nursing facility or other similar institution).

Mobile health services, specifically contracted for the study, may be used to supplement telephone/telehealth visits to perform study visit procedures, such as collecting laboratory samples, evaluating vital signs, and/or obtaining a 12-lead ECG, after approval by the Medical Monitor or designee, as described in Section 11.5.1.

## 9.2. Number of Patients

Approximately 348 patients will be randomly assigned to receive a single dose of exebacase or placebo. The sample size calculation is provided in Section 15.3.

## 9.3. Treatment Assignment

Patients will be randomly assigned in a 2:1 ratio to receive a single dose of exebacase (approximately 232 patients) or placebo (approximately 116 patients).

## 9.4. Dosing and Dose Adjustment Criteria

### 9.4.1. Study Drug

Patients will receive a single infusion of exebacase or placebo as soon as possible after randomization. Exebacase and placebo will be diluted and administered as approximately a 2-hour IV infusion, as specified in the Pharmacy Manual.

The dosing scheme is as follows:

- Patients with normal renal function or mild renal impairment (CrCl* ≥60 mL/min) will be administered a dose of **18 mg** of exebacase.
- Patients with moderate or severe renal impairment (CrCl* of 15 to <60 mL/min) will be administered a dose of **12 mg** of exebacase.
- Patients with ESRD (CrCl* <15 mL/min), including those on hemodialysis, will be administered a dose of **8 mg** of exebacase. In patients receiving hemodialysis, study drug will be administered either ≥8 hours before the start of hemodialysis or ≥4 hours after the end of hemodialysis.

*Note: CrCl will be calculated by Cockcroft-Gault formula (provided in Section 12.8.1.1) using ideal body weight in patients with BMI ≥30 kg/m$^2$ and serum creatinine result obtained locally as close to the start of study drug dosing as possible (but not more than approximately 24 hours before the start of study drug dosing; see Section 12.8.1).

The study drugs are described in additional detail in Section 13.

#### 9.4.1.1. Observation During Study Drug for Potential Allergic Reactions/Anaphylaxis

Patients must be observed during exebacase/placebo infusion by someone from the clinical care team or research team with patient care experience, and vital signs (blood pressure, respiratory rate, and heart rate, and temperature) will be performed approximately 30 to 40 minutes after the start of infusion and as clinically indicated during the infusion.

While not observed in the Phase 1 or Phase 2 studies, if a patient has clinical signs and symptoms of a potential allergic reaction that may be attributed to study drug, the following must be done:

- The infusion must be stopped immediately and vital signs checked; if hypotension or oxygen desaturation are present with or without skin flushing, hives, or rash, epinephrine should be administered immediately intramuscularly. Additional treatments for sequelae of suspected anaphylactic reaction should be provided in accordance with standard medical practice.
- A blood sample for exebacase-specific IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample at screening will be sent to a central laboratory for testing.

The clinical criteria for diagnosing anaphylaxis are described in Table 7 [Simons 2011]. Anaphylaxis will be reported as an SAE (see Section 14).

**Table 7: Clinical Criteria for Diagnosing Anaphylaxis**

| |
|---|
| Anaphylaxis is highly likely when any one of the following 2 criteria is fulfilled:<br>1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen lips-tongue-uvula), **AND** at least 1 of the following:<br>a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)<br>b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)<br>**OR**<br>2. Two or more of the following that occur rapidly after exposure to *a likely allergen[1] for that patient* (minutes to several hours)<br>a. Involvement of the skin-mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula)<br>b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)<br>c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)<br>d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting) |

Source: Simons 2011

1. Or other trigger, for example, immunologic but IgE-independent, or non-immunologic (direct) mast cell activation.

### 9.4.2. Standard-of-Care Antibiotics (SoCA)

The SoCA will be selected by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) based on recommendations in the protocol. These are based on authoritative treatment guidelines [Liu 2011, Baddour 2015] and include daptomycin or vancomycin for MRSA and semi-synthetic penicillins (e.g., nafcillin, oxacillin, cloxacillin, flucloxacillin) and first-generation cephalosporins (e.g., cefazolin) for MSSA. Daptomycin or vancomycin may be used for patients with MSSA with a known history of beta-lactam allergy or other reason that beta-lactam cannot be used. The known allergy will be documented in the eCRF.

Antibiotics other than those listed above should not be used instead of or in addition to SoCA to treat the *S. aureus* BSI/IE on a routine basis; if a non-protocol recommended antibiotic needs to be added, the medical reason for doing so (e.g., lack of clinical response, intolerance, etc.) should be documented in the eCRF. If a patient is transferred to another facility (e.g., skilled nursing facility or rehabilitation) that results in a change to SoCA (e.g., the SoCA is not available for use on the formulary at the facility), the reason for change in the eCRF should reflect this.

Note: Patients who are receiving teicoplanin, linezolid, telavancin, beta-lactam/beta-lactam inhibitors (e.g., piperacillin-tazobactam), carbapenems, fourth- or fifth-generation cephalosporins (e.g., cefepime, ceftaroline fosamil), and/or sulfamethoxazole/trimethoprim are eligible for the study provided that treatment is switched to a protocol-specified appropriate SoCA, as described above. Patients with persistent *S. aureus* bacteremia for which treatment with ceftaroline fosamil or other non-protocol-recommended antibiotic (e.g., rifampin, gentamicin, other beta lactam)

was instituted prior to randomization due to lack of response or intolerance (i.e., added to or switched from a protocol-recommended SoCA) may remain on the non-protocol-recommended antibiotic after randomization, if approved by the Medical Monitor.

Vancomycin or daptomycin used in combination with beta-lactams has not been shown to offer benefit and may increase the risk of kidney injury [Tong 2020]; therefore, this combination should not routinely be used in this study as first-line therapy.

If susceptibility is not known at the time of randomization, the patient will be treated empirically based on local susceptibility patterns and local guidelines and practice; if prevalence of MRSA is high, empiric treatment with either daptomycin or vancomycin is recommended until susceptibility results become available. Once susceptibility data are available, SoCA may be changed at the Investigator's/Sub-Investigator's (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) discretion based on susceptibility results to one of the SoCA options described above.

The duration of SoCA will generally be from 2 to 8 weeks (14 to 56 days). If a longer duration of treatment with SoCA is anticipated, this must be discussed prior to randomization with the Medical Monitor. Long-term oral antibiotic suppression therapy (e.g., for osteomyelitis), is not considered to be SoCA for *S. aureus* BSI/IE and would be considered a "concomitant medication". Treatment with oral step-down antibiotics is not permitted, except in adolescents. The SoCA will be administered as specified in the manufacturer's prescribing information.

Recommended doses for SoCA in adult patients are listed below. Doses for adolescent patients and patients with renal impairment should be guided by prescribing information and local guidelines.

- Nafcillin or equivalent: 12 g every 24 hours divided into 4 to 6 infusions daily
- Cefazolin: 6 g every 24 hours divided into 3 infusions daily
- Vancomycin: 30 mg/kg every 24 hours divided into every 12-hour (q12h) dosing with vancomycin trough levels of 10 to 20 µg/mL or to attain an AUC of 400 to 600 mg*h/L (assuming an MIC of 1 mg/L) [Ryback 2020].
    - Vancomycin dosing should be adjusted based on trough levels. It is recommended that trough levels are repeated after adjustment of vancomycin dosing. Vancomycin trough levels will be recorded in the eCRF.
    - Study drug should not be infused at the same time as SoCA treatment and, if possible, any other medications. Since there are known potential side effects of vancomycin (e.g., erythematous, pruritic rash on the face, neck and upper body, and other symptoms), study drug should be administered either prior to the start of vancomycin infusion or a minimum of 1 hour after vancomycin infusion is complete.
- Daptomycin: 6 to 8 mg/kg once daily

The manufacturer's prescribing information for SoCA should be referenced for full dosing information.

Note: If a patient is put on long-term antibiotic suppression therapy (for example, in a patient with osteomyelitis), the suppression therapy is NOT considered part of SoCA.

# 10. SELECTION AND DISCONTINUATION OF PATIENTS

## 10.1. Inclusion Criteria

The following inclusion criteria must be met at the time of screening (i.e., within approximately 24 hours before randomization), unless otherwise noted below, in order for the patient to be eligible for enrollment:

1. Male or female, 12 years of age or older.
2. Within 72 hours* before randomization, blood culture positive for *S. aureus* determined by rapid diagnostic test or conventional method, or Gram stain showing Gram-positive cocci in clusters and either positive tube coagulase test or positive latex slide agglutination test from blood culture specimens.
   Note: The 72-hour* time period starts at the time the specimen is collected for blood culture. Any *S. aureus*-positive blood culture collected within the 72 hours* before randomization can be used to support enrollment of the patient.

   *There is an approximately +1-hour window to randomize the patient after the 72-hour window (i.e., approximately 73 hours) to account for any technical issues with randomization. If the patient is randomized within the approximately +1-hour window, please inform the Medical Monitor or designee.
3. At least two of the following signs or symptoms attributable to *S. aureus* BSI/IE within approximately 24 hours before randomization. If more than one measurement is taken within the approximately 24 hours before randomization, the most abnormal value is used for inclusion.
   a. Shortness of breath
   b. Sweating
   c. Chills and/or rigors
   d. Fatigue
   e. Confusion
   f. Pain associated with metastatic foci
   g. Fever (oral temperature equivalent ≥38.0°C [≥100.4°F]) or hypothermia (oral temperature equivalent <35°C [<95°F])

h. Leukocytosis (white blood cell [WBC] count >10,000/µL) [CTCAE 2017], leukopenia (WBC <4000/µL), or bandemia (>10% immature neutrophils [bands] regardless of total peripheral WBC)

i. Tachycardia (heart rate >100 bpm)

j. Tachypnea (respiratory rate >20 breaths/min)

k. Hypotension (systolic blood pressure <90 mmHg)

4. Patient must have:

a. Known or suspected R-IE (involvement of pulmonic and/or tricuspid valve[s]) based on Modified Duke Criteria (defined in Table 8)

**or**

b. Known or suspected complicated *S. aureus* BSI, demonstrated as one or more of the following:

i. Blood culture positive for *S. aureus* on more than one day

ii. Clots in the vein at or near the catheter site seen on ultrasound or other method (e.g., MRI, echocardiogram, surgery)

iii. Signs or symptoms of metastatic foci of *S. aureus* infection (e.g., splenic abscess, deep tissue abscess not associated with open wound or other local source of infection, septic pulmonary emboli) or hematogenous seeding (e.g., of the renal system evidenced by *S. aureus* bacteriuria [in absence of other source such as indwelling ureteral catheter], septic arthritis, osteomyelitis) confirmed by physical examination, imaging, and/or culture (Sections 12.10 and 12.12)
Note: Patients who present with acute osteomyelitis as the first manifestation of *S aureus* BSI (e.g., adolescents) may be enrolled even if original source of infection is not known.

iv. Persistent fever (oral temperature equivalent ≥38.0°C [≥100.4°F]) for 72 hours or more

v. Met criteria for sepsis or septic shock using the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score (definition in Section 23.1 [adapted from Singer 2016]) during the time of diagnosis/presumptive diagnosis of BSI.
If the SOFA score is the only criteria for complicated *S. aureus* BSI that is met, contact the Medical Monitor prior to randomization.

vi. Significantly immunocompromised:

- AIDS (HIV positive with an AIDS-defining condition or a CD4 count of approximately ≤200 cells/mm³ within approximately 90 days)
- Severe leukopenia defined as absolute neutrophil count (ANC) of approximately ≤500 cells/mL in the 7 days prior to the qualifying blood culture or during the screening window
- Post organ transplantation including autologous bone marrow or stem cell transplantation and on immunosuppressive therapy for the organ transplant around the time of presentation with the *S. aureus* BSI/IE
- On treatment for active graft vs. host disease
- On immunosuppressive therapy, such as:
  - Biologics such as infliximab, monoclonal antibodies such as daclizumab, methotrexate, cyclophosphamide, or similar agents. A list of similar agents is in Appendix 4 in Section 23.4.
  - Patients who have taken ≥10 mg of prednisone or equivalent for 5 days or more.
- On myelosuppressive chemotherapy or immunotherapy
- Advanced cirrhosis

**or**

c. At least one of the following risk factors for complicated *S. aureus* BSI:

i. Preexisting right-sided valvular heart disease

ii. Surgery (e.g., orthopedic, cardiothoracic, or intraabdominal surgery) within the previous 30 days that puts the patient at risk for nosocomial bacteremia

iii. Extravascular foreign material. Note: Catheters including ports, AV fistulas and related dialysis access points are considered intravascular foreign material.

iv. Hemodialysis

5. Patient is not pregnant or breastfeeding and meets one of the following criteria:

a. A female patient who is not of childbearing potential is eligible without requiring the use of contraception. This includes female patients who have not undergone menarche or who are documented to be surgically sterile (e.g., hysterectomy, or removal of both ovaries, or tubal ligation) or postmenopausal (i.e., amenorrhea >1 year and follicle stimulating hormone [FSH] >40 mIU/mL) with a negative pregnancy test. FSH and pregnancy testing is not required in postmenopausal females with amenorrhea for >2 years.

b. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to remain abstinent* or use 2 methods of contraception and refrain from donating sperm (male patients) from screening through 30 days after receiving the study drug.

   * Abstinence is defined as refraining from heterosexual intercourse from screening through 30 days after receiving the study drug; the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will consider whether abstinence is consistent with the preferred and usual lifestyle of the patient.

   Acceptable methods of contraception include either:

   - Hormonal contraception (injection, implant, pill, patch, or vaginal ring) and a condom or diaphragm with spermicide, or
   - Intrauterine device (IUD) and a condom or diaphragm

c. A male patient who is not of reproductive potential is eligible without requiring the use of contraception. This includes males who have undergone a successful vasectomy, defined as (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.

6. Willing and able to provide written informed consent or assent. If the patient is not able to provide written informed consent or assent, written informed consent may be provided by the patient's legally acceptable representative as permissible based on local laws and regulations. For patients 12 to <18 years of age, written informed consent from the patient's parent/guardian or other legally acceptable representative will be obtained according to the site's IRB requirements. For emancipated minors, written informed consent will be obtained according to the site's IRB requirements.

## 10.2. Exclusion Criteria

1. Patient previously received exebacase.
2. Known or suspected left-sided IE (involvement of mitral and/or aortic valve[s]) based on Modified Duke Criteria (defined in Table 8).
   Note: In adult patients that have clinical findings suggestive of L-IE (new murmur, worsening cardiac function, and/or peripheral or central nervous embolic phenomenon), a TEE will be performed before randomization to rule out mitral and/or aortic valve vegetation(s) or the patient will be excluded from the study. In cases where there is an alternative cause of new heart failure or cerebral emboli, a patient with a negative TTE for L-IE may be discussed with the Medical Monitor for potential enrollment. In patients with persistent bacteremia for ≥3 days (i.e., blood cultures positive for *S. aureus* for ≥3 days), an echocardiogram will be performed before randomization to rule out L-IE. A TTE may be performed with permission from the Medical Monitor. If this echocardiogram is not

performed or L-IE is not ruled out by this echocardiogram, the patient should not be randomized. In adolescents (12 to <18 years of age), echocardiograms (TTE or TEE) will be performed as clinically indicated taking into consideration risk factors for endocarditis (e.g., structurally abnormal heart [including pacemakers]), clinical features suggestive of endocarditis (e.g., new murmur), or persistent bacteremia [McMullan 2020].

3. Treatment with any potentially effective systemic anti-staphylococcal antibiotic for more than 72 hours* within 7 days before randomization.
   Exception: Documented *S. aureus* resistance to the prior systemic antibiotics and/or persistent *S. aureus*-positive blood cultures while on the systemic antibiotics.

   *There is an approximately +1-hour window to randomize the patient after the 72-hour window (i.e., approximately 73 hours) to account for any technical issues with randomization. If the patient is randomized within the approximately +1-hour window, please inform the Medical Monitor or designee.

4. Current or planned treatment within the 14 days following randomization with dalbavancin or oritavancin.
   Notes:

   - Patients who are receiving teicoplanin, linezolid, telavancin, beta-lactam/beta-lactam inhibitors (e.g., piperacillin-tazobactam), carbapenems, fourth- or fifth-generation cephalosporins (e.g., cefepime, ceftaroline fosamil), and/or sulfamethoxazole/trimethoprim are eligible for the study provided that treatment is switched to a protocol-specified appropriate SoCA (appropriate SoCA includes daptomycin and vancomycin for MRSA and semi-synthetic penicillins [e.g., nafcillin, oxacillin, cloxacillin, flucloxacillin] and first-generation cephalosporins [e.g., cefazolin] for MSSA.

   - Daptomycin or vancomycin may be used for patients with MSSA with a known history of beta-lactam allergy or other reason that beta-lactam cannot be used.

   - Patients with persistent *S. aureus* bacteremia for which treatment with ceftaroline fosamil or other non-protocol-recommended antibiotic (e.g., rifampin, gentamicin, other beta lactam) was instituted prior to randomization due to lack of response or intolerance (i.e., added to or switched from a protocol-recommended SoCA) may remain on the non-protocol-recommended antibiotic after randomization, if approved by the Medical Monitor.

   - Vancomycin or daptomycin used in combination with beta-lactams has not been shown to offer benefit and may increase the risk of kidney injury [Tong 2020]; therefore, this combination should not routinely be used in this study as first-line therapy.

5. Removed (Protocol Amendment 4).

6. Presence of any removable or surgically managed infection source (e.g., intravascular catheter, abscess) that will not be removed or debrided based upon standard medical practice within approximately 72 hours after randomization

   Note: Other hemodialysis access types (i.e., AV fistulas or AV grafts) and surgically managed infection sources that are known or suspected to be infected will be evaluated for removal/replacement, if clinically feasible. If removal/debridement is not feasible based on standard medical practice, the patient should be discussed with the Medical Monitor for potential enrollment.

7. Presence of prosthetic valve or cardiac valve support ring, or presence of known or suspected infected hardware* (orthopedic), prosthetic joint*, or cardiac device (e.g., implantable cardioverter defibrillator [ICD], permanent pacemaker). Note: Patients who have *S. aureus* bacteremia after the removal of infected hardware or cardiac device may be included in the study.

   *Patients with planned surgery for known or suspected infected non-cardiac hardware or prosthetic joint may be enrolled if surgical removal is planned within 5 days after randomization, with approval of the Medical Monitor.

8. Removed (Protocol Amendment 5).

9. Patient with **BOTH** asplenia and CrCl <60 mL/min including those on dialysis (risk for reduced ability to catabolize exebacase). Note: CrCl will be calculated by Cockcroft-Gault formula (provided in Section 12.8.1.1) using ideal body weight in patients with BMI ≥30 kg/m$^2$ and serum creatinine result obtained locally (see Section 12.8.1).

10. Patient receiving continuous renal replacement therapy (CRRT) within 4 hours prior to dosing and/or within 8 hours after dosing.

11. Known polymicrobial BSI (i.e., more than one pathogen in the blood). Note: Culture results that include organisms that are considered contaminants do not exclude the patient.

12. Patient with known, ongoing systemic infection caused by other bacterial pathogen(s) (i.e., other than *S. aureus*) and/or fungal pathogen(s) and/or patient who has a known positive coronavirus disease 2019 (COVID-19) diagnostic test at the time of screening. Patients who previously had COVID-19 and are COVID-19-negative by diagnostic test are eligible for enrollment. Note: COVID-19 testing should be performed as clinically indicated in accordance with local standard medical practice.

13. Patient is not expected to survive through Day 14 of the study due to underlying comorbidity (e.g., terminal end-stage cancer) and/or patient has an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of >30.

14. Patient participated or plans to participate in another interventional investigational drug, device, or diagnostic trial involving administration of an investigational agent within 30 days or 5 half-lives of investigational drug, whichever is longer, prior to or during the study.

Note: Patients who have received agents under FDA Emergency Use Authorization (EUA) for COVID-19 prevention (e.g., vaccines or Evusheld or similar agents) or for COVID-19 treatment under FDA EAU are not excluded.

15. Other comorbid condition or laboratory abnormality that would, in the opinion of the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol), pose a safety risk for the patient to participate or pose a risk to the patient's ability to complete the study.
16. Patient is employed by the Sponsor or a member of the investigational site study team (i.e., on the Delegation of Authority Log) or is a first degree relative of a person employed by the Sponsor or a member of the investigational site study team (i.e., on the Delegation of Authority Log). Patient is institutionalized by administrative or court order.
17. Patient is not willing or able to comply with the protocol requirements.

## 10.3. Discontinuation Criteria

### 10.3.1. Discontinuation of Study Drug

Reasons for discontinuation (i.e., withdrawal) of study drug will be recorded in the eCRF and include the following:

- Patient is unable or unwilling to complete the study drug infusion
- Patient (or the patient's legally acceptable representative/parent/guardian) withdraws informed consent/assent at any time during study drug infusion
- Clinical signs and symptoms of allergic reaction or anaphylaxis to study drug (see Section 9.4.1.1 for procedures to be performed in the event of anaphylaxis)
- AE (whether or not related to study drug) that precludes further infusion of study drug in the judgment of the Investigator and/or Sponsor. Note: Any AE that results in discontinuation (i.e., withdrawal) of the study drug infusion is considered an adverse event of clinical interest (AECI) and must be reported within 24 hours (Section 14.9).
- The Investigator considers that it is in the patient's best interest not to continue the study drug infusion
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Patients who discontinue study drug will continue to participate in study visits unless consent/assent is withdrawn (see the next section; Section 10.3.2).

### 10.3.2. Discontinuation from the Study

Reasons for study discontinuation will be recorded in the eCRF and include the following:

- Patient is unable or unwilling to adhere to the protocol
- Patient (or the patient's legally acceptable representative/parent/guardian) withdraws informed consent/assent
- AE (whether or not related to study drug) that precludes further participation in the study in the judgment of the Investigator and/or Sponsor. Note: Since death due to any cause is a component of the clinical failure definition for efficacy (as defined in Table 10 in Section 12.18), patients who die during the study will be treated as having completed the study.
- Patient is lost to follow-up
- The Investigator considers that it is in the patient's best interest not to continue participation in the study. The Investigator will contact the Sponsor in advance if the Investigator is considering withdrawing the patient from the study.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Patients who discontinue the study will not participate in further study visits, but AEs will be followed as described in Section 14.12 unless informed consent/assent is withdrawn.

In addition, vital status (whether the patient is alive or dead, or last known date alive if vital status is unknown) will be obtained at Days 14, 30, and 60 for all patients, including patients that discontinue the study or withdraw consent/assent (as described in the informed consent/assent form). All efforts must be made to obtain vital status on all patients through Day 60. Vital status data are important for both the safety analysis (to have an accurate accounting of patients who died) and the efficacy analysis ("death due to any cause" is a reason for failure for clinical outcome). The patient's vital status will be determined using available sources (e.g., the patient, patient's contacts, hospital and other medical records, and public records, such as social media, obituaries, social security death index), as described in the informed consent/assent form and FDA guidance (see Section 12.17).

## 10.4. Replacement of Patients

Patients who withdraw from study drug and/or the study will not be replaced.

## 10.5. Rescreening of Patients

Patients not fulfilling the entry criteria and not randomized may be rescreened for participation if their eligibility characteristics have changed. Screening procedures that fall within the screening window do not need to be repeated.

## 10.6. Criteria for Study Termination

The end of the study will occur when the last patient completes the study (last patient last visit) or discontinues from the study.

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons or if required by regulatory authorities.

# 11. SCHEDULE OF OBSERVATIONS

The study schematic and schedule of assessments are provided in Sections 3 and 4, respectively. The study procedures/assessments performed at each visit are described in the subsections that follow.

## 11.1. Study Duration

Patients will receive a single dose of exebacase or placebo in addition to SoCA. The duration of SoCA will generally be from 2 to 8 weeks (14 to 56 days). If a longer duration of treatment with SoCA is anticipated, this must be discussed prior to randomization with the Medical Monitor. Long-term oral antibiotic suppression therapy (e.g., for osteomyelitis), is not considered to be SoCA for *S. aureus* BSI/IE and would be considered a "concomitant medication". The duration of the study for each patient will be approximately 60 days (±7 days).

## 11.2. Visit Windows

Visit windows are as follows:

Day 7 (±1 day)

Day 14 (±1 day)

Day 30 (±4 days)

Day 60 (±7 days)

## 11.3. Screening

Patients will be screened to determine whether or not they meet the eligibility criteria for the study. Patients will be randomized as soon as possible after confirmation of study eligibility. However, to provide flexibility, screening assessments may be performed within approximately 24 hours before randomization, unless otherwise noted. The following assessments/procedures will be performed during screening:

- Informed consent/assent (see Section 12.1).
- Review of inclusion/exclusion criteria (see Sections 10.1, 10.2, and 12.2).

  - The qSOFA score will be determined for all patients (see Section 12.2.2). In patients that have at least 2 criteria of qSOFA, a SOFA score will be performed (see Section 23.1) to determine whether the patient meets the criteria for sepsis and/or septic shock per the inclusion criteria.
  - Baseline APACHE II score will be calculated for all patients (see Sections 12.2.3 and 23.2). Patients with APACHE II score of >30 are excluded from the study.
- Medical history for 1 year prior to screening, including relevant previous and current medical diagnoses and major surgical procedures (Section 12.4).
- Diagnosis determined by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) based on the definitions in Section 12.5.
- Risk factors for complicated *S. aureus* BSI (see Section 12.6).
- Make all efforts to determine the source of *S. aureus* BSI/IE (e.g., full physical examination, imaging as needed, cultures of other infected body sites or catheters that may be considered the source) preferably during screening (Section 12.7).
- Limited laboratory tests may need to be performed by the site's local laboratory during screening so that timely results are available for study eligibility determination, stratification, and to determine the dose of study drug (based on CrCl). The specific laboratory tests that are required to be available locally are described in Section 12.8.1.
- Blood and urine samples for clinical safety laboratory tests will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) or after randomization and before dosing; samples will be sent to the central laboratory for testing (see Section 12.8.2.1). If a blood or urine sample for safety laboratory testing by the central laboratory is not able to be obtained at a given timepoint/visit, the local laboratory results may be entered into the eCRF for that timepoint/visit, if feasible. For adolescents, local clinical laboratory results during the screening window (or after randomization and before dosing) can substitute for central safety laboratory tests and will be entered into the eCRF.
- For females of childbearing potential only: urine or serum pregnancy test performed locally during screening for eligibility determination. Blood sample for serum pregnancy test will be collected for women of childbearing potential during screening (for patients who meet eligibility criteria and are expected to be randomized); samples will be sent to the central laboratory for testing (see Section 12.8.2.2).

- Blood samples for immunogenicity:
  - Blood sample for exebacase-specific ADA testing will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) or after randomization and before dosing; the ADA sample will be sent to the central laboratory for testing (Section 12.8.2.3).
  - Blood samples for exebacase-specific IgE testing will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) or after randomization and before dosing and retained at the site. If a patient has clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug (Section 9.4.1.1), a blood sample for exebacase-specific IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample at screening will be sent to a central laboratory for testing (Section 12.8.2.3).
- Blood sample for PK: the pre-dose sample will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized or after randomization and before dosing); samples will be sent to the central laboratory for testing (Section 12.8.2.4).
- Blood cultures, as follows:
  - The "qualifying" blood culture from specimens collected within approximately 72 hours before randomization (per the inclusion criteria in Section 10.1) will be recorded in the eCRF and the *S. aureus* isolate should be sent to the central laboratory. The site will make all efforts to work with the local microbiology laboratory to ensure that, wherever possible, the *S. aureus* isolate from the qualifying blood culture is retained and sent to the central laboratory.
    - Note: Since susceptibility of the *S. aureus* isolate is a stratification factor (Section 12.3), the site will make all efforts to work with the local microbiology laboratory to ensure that susceptibility results from blood cultures are obtained before randomization to enable stratification by MRSA or MSSA. If a blood culture was performed for the current *S. aureus* infection prior to the qualifying blood culture, susceptibility results from the prior blood culture may be used. If the patient has a concomitant *S. aureus* infection at another body site from which susceptibility results are available (e.g., skin, abscess), the susceptibility results from this other culture may be used. If the patient is known to be colonized with MRSA, MRSA may be selected for the stratification factor.
  - In addition to the study-qualifying blood culture from specimens collected within approximately 72 hours before randomization, 1 aerobic blood culture will be collected during screening (or after randomization and before dosing), collected via peripheral venipuncture when possible.

  - Results of all blood cultures performed (from the initial *S. aureus*-positive culture) will be entered in the eCRF (whether positive or negative for *S. aureus*).
  - All *S. aureus* isolates, including from cultures collected pre-study, should be sent to the central laboratory (see Section 12.8.2.5).
- Other (non-blood) cultures should be performed to determine the source of *S. aureus* BSI/IE (Section 12.7) and evaluate metastatic foci (Section 12.12). Results of other (non-blood) cultures (whether positive or negative for *S. aureus*) will be entered in the eCRF, and all *S. aureus* isolates, including from cultures collected pre-study, should be sent to the central laboratory (Section 12.8.2.6).
- 12-lead ECG at screening or after randomization and before dosing (Section 12.9).
- Complete physical examination, including body weight and height (see Section 12.10).
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature) (Section 12.11).
  - If more than one vital sign measurement is taken within the approximately 24 hours prior to randomization, the most abnormal value will be recorded in the eCRF.
- Metastatic foci and septic emboli evaluation will be evaluated; diagnostic testing to assess metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures) will be performed as clinically indicated (see Section 12.12).
- Signs and symptoms attributable to *S. aureus* BSI/IE. Select symptoms will also be evaluated at pre-BSI/IE. Pre-BSI/IE is the patient's "usual state of health" before the BSI/IE started. The specific signs and symptoms assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) are described in Section 12.13.
- Medication review (see Sections 13.6 and 13.7).
- AE assessment from the time informed consent/assent is obtained (see Section 14).

## 11.4. Day 1: Study Drug Dosing

For the purpose of the visit structure, the day of exebacase/placebo dosing is considered Day 1 of the study. The following assessments/procedures will be performed on the day of dosing:

- Randomization: patients who are screened and determined to be eligible for the study will be randomly assigned to exebacase or placebo via an Interactive Response Technology (IRT) system.
  - The randomization will be stratified by poorly controlled diabetes (yes or no) defined below and susceptibility of the *S. aureus* isolate (MRSA, MSSA, or unknown) will be entered into the IRT system. For stratification, poorly controlled diabetes is defined as a HgA1C ≥8% within approximately 90 days before randomization. A HgA1C test is not

required for patients with no medical history of diabetes and no suspicion of diabetes during the screening period. These patients will be stratified to "no" for poorly controlled diabetes. A HgA1C test should be performed in patients with medical history of diabetes or suspicion of diabetes during screening for whom a HgA1C test result within the approximately 90 days prior to randomization is not available. If a HgA1C is unavailable and testing cannot be performed for these patients prior to randomization, contact the Medical Monitor to determine how the patient should be stratified based on available clinical information. All efforts will be made to obtain susceptibility results from blood cultures before randomization to enable stratification by MRSA or MSSA. If a blood culture was performed for the current *S. aureus* infection prior to the qualifying blood culture, susceptibility results from the prior blood culture may be used. If the patient has a concomitant *S. aureus* infection at another body site from which susceptibility results are available (e.g., skin, abscess), the susceptibility results from this other culture may be used. If the patient is known to be colonized with MRSA, MRSA may be selected for the stratification factor (Section 12.8.2.5).

  - CrCl will be entered into the IRT system and the system will provide the dose of study drug (Section 9.4). Serum creatinine to calculate CrCl will be performed as close to the start of study drug dosing as possible (but not more than approximately 24 hours before the start of study drug dosing; Section 12.8.1). The Cockcroft-Gault formula for calculating CrCl using ideal body weight in patients with BMI ≥30 kg/m$^2$ and serum creatinine result obtained locally is provided in Section 12.8.1.1.
  - The IRT system will also provide the PK group (described in more detail later in this section).

- Study drug dosing: Exebacase/placebo dosing will occur as soon as possible after randomization. Study drug dosing is described in Sections 9.4.1, 13, and the Pharmacy Manual.
  - Patients must be observed during the study drug infusion by someone from the clinical care team or research team with patient care experience (Section 9.4.1.1).
  - If a patient has clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug (Section 9.4.1.1), a blood sample for exebacase-specific IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample collected at screening will be sent to the central laboratory for testing (Section 12.8.2.3).
- If not already done during screening (as preferred; Section 11.3 above), make all efforts to determine the source of *S. aureus* BSI/IE (e.g., full physical examination, imaging as needed, cultures of other infected body sites or catheters that may be considered the source) within 1 week after randomization (Section 12.7).

- Blood and urine samples for clinical safety laboratory tests will be collected approximately 24 hours post-dose (Day 2) and sent to the central laboratory for testing (see Section 12.8.2.1). If a blood or urine sample for safety laboratory testing by the central laboratory is not able to be obtained at a given timepoint/visit, the local laboratory results may be entered into the eCRF for that timepoint/visit, if feasible. For adolescents, local clinical laboratory results from during the approximately 24 hours post-dose (Day 2) can substitute for central safety laboratory tests and will be entered into the eCRF.
- All patients will be assigned to one of two PK sampling schemes and blood samples will be collected at 3 timepoints as listed below, and sent to the central laboratory for measurement of exebacase (Section 12.8.2.4). The IRT system will also provide the PK group.
  - PK Group 1: pre-dose (collected during screening for patients who meet eligibility criteria and are expected to be randomized or after randomization and before dosing), within 5 to 25 minutes after the end of infusion, and between 3 to 5 hours after the end of infusion.
  - PK Group 2: pre-dose (collected during screening for patients who meet eligibility criteria and are expected to be randomized or after randomization and before dosing), within 5 to 25 minutes after the end of infusion, and between 8 to 12 hours after the end of infusion.
- Blood culture: One aerobic blood culture will be collected daily during the study until 2 consecutive negative cultures followed out to negative for at least 48 hours on 2 different days are obtained after exebacase/placebo administration (collected via peripheral venipuncture when possible). Note: blood cultures may be collected every other day for adolescents.
  - Results of all blood cultures (whether positive or negative for *S. aureus*) will be entered in the eCRF.
  - All *S. aureus* isolates will be sent to the central laboratory (Section 12.8.2.5).
- Other (non-blood) cultures should be performed to determine the source of *S. aureus* BSI/IE (Section 12.7) and evaluate metastatic foci (Section 12.12), and as clinically indicated during the study. Results of other (non-blood) cultures (whether positive or negative for *S. aureus*) will be entered in the eCRF, and all *S. aureus* isolates will be sent to the central laboratory (Section 12.8.2.6).
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature) will be performed approximately 30 to 40 minutes after the start of infusion and as clinically indicated during the infusion (Section 12.11).
- Metastatic foci and septic emboli evaluation will be evaluated; diagnostic testing to assess metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures) will be performed as clinically indicated (see Section 12.12).

- Signs and symptoms attributable to *S. aureus* BSI/IE. The specific signs and symptoms assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) are described in Section 12.13.
- Echocardiography:
  - All adult patients (≥18 years of age) will have a TTE or TEE within 3 days before or after randomization. All efforts will be made to perform the TTE or TEE before randomization.
    - Where possible, a TEE will be performed and is recommended in patients with BMI >30 kg/m$^2$; the TEE may be performed within 3 days before or after randomization unless the TEE is performed due to clinical suspicion of L-IE (see below).
    - In patients that have clinical findings suggestive of L-IE (new murmur, worsening cardiac function, and/or peripheral or central nervous embolic phenomenon), a TEE will be performed before randomization to rule out mitral and/or aortic valve vegetation(s) or the patient will be excluded from the study per exclusion criterion #2 (Section 10.2). In cases where there is an alternative cause of new heart failure or cerebral emboli, a patient with a negative TTE for L-IE may be discussed with the Medical Monitor for potential enrollment.
    - In patients with persistent bacteremia for ≥3 days (i.e., blood cultures positive for *S. aureus* for ≥3 days), an echocardiogram will be performed before randomization to rule out L-IE. A TTE may be used performed with permission of the Medical Monitor. If this echocardiogram is not performed or L-IE is not ruled out by this echocardiogram, the patient should not be randomized.
  - In adolescents (12 to <18 years of age), echocardiograms (TTE or TEE) will be performed as clinically indicated taking into consideration risk factors for endocarditis, (e.g., structurally abnormal heart [including pacemakers]), clinical features suggestive of endocarditis (e.g., new murmur), or persistent bacteremia [McMullan 2020], described in Section 12.14.
  - If the patient had an echocardiogram performed prior to the study that was intended to evaluate the current infection, it will be sent to the central echocardiography laboratory as directed by the Sponsor and an additional TTE or TEE is not required unless as indicated above, but should be discussed with the Medical Monitor if obtained ≥3 days prior to randomization.
  - The results of all echocardiograms will be entered in the eCRF. Images from all echocardiograms will be provided to the central echocardiography laboratory as directed by the Sponsor.

- If not already done prior to the study, intravenous catheters known or suspected to be infected must be removed, and as clinically needed replaced, preferably at a different site, as soon as possible within approximately 72 hours after randomization (Section 12.15). Other hemodialysis access types (i.e., AV fistulas or AV grafts) that are known or suspected to be infected will be evaluated for removal/replacement, if clinically feasible. If removal/debridement is not feasible based on standard medical practice, the patient should be discussed with the Medical Monitor for potential enrollment.
- In patients with CVCs, ultrasounds to evaluate clots in the vein should be performed within approximately 48 hours after randomization, unless the clot in the vein has been detected within this timeframe via other method (e.g., imaging such as CT scan or MRI or direct visualization during surgery) (Section 12.16).
- Medication review (see Sections 13.6 and 13.7).
- AE assessment (see Section 14).

## 11.5. Days 7, 14, 30, 60, and Daily Assessments

Study visits are performed on Days 7, 14, 30, and 60 after study drug dosing. Visit windows are as follows: Day 7 (±1 day), Day 14 (±1 day), Day 30 (±4 days), Day 60 (±7 days). In addition, some study assessments/procedures are performed daily. The following assessments/procedures will be performed at the timepoints noted below:

- The duration of SoCA will generally be from 2 to 8 weeks (14 to 56 days). If a longer duration of treatment with SoCA is anticipated, this must be discussed prior to randomization with the Medical Monitor. Long-term oral antibiotic suppression therapy (e.g., for osteomyelitis), is not considered to be SoCA for *S. aureus* BSI/IE and would be considered a "concomitant medication" as described in Section 9.4.2.
  - The eCRF will collect information on the entire course of SoCA for the patient's current episode of *S. aureus* BSI/IE, including SoCA received prior to the patient's entry in the study.
- Diagnosis determined by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) on **Day 7** based on the definitions in Section 12.5.
- If not already done during screening (as preferred; Section 11.3 above), make all efforts to determine the source of *S. aureus* BSI/IE (e.g., full physical examination, imaging as needed, cultures of other infected body sites or catheters that may be considered the source) **within 1 week after randomization** (Section 12.7). The resolution of the source of *S. aureus* BSI/IE will be evaluated at **Days 7, 14, 30, and 60**.

- Blood and urine samples for clinical safety laboratory tests will be collected on **Day 14 for adults* and Day 30** and sent to the central laboratory (see Section 12.8.2.1).
  *The collection of Day 14 samples is not required for adolescents. Results from local clinical laboratory testing completed within the Day 14 visit window should be entered into the eCRF if available and feasible. For all patients, if a blood or urine sample for safety laboratory testing by the central laboratory is not able to be obtained at a given timepoint/visit, the local laboratory results may be entered into the eCRF for that timepoint/visit, if feasible. If a blood or urine sample for safety laboratory testing by the central laboratory or local laboratory results are not able to be obtained at the Day 30 visit, samples may be collected between the Day 30 and 60 visits when collecting the blood sample(s) for exebacase-specific ADA and pregnancy testing (if applicable).
  For adolescents, the results of local clinical laboratory testing during the screening window and at all other timepoints corresponding to the protocol can substitute for central safety laboratory tests and will be entered into the eCRF; samples for ADA and IgE must be collected at the timepoints specified in the protocol and sent to the central laboratory.
- Blood sample for serum pregnancy test will be collected between the **Days 30 and 60 visits** for women of childbearing potential only and sent to the central laboratory for testing (see Section 12.8.2.2).
- Blood cultures: One aerobic blood culture will be collected **daily** during the study until 2 consecutive negative cultures followed out to negative for at least 48 hours on 2 different days are obtained after exebacase/placebo administration (via peripheral venipuncture when possible). Additional blood cultures will be performed as clinically indicated.
  Note: blood cultures may be collected every other day for adolescents.
  - Results of all blood cultures (whether positive or negative for *S. aureus*) will be entered in the eCRF.
  - All *S. aureus* isolates will be sent to the central laboratory (Section 12.8.2.5).
- Other (non-blood) cultures should be performed to determine the source of *S. aureus* BSI/IE (Section 12.7) and evaluate metastatic foci (Section 12.12), and as clinically indicated during the study. Results of other (non-blood) cultures (whether positive or negative for *S. aureus*) will be entered in the eCRF, and all *S. aureus* isolates will be sent to the central laboratory (Section 12.8.2.6).
- 12-lead ECG on **Day 14** (see Section 12.9).
- Complete physical examination on **Days 7, 14, 30, and 60** (see Section 12.10).
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature) will be performed at the Day 7, 14, 30, and 60 visits for visits performed "in person" or may be obtained via the study-specific mobile health service, if feasible (Section 12.11).

  - If more than one vital sign measurement is taken on the same day, the most abnormal value will be recorded in the eCRF.

- Metastatic foci and septic emboli evaluation will be evaluated at the **Day 7, 14, 30, and 60** visits; diagnostic testing to assess metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures) will be performed as clinically indicated (see Section 12.12). Note: For the assessment of clinical outcome (Section 12.18), metastatic foci identified through Day 7 are considered part of the patient's baseline *S. aureus* BSI/IE; new metastatic foci identified after Day 7 or new septic emboli after study drug dosing are considered complications of *S. aureus* BSI/IE for the purpose of assessing clinical outcome. New septic emboli are defined as an acute presentation of septic emboli after dosing and are a reason for failure for clinical outcome; septic emboli that are incidentally found on imaging are considered part of the patient's baseline *S. aureus* BSI/IE if found before Day 7.
- Signs and symptoms attributable to *S. aureus* BSI/IE will be evaluated at the **Day 7, 14, 30, and 60** visits. Additionally, if SoCA is changed after study drug dosing due to lack of clinical response, signs and symptoms will be assessed on the day of the SoCA change. The specific signs and symptoms assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) are described in Section 12.13.
- Echocardiography:
  - If the echocardiogram was not already done before randomization (as preferred and required for certain patients; see Section 11.4 above), a TTE or TEE will be performed **within 3 days after randomization for adult patients**. In adolescents (12 to <18 years of age), echocardiograms will be performed as clinically indicated (Section 12.14).
  - Follow-up echocardiograms will be performed as clinically indicated.
  - The results of all echocardiograms performed through the Day 60 visit will be entered in the eCRF. Images from all echocardiograms through the Day 60 visit will be provided to the central echocardiography laboratory as directed by the Sponsor (see Section 12.14).
- If not already done, IV catheters known or suspected to be infected must be removed, and as clinically needed replaced, preferably at a different site, **as soon as possible within approximately 72 hours after randomization**. Other hemodialysis access types (i.e., AV fistulas or AV grafts) that are known or suspected to be infected will be evaluated for removal/replacement, if clinically feasible. If removal/debridement is not feasible based on standard medical practice, the patient should be discussed with the Medical Monitor for potential enrollment (Section 12.15).

- If not already done, in patients with CVCs, ultrasounds to evaluate clots in the vein should be performed **within approximately 48 hours after randomization,** unless the clot in the vein has been detected within this timeframe via other method (e.g., imaging such as CT scan or MRI or direct visualization during surgery) (Section 12.16).
- Blood samples for exebacase-specific ADA will be collected **on any day between the Day 30 and Day 60 visit windows (i.e., between Day 26 and Day 67)** and sent to the central laboratory for testing (Section 12.8.2.3).
- Ongoing medication review **through the Day 60 visit** (Sections 13.6 and 13.7).
- Ongoing AE assessment **through the Day 60 visit** (Section 14).
- Clinical outcome will be assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) at **Days 14, 30, and 60**. The clinical outcome definitions are in Section 12.18.
- Vital status (whether the patient is alive or dead, or last known date alive if vital status is unknown) will be obtained at **Days 14, 30, and 60** for all patients, including patients that discontinue the study or withdraw consent/assent (as described in the informed consent/assent form). The patient's vital status will be determined using available sources (e.g., the patient, patient's contacts, hospital and other medical records, and public records, such as social media, obituaries, social security death index), as described in the informed consent/assent form and FDA guidance (see Section 12.17).
- Health resource utilization information will be collected **through Day 60** (Section 12.20).

### 11.5.1. Visits Performed Remotely by Telephone/Telehealth, Use of Medical Records, and Use of Mobile Health Services

Every attempt must be made to ensure the patient returns for study visits, including offering support to the patient to facilitate return for the visit (e.g., reimbursement of travel expenses). If extenuating circumstances prevent the patient from returning to the study site for a visit, the site must contact the Medical Monitor or designee* to discuss whether a visit may be conducted by telephone or other telehealth technology (e.g., videoconference) in order to facilitate collection of as much data as possible for the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) to assess clinical outcome. It will be recorded in the eCRF that the visit was conducted by telephone/telehealth. The information to be collected during a telephone/telehealth visit is listed subsequently in this section.

* For patients that have travel restrictions due to COVID-19, the Day 30 or Day 60 visit may be conducted by telephone/telehealth without Medical Monitor pre-approval. The reason for the telephone/telehealth visit (i.e., COVID-19) will be documented in the eCRF. All efforts should be made to collect laboratory samples, if feasible.

The following information will be collected during the telephone/telehealth visit and entered in the eCRFs: any AEs that may have occurred since the last visit and outcome of any ongoing AEs, thorough medical review of body systems to assess signs and symptoms of *S. aureus* BSI/IE, outcome of pre-existing or presence of new metastatic foci, outcome of primary source of infection, SoCA and reasons for any changes in SoCA, concomitant medications, surgeries/procedures, vital status, and clinical outcome.

Medical records* may be used to supplement information obtained during the telephone/telehealth visit. If the patient is at another facility (e.g., nursing home, another hospital), the site will obtain medical records from that facility whenever possible.

In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records* alone may be used for physical examinations, signs/symptoms, and metastatic foci/septic emboli assessments after contacting the Medical Monitor or designee.

* When medical records are used alone or to supplement information collected during the telephone/telehealth visit, the physical examinations, signs/symptoms, and metastatic foci/septic emboli assessments extracted from the medical record will be recorded in the site's source documents and entered in the relevant eCRFs. The Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) is expected to review, sign, and date the assessments extracted from the medical record and recorded in the site's source documents. Symptom severity assessments must be made in accordance with Table 9. The eCRFs will be verified by the site monitor using these source documents.

Mobile health services, specifically contracted for the study, may be used to supplement telephone/telehealth visits to perform study visit procedures, such as collecting laboratory samples, evaluating vital signs, and/or obtaining a 12-lead ECG, after approval by the Medical Monitor or designee.

Mobile health services may include:

- Day 14: Collection of laboratory samples, evaluation of vital signs, and performance of a 12-lead ECG.
- Day 30: Collection of laboratory samples and evaluation of vital signs.
- Day 30 to Day 60: Samples for exebacase-specific ADA and pregnancy testing may be collected between the Day 30 and Day 60 visit windows (i.e., between Day 26 to Day 67).

If a blood or urine sample for safety laboratory testing by the central laboratory or local laboratory results are not able to be obtained at the Day 30 visit, samples may be collected on any day between the Day 30 and 60 visit windows (i.e., between Day 26 and Day 67) when collecting the blood sample(s) for exebacase-specific ADA and pregnancy test (if applicable).

Alternatively, local laboratory, vital signs, and ECG data obtained in conjunction with the Day 7, 14, 30, or 60 visits may be used for the study if available (including using data from medical records of another hospital, skilled nursing facility or other similar institution).

# 12. STUDY ASSESSMENTS

The study schematic and schedule of assessments are provided in Sections 3 and 4, respectively. The study procedures/assessments performed at each visit are described in the subsections under Section 11. The individual procedures/assessments are described in detail in the subsections that follow.

## 12.1. Informed Consent/Assent

Each patient must provide written informed consent or assent before any study-specific assessment or procedures are performed. Some patients who will be eligible for the study may not be able to give written informed consent or assent themselves due to reasons such as sedation, unconscious state, etc. Therefore, in a situation where a patient is unable to provide written informed consent or assent for themselves, written informed consent may be provided by the patient's legally acceptable representative, as permissible based on local laws and regulations. In such cases, if the patient regains the ability to supply informed consent or assent themselves, they should be reconsented/assented. For patients 12 to <18 years of age, written informed consent from the patient's parent/guardian or other legally acceptable representative will be obtained according to the site's IRB requirements. For emancipated minors, written informed consent will be obtained according to the site's IRB requirements. The informed consent process is described in Section 19.2.

## 12.2. Inclusion/Exclusion Criteria Review

The inclusion and exclusion criteria described in Sections 10.1 and 10.2, respectively, will be reviewed to determine whether the patient is eligible for the study. For patients who are not eligible, the specific inclusion criteria not met, exclusion criteria met, and/or other reasons for screen failure will be entered in the IRT system. Study eligibility will be adjudicated by the AC (Section 12.23).

### 12.2.1. Contraception Requirements

Contraception requirements are described in the inclusion criteria (Section 10.1).
The manufacturer's prescribing information for SoCA will be referenced for information related to pregnancy and contraception.

### 12.2.2. Quick SOFA and SOFA Scores

Sepsis and/or septic shock based on the SOFA score are criteria for complicated *S. aureus* BSI according to the inclusion criterion #4 (Section 10.1) and the diagnosis definition in Table 8 (Section 12.5). During screening, the quick SOFA (qSOFA) score will be determined for all patients. The qSOFA score is used to rapidly identify patients as being more likely to have poor outcomes typical of sepsis [Singer 2016], and is defined as having at least 2 of the following clinical criteria: respiratory rate ≥22/min, altered mental status, and/or systolic blood pressure ≤100 mmHg. In patients that have at least 2 of these clinical criteria, a SOFA score will be performed to determine whether the patient meets the criteria for sepsis and/or septic shock. The SOFA score will be determined according to the criteria described in the Appendix 1 (Section 23.1). If arterial blood gas (ABG) data is not available from testing performed as part of clinical care, oxygen saturation (SpO2) may be used to determine the SOFA score by converting to partial pressure of oxygen (PaO2) (see Oxygen Conversion Table; Table 14) and the fraction of inspired oxygen (FiO2) may be estimated using the Estimated FiO2 Table (Table 15) provided in Section 23.3, Appendix 3.

### 12.2.3. APACHE II Score

Baseline APACHE II score will be calculated for all patients. Per exclusion criterion #15 (Section 10.2), patients with APACHE II score of >30 are excluded from the study. The APACHE II score form is provided in the appendix (Section 23.2, Appendix 2). If ABG data is not available from testing performed as part of clinical care, SpO2 may be used to determine the APACHE II score by converting to PaO2 (see Oxygen Conversion Table; Table 14) and the FiO2 may be estimated using the Estimated FiO2 Table (Table 15) provided in Section 23.3, Appendix 3, and serum bicarbonate may be used for pH.

## 12.3. Randomization

Patients who are screened and determined to be eligible for the study will be randomly assigned to receive exebacase or placebo in a 2:1 ratio via the IRT system. Randomized patients will be assigned the treatment corresponding to the next available randomization number in the respective stratum from the computer-generated randomization schedule. A patient is considered randomized when a randomization transaction is recorded in the IRT. Study drug dosing will occur as soon as possible after randomization (Section 9.4.1).

The randomization will be stratified by poorly controlled diabetes (yes or no) as defined below and susceptibility of the *S. aureus* isolate (MRSA, MSSA, or unknown) will be entered into the IRT system. For stratification, poorly controlled diabetes is defined as a HgA1C ≥8% within approximately 90 days before randomization. A HgA1C test is not required for patients with no medical history of diabetes and no suspicion of diabetes during the screening period. These patients will be stratified to “no” for poorly controlled diabetes. A HgA1C test should be performed in patients with medical history of diabetes or suspicion of diabetes during screening for whom a HgA1C test result within the approximately 90 days prior to randomization is not

available. If a HgA1C is unavailable and testing cannot be performed for these patients prior to randomization, contact the Medical Monitor to determine how the patient should be stratified based on available clinical information. All efforts will be made to obtain susceptibility results from blood cultures before randomization to enable stratification by MRSA or MSSA. If a blood culture was performed for the current *S. aureus* infection prior to the qualifying blood culture, susceptibility results from the prior blood culture may be used. If the patient has a concomitant *S. aureus* infection at another body site from which susceptibility results are available (e.g., skin, abscess), the susceptibility results from this other culture may be used. If the patient is known to be colonized with MRSA, MRSA may be selected for the stratification factor (Section 12.8.2.5).

Creatinine clearance value will be entered into the IRT system and the system will provide the dose of study drug based on the CrCl value (Section 9.4.1). Serum creatinine to calculate CrCl will be performed as close to the start of study drug dosing as possible (but not more than approximately 24 hours before the start of study drug dosing; Section 12.8.1).
The Cockcroft-Gault formula for calculating CrCl using ideal body weight in patients with BMI ≥30 kg/m$^2$ and serum creatinine result obtained locally is provided in Section 12.8.1.1.

The IRT system will also provide the PK group (Section 12.8.2.4).

## 12.4. Medical History

Medical history for 1 year prior to screening will be recorded in the eCRF. Medical history will include relevant previous and current medical diagnoses and major surgical procedures.
The current episode of *S. aureus* BSI/IE (the disease under study) should not be recorded on the Medical History eCRF since this is collected separately (i.e., on the Diagnosis eCRF).

## 12.5. Diagnosis

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will determine diagnosis during screening and on Day 7. Final diagnosis will be adjudicated by the AC (Section 12.23). This adjudicated final diagnosis will be used for the analysis. The diagnosis definitions that will be used by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) and AC are provided in Table 8.

**Table 8: Diagnosis Definitions**

| Diagnosis | Definition |
|---|---|
| *S. aureus* R-IE | Definite or possible R-IE based on the Modified Duke Criteria [adapted from Li 2000], as defined below, with involvement of **pulmonic and/or tricuspid** valve(s).<br>1. **Definite** diagnosis: presence of 2 major, 1 major and 3 minor, or 5 minor criteria, or<br>2. **Possible** diagnosis:1 major criterion and 1 minor criterion, or 3 minor criteria<br>Major and minor criteria are as follows:<br>A. Major clinical criteria:<br>1. Blood cultures positive:<br>a. *S. aureus* (in the absence of a primary focus) identified from 2 separate blood cultures<br>b. *S. aureus* identified from persistently positive blood cultures (at least 2 positive cultures of blood samples drawn >12 hours apart, or positive results of all of 3 or a majority of 4 or more separate blood cultures [with first and last samples drawn at least 1 hour apart])<br>2. Evidence of endocardial involvement:<br>a. Echocardiogram positive for IE with pendulum-like intracardiac mass on valve or supporting structures, or in the path of regurgitant jets<br>b. New valvular regurgitation (worsening or changing of preexisting murmur not a sufficient criterion) when confirmed by echocardiogram<br>B. Minor clinical criteria:<br>1. Predisposition to IE, such as predisposing heart condition, or intravenous drug use<br>2. Fever, defined as oral temperature equivalent >38.0°C (>100.4°F)<br>3. Vascular phenomena, such as conjunctival hemorrhage, and Janeway's lesions<br>4. Immunologic phenomena, such as glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor<br>5. Microbiologic evidence: positive blood cultures for *S. aureus* but with no major clinical criterion met or serologic evidence of active infection |

Table continued on next page

**Table 8: Diagnosis Definitions (Continued)**

| Diagnosis | Definition |
|---|---|
| Complicated *S. aureus* BSI | • Patient did **not** have IE based on the Modified Duke Criteria, *S. aureus* was isolated from blood culture; and patient had one or more of the following:<br>o Blood culture positive for *S. aureus* on more than one day<br>o Clots in the vein at or near the catheter site seen on ultrasound or other method (e.g., MRI, echocardiogram, surgery)<br>o Signs or symptoms of metastatic foci of infection (e.g., splenic abscess, deep tissue abscess not associated with open wound or other local source of infection, septic pulmonary emboli) or hematogenous seeding (e.g., of the renal system evidenced by *S. aureus* bacteriuria [in absence of other source such as indwelling ureteral catheter], septic arthritis, osteomyelitis) confirmed by physical examination, imaging, and/or culture<br>Note: Patients who present with acute osteomyelitis as the first manifestation of *S aureus* BSI (e.g., adolescents) may be enrolled even if original source of infection is not known.<br>o Persistent fever (oral temperature equivalent ≥38.0°C [≥100.4°F]) for 72 hours or more<br>o Met criteria for sepsis or septic shock using the SOFA score (definition in Section 23 [adapted from Singer 2016]) during the time of diagnosis/presumptive diagnosis of BSI<br>o Significantly immunocompromised:<br>▪ AIDS (HIV positive with an AIDS-defining condition or a CD4 count of approximately ≤200 cells/mm³ within approximately 90 days)<br>▪ Severe leukopenia defined as ANC of approximately ≤500 cells/mL in the 7 days prior to the qualifying blood culture or during the screening window<br>▪ Post organ transplantation including autologous bone marrow or stem cell transplantation and on immunosuppressive therapy for the organ transplant around the time of presentation with the *S. aureus* BSI/IE<br>▪ On treatment for active graft vs. host disease<br>▪ On immunosuppressive therapy, such as:<br>• Biologics such as infliximab, monoclonal antibodies such as daclizumab, methotrexate, cyclophosphamide, or similar agents. A list of similar agents is in Appendix 4 in Section 23.4.<br>• Patients who have taken ≥10 mg of prednisone or equivalent for 5 days or more.<br>▪ On myelosuppressive chemotherapy or immunotherapy<br>▪ Advanced cirrhosis |

Table continued on next page

**Table 8: Diagnosis Definitions (Continued)**

| | |
|---|---|
| *S. aureus* L-IE[1] | • Definite or possible L-IE based on the Modified Duke Criteria, with involvement of **mitral and/or aortic** valve(s) |
| *S. aureus* L-IE and R-IE[1] | • Definite or possible L-IE and R-IE based on the Modified Duke Criteria, with involvement of **mitral and/or aortic** valve(s) and **pulmonic and/or tricuspid** valve(s). |
| Uncomplicated *S. aureus* BSI[1] | • Patient did **not** have IE based on the Modified Duke Criteria; and<br>• *S. aureus* was isolated from blood culture; and<br>• Patient did **not** meet criteria for complicated *S. aureus* BSI |

Abbreviations: BSI=bloodstream infection; IE=infective endocarditis; L-IE=left-sided infective endocarditis; R-IE=right-sided infective endocarditis

1. Patients with known or suspected L-IE or uncomplicated *S. aureus* BSI are not eligible for the study. The diagnosis definitions are included here in the event that patients are determined to have these diagnoses post-randomization. If patients with L-IE or uncomplicated *S. aureus* BSI are enrolled, they will continue in the study and be followed for safety and efficacy.

## 12.6. Risk Factors

The following risk factors for complicated *S. aureus* BSI, as described in the inclusion criteria (Section 10.1), will be recorded in the eCRF:

- Preexisting right-sided valvular heart disease
- Surgery within the previous 30 days that puts the patient at risk for nosocomial bacteremia (e.g., orthopedic, cardiothoracic, or intraabdominal surgery)
- Extravascular foreign material. Note: Catheters including ports, AV fistulas and related dialysis access points are considered intravascular foreign material.
- Hemodialysis

## 12.7. Source of *S. aureus* Infection

All efforts will be made to determine the source of *S. aureus* BSI/IE (e.g., full physical examination, imaging as needed, cultures of other infected body sites or catheters that may be considered the source), preferably during screening or within 1 week after randomization. The source of *S. aureus* BSI/IE will be recorded in the eCRF. The resolution of the source of *S. aureus* BSI/IE will be evaluated at Days 7, 14, 30, and 60.

The primary source of BSI/IE and adequacy of source control will be adjudicated by the AC.

## 12.8. Laboratory Tests

### 12.8.1. Laboratory Tests Performed by the Local Laboratory

The central laboratory will not be providing 'real-time' results; therefore, limited laboratory tests may need to be performed by the site's local laboratory during screening so that timely results are available for study eligibility determination, stratification, and to determine the dose of study drug (based on CrCl using ideal body weight; see below). If local laboratory results are already

available within the approximately 72 hours prior to screening from standard-of-care/routine testing, these results may be used to support eligibility determination, unless otherwise specified below in underlined text. The laboratory tests that are required to be available locally are as follows:

- Serum creatinine to calculate CrCl will be performed as close to the start of study drug dosing as possible (but not more than approximately 24 hours before the start of study drug dosing). CrCl is used for eligibility determination (in patients who are asplenic; see exclusion criterion #11 in Section 10.2) and to determine the dose of study drug (see Section 9.4.1). Therefore, is important to use the serum creatinine result obtained closest to the start of study drug dosing to determine CrCl to guide dosing. The Cockcroft-Gault formula for calculating CrCl using serum creatinine result and ideal body weight in patients with BMI ≥30 kg/m$^2$ is provided in Section 12.8.1.1.
- If a HgA1C value is not already available approximately 90 days before randomization in patients with medical history of diabetes or suspicion of diabetes during screening, a HgA1C will be performed to determine if diabetes is poorly controlled (since poorly controlled diabetes, defined as a HgA1C of ≥8% within approximately 90 days before randomization, is a stratification factor; see Section 12.3). If a HgA1C testing cannot be performed for patients with diabetes prior to randomization, contact the Medical Monitor to determine how the patient should be stratified based on available clinical information. A HgA1C test is not required for patients with no medical history of diabetes and no suspicion of diabetes during the screening period. These patients will be stratified to "no" poorly controlled diabetes.
- Urine or serum β-hCG pregnancy test (for women of childbearing potential; see inclusion criteria in Sections 10.1 and 12.8.2.2)
- FSH (to confirm postmenopausal status as applicable; see inclusion criteria in Section 10.1)
- Laboratory tests for SOFA score as needed (see Sections 12.2.2 and 23.1)
- Laboratory tests for APACHE II score (see Sections 12.2.3 and 23.2)
- Other safety laboratory tests may be performed locally at the Investigator's/ Sub-Investigator's (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) discretion to assess the patient in general for study eligibility or during the study per the site's standard-of-care for routine clinical management of the patient.

Note: If a blood or urine sample for safety laboratory testing by the central laboratory is not able to be obtained at a given timepoint/visit, the local laboratory results may be entered in the eCRF for that timepoint/visit, if feasible. For adolescents, the results of local clinical laboratory testing during the screening window and at all other timepoints corresponding to the protocol can substitute for central safety laboratory tests and will be entered into the eCRF; samples for

ADA and IgE must be collected at the timepoints specified in the protocol and sent to the central laboratory.

#### 12.8.1.1. Estimated Creatinine Clearance by Cockcroft-Gault

Estimated CrCl will be calculated for eligibility determination (in patients who are asplenic; see exclusion criterion #11 in Section 10.2) and to determine the dose of study drug (see Section 9.4.1) using the serum creatinine result obtained locally as close to the start of study drug dosing as possible (but not more than approximately 24 hours before the start of study drug dosing), as described above in Section 12.8.1. Estimated CrCl is calculated by Cockcroft-Gault formula as follows:

***In Patients with BMI <30 kg/m$^2$:***

Estimated CrCl = [(140 – age) x weight in kg]/[72 x serum creatinine in mg/dL]
[x 0.85 if female].

***In Patients with BMI ≥30 kg/m$^2$:***

Estimated CrCl = [(140 – age) x **ideal body weight** in kg]/[72 x serum creatinine in mg/dL]
[x 0.85 if female].

- For height in inches: Ideal body weight = 2.3 kg x each inch over 5 feet + **W**
- For height in cm: Ideal body weight = 0.9 kilograms × (height (cm) − 152) + **W**

  **W** = 50 kg for males; 45.5 kg for females

### 12.8.2. Laboratory Sample Collection for Sending to Central Laboratory

The following subsections describe the laboratory samples that will be collected and sent to the central laboratory. The details for sample collection, preparation, and shipping to the central laboratory will be provided in a separate laboratory manual.

#### 12.8.2.1. Samples for Safety Laboratory Testing

Blood and urine samples for safety laboratory tests (biochemistry, hematology, coagulation, and urinalysis) will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) or after randomization and before dosing, approximately 24 hours after study drug administration (Day 2), on Day14 for adults*, and on Day 30; the samples will be sent to a central laboratory for testing. *The collection of Day 14 samples is not required for adolescents. Results from local clinical laboratory testing completed within the Day 14 visit window should be entered into the eCRF if available and feasible.

Note: For all patients, if a blood or urine sample for safety laboratory testing by the central laboratory is not able to be obtained at a given timepoint/visit, the local laboratory results may be entered into the eCRF for that timepoint/visit, if feasible. If a blood or urine sample for safety laboratory testing by the central laboratory or local laboratory results are not able to be obtained

at the Day 30 visit, samples may be collected on any day between the Day 30 and 60 visit windows (i.e., between Day 26 and Day 67) when collecting the blood sample(s) for exebacase-specific ADA and pregnancy test (if applicable).

Note: For adolescents, the results of local clinical laboratory testing during the screening window and at all other timepoints corresponding to the protocol can substitute for central safety laboratory tests and will be entered into the eCRF; samples for ADA and IgE must be collected at the timepoints specified in the protocol and sent to the central laboratory.

#### 12.8.2.2. Samples for Pregnancy Testing

For females of childbearing potential only, blood samples for serum pregnancy test will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) and between the Days 30 and 60 visits and sent to the central laboratory for testing. (Note: A urine or serum pregnancy test will be done locally as part of screening for eligibility; Section 12.8.1).

#### 12.8.2.3. Samples for Immunogenicity

Blood samples for exebacase-specific ADA will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) or after randomization and before dosing and on any day between the Day 30 and Day 60 visit windows (i.e., between Day 26 and Day 67); samples are sent to the central laboratory for testing.

Blood samples for exebacase-specific IgE testing will be collected during screening (for patients who meet eligibility criteria and are expected to be randomized) and retained at the site. If a patient has treatment-emergent clinical signs or symptoms of a potential allergic reaction that may be attributed to study drug (Section 9.4.1.1), a blood sample for exebacase-specific IgE will be collected as soon as possible within 2 hours of the event, if feasible, and both this sample and the IgE sample at screening will be sent to a central laboratory for testing.

#### 12.8.2.4. Samples for Pharmacokinetics

All patients will be assigned to one of two PK sampling schemes and blood samples will be collected at 3 timepoints as listed below, and sent to the central laboratory for measurement of exebacase:

- PK Group 1: pre-dose (collected during screening for patients who meet eligibility criteria and are expected to be randomized or after randomization and before dosing), within 5 to 25 minutes after the end of infusion, and between 3 to 5 hours after the end of infusion.
- PK Group 2: pre-dose (collected during screening for patients who meet eligibility criteria and are expected to be randomized or after randomization and before dosing), within 5 to 25 minutes after the end of infusion, and between 8 to 12 hours after the end of infusion.

The actual time of PK sample collection, actual time of start and end of infusion, actual rate of volume and rate of infusion, and dosing information will be recorded.

#### 12.8.2.5. Blood Cultures

Blood cultures will be collected from a peripheral venipuncture site when possible. The study site's local microbiology laboratory will perform identification and *in vitro* susceptibility testing to SoCA according to local practices. The results of all blood cultures (whether positive or negative for *S. aureus*) performed (from the initial *S. aureus*-positive blood culture collected pre-study through the Day 60 visit) will be entered in the eCRF. The *S. aureus* isolates from all blood cultures (from the initial *S. aureus*-positive blood culture collected pre-study through the Day 60 visit) should be sent to the central laboratory. If two blood cultures are drawn at the same timepoint, only one *S. aureus* isolate from the blood cultures will be sent to the central laboratory. Blood cultures will be performed at the following timepoints:

- Qualifying blood culture: The "qualifying" blood culture from specimens collected within approximately 72 hours before randomization (per the inclusion criteria in Section 10.1) will be recorded in the eCRF and the *S. aureus* isolate should be sent to the central laboratory. The site will make all efforts to work with the local microbiology laboratory to ensure that, wherever possible, the *S. aureus* isolate from the qualifying blood culture is retained and sent to the central laboratory.
  - Note: Since susceptibility of the *S. aureus* isolate is a stratification factor (Section 12.3), the site will make all efforts to work with the local microbiology laboratory to ensure that susceptibility results from blood cultures are obtained before randomization to enable stratification by MRSA or MSSA. If a blood culture was performed for the current *S. aureus* infection prior to the qualifying blood culture, susceptibility results from the prior blood culture may be used. If the patient has a concomitant *S. aureus* infection at another body site from which susceptibility results are available (e.g., skin, abscess), the susceptibility results from this other culture may be used. If the patient is known to be colonized with MRSA, MRSA may be selected for the stratification factor.
- Screening: One aerobic blood culture will be collected during screening (or after randomization and before dosing).
- Daily: One aerobic blood culture will be collected daily during the study until 2 consecutive negative cultures followed out to negative for at least 48 hours on 2 different days are obtained after exebacase/placebo administration. Note: blood cultures may be collected every other day for adolescents.
- Additional blood cultures will be performed as clinically indicated.

#### 12.8.2.5.1. Microbiological Sample Collection and Processing

The details for microbiological sample collection, processing, and shipping to the central laboratory will be provided in a separate Laboratory Manual.

Blood samples must be transported to the local microbiology laboratory as soon as possible and incubated within less than 24 hours of collection.

*Organism Identification*

When growth is present in the blood culture bottle, a Gram stain must be performed. Gram-positive cocci in clusters are indicative of a presumptive staphylococcal infection. For this study, rapid identification and differentiation of *S. aureus* from coagulase-negative staphylococci is critical to patient enrollment. Local microbiology laboratories are encouraged to utilize the direct tube coagulase test, when available, to identify *S. aureus*. Patients may be enrolled if their Gram stain shows Gram-positive cocci in clusters and either the direct tube coagulase test is positive after 4 hours of incubation indicating *S. aureus* or latex slide agglutination test is positive.

Additionally, patients may be enrolled based on rapid diagnostic test results if an FDA-cleared or CE-IVD certified rapid diagnostic for *S. aureus* is available at the site. Examples of rapid diagnostic tests are listed in the table below.

**Examples of FDA cleared and CE-IVD Certified Rapid Diagnostic Tests for Detection of *S. aureus* Directly from Positive Blood Cultures**

| Manufacturer | Test Name |
|---|---|
| Alere (Abbott) | BinaxNOW *S. aureus* |
| Biofire Diagnostics (BioMerieux Company) | Film Array System and BCID Panel |
| AdvanDX (OpGen Company) | PNA QuickFISH and mecA XpressFISH |
| Luminex | Verigene |
| Cepheid | GeneXpert |
| Miacom-MetaSystems | hemoFISH Masterpanel |
| GenMark | ePlex |
| Accelerate Diagnostics | PhenoTest |

Organisms must be isolated in pure culture and identified according to the local laboratory's standard operating procedures. Patients who have a negative result for *S. aureus* on blood culture or have a missing blood culture(s) will continue to be followed in the study. Only *S. aureus* strains will be sent to the central microbiology laboratory for confirmation of identification and standardized susceptibility testing. The local laboratory results of Gram stain, organism identification, and rapid diagnostic testing will be recorded in the eCRF.

*Diagnostic Testing*

Laboratories routinely using and clinical reporting the results of FDA-approved assays for the detection of *mec A* or *mecA/C* genes should record the results of the diagnostic test in the eCRF.

*Susceptibility Testing*

Susceptibility testing of *S. aureus* will be performed according to the local laboratory's standard operating procedures and in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI) and/or European Committee on Antimicrobial Susceptibility Testing (EUCAST). At a minimum, the local laboratory will test susceptibilities to daptomycin, vancomycin, and oxacillin or cefoxitin (CLSI recommended surrogate for oxacillin to detect MRSA). The results of susceptibility testing will be recorded in the eCRF.

*Archiving and Shipment of Isolates*

All *S. aureus* strains will be stored frozen at -70°C (in a non-automatic defrost freezer) at the site's local microbiology laboratory as backup samples. The *S. aureus* isolates will be shipped to the designated central microbiology laboratory as directed in a separate microbiology laboratory manual. Backup isolates must be stored at the site until notification from ContraFect or designee that they can be discarded.

*Testing at the Central Laboratory*

The central microbiology laboratory will repeat the identification and perform *in vitro* susceptibility testing of isolates; the central laboratory results will be used for the analysis. Further evaluation to identify the potential mechanism of resistance may be performed.

#### 12.8.2.6. Other (Non-Blood) Cultures

"Other" cultures (i.e., cultures from catheter tips or body sites or body fluids other than blood) will be performed to determine the source of *S. aureus* BSI/IE (Section 12.7) and evaluate metastatic foci (Section 12.12), and as clinically indicated during the study. The results of all other (non-blood) cultures (whether positive or negative for *S. aureus*) collected pre-study through the Day 60 visit will be recorded in the eCRF. *S. aureus* isolates from all other (non-blood) cultures collected pre-study through the Day 60 visit should be sent to the central laboratory.

### 12.8.3. Laboratory Tests Performed by the Central Laboratory(ies)

The central laboratory(ies) will not be providing 'real-time' results; therefore, limited laboratory tests may be performed locally to assess the patient for study eligibility/determine study drug dose, during the study per the site's standard-of-care for routine clinical management of the patient, or for adolescent patients (as described in Section 12.8.1).

The following laboratory tests will be performed at the central laboratory(ies):

- Biochemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total, direct, indirect), blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein. (Timepoints for sample collection are described in Section 12.8.2.1).
- Hematology: hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) distribution width, RBC count, WBC count, WBC differential (% and absolute), basophils, eosinophils, lymphocytes, monocytes, neutrophils, immature neutrophils. (Timepoints for sample collection are described in Section 12.8.2.1).
- Coagulation: Prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT). (Timepoints for sample collection are described in Section 12.8.2.1).
- Urinalysis: color and appearance, pH and specific gravity, bilirubin, glucose, ketones, leukocytes*, nitrite, protein, urobilinogen. *Leukocytes will only be resulted in the event that the macroscopic analysis flags positive (abnormal) for the following results and will reflex to a technologist microscopic review: protein, blood, leukocyte esterase, nitrite. (Timepoints for sample collection are described in Section 12.8.2.1).
- Pregnancy: serum β-hCG. (Timepoints for sample collection are described in Section 12.8.2.2).
- Immunogenicity: exebacase-specific ADA and IgE. (Timepoints for sample collection are described in Section 12.8.2.3).
- Pharmacokinetics: blood levels of exebacase. (Timepoints for sample collection are described in Section 12.8.2.4).
- Microbiology: identification and susceptibility of *S. aureus* isolates from blood cultures and other cultures. Further evaluation to identify the potential mechanism of resistance may be performed. (Timepoints for sample collection are described in Sections 12.8.2.5 and 12.8.2.6).

## 12.9. 12-Lead Electrocardiogram

A 12-lead ECG will be performed during screening (or after randomization and before dosing) and on Day 14. Additional 12-lead ECGs will be performed as clinically indicated. Heart rate, PR interval, QRS, QT, QTcB, and QTCF values, if available, will be recorded in the eCRF. Any clinically relevant abnormality on the screening ECG will be recorded as medical history; any clinically relevant abnormality on the Day 14 ECG will be recorded as an AE.

## 12.10. Physical Examination and Weight/Height

Complete physical examinations and review of body systems will be performed during screening and at the Day 7, 14, 30, and 60 visits. Additional physical examinations will be performed as clinically indicated. The complete physical examinations will include evaluation of general, head, eye, ear, nose, and throat (HEENT), cardiovascular, skin for any evidence of emboli, musculoskeletal, respiratory, gastrointestinal, neurological systems, and signs of pain. The physical examinations will include a close evaluation for any new or worsening signs or symptoms (e.g., pain, shortness of breath) of suspected new metastatic foci of infection or suspected septic emboli. Diagnostic testing (e.g., imaging, aspiration, and/or cultures) will be performed as clinically indicated to confirm suspected new metastatic foci or septic emboli. The physical examination will also include an evaluation of the primary source of *S. aureus* BSI/IE. Weight and height will be measured during screening. If it is not possible to measure weight and height during screening, a recently available historical weight and height will be used. Physical examination findings and weight/height will be recorded on the relevant eCRFs.

Every effort should be made to perform study visits "in person" by the Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol). If it is not feasible to evaluate the patient "in person" at study visits, telephone/telehealth visits may be performed under the circumstances described in Section 11.5.1. A physical examination/vital signs are not required for visits performed remotely by telephone/telehealth; however, a complete medical review of body systems will be performed during the telephone/telehealth visit and medical records* may be used to supplement these telephone/telehealth visits (e.g., sign and symptom evaluation and physical exam findings) to assess the patient's clinical status, primary source of infection, and the status of any pre-existing or presence of new metastatic foci. The findings will be entered into the relevant eCRFs.

In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records* alone may be used for physical examination assessments after contacting the Medical Monitor or designee.

* When medical records are used alone or to supplement information collected during the telephone/telehealth visit, the physical examination assessments extracted from the medical record will be recorded in the site's source documents and entered in the relevant eCRFs. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) is expected to review, sign, and date the physical examination assessments extracted from the medical record and recorded in the site's source documents. The eCRFs will be verified by the site monitor using these source documents.

## 12.11. Vital Signs

Vital signs (blood pressure, respiratory rate, heart rate, and temperature) will be performed during screening, approximately 30 to 40 minutes after the start of infusion and as clinically indicated during the infusion, and at the Day 7, 14, 30, and 60 visits for visits performed "in person" or may be obtained via the study-specific mobile health service (Section 11.5.1). If it is not possible to perform vital signs "in person" or via the study-specific mobile health service, medical records may be used. The vital sign assessments extracted from the medical record will be recorded in the site's source documents and entered in the relevant eCRFs, and will be used to support the assessment of signs/symptoms as described in Section 12.13.

At screening, if more than one measurement is taken within the approximately 24 hours before randomization, the most abnormal value is recorded in the eCRF. At Days 7, 14, 30, and 60, if more than one measurement is taken on a given day, the most abnormal value will be recorded in the eCRF.

## 12.12. Metastatic Foci and Septic Emboli

Patients will be evaluated for existing and new metastatic foci (e.g., deep tissue abscess, septic arthritis, etc.) and septic emboli (e.g., to the brain, lung, etc.) during screening. Presence of new or worsening of existing metastatic foci/septic emboli will be evaluated at the Day 7, 14, 30, and 60 visits. Diagnostic testing will be performed as clinically indicated to assess metastatic foci or septic emboli (e.g., imaging, aspiration, and/or cultures). For non-blood sites of *S. aureus* infection, the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will determine whether this is the source of *S. aureus* BSI/IE (Section 12.7) or a metastatic focus (Section 12.12).

Every effort should be made to perform study visits "in person", by the Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol), and preferably by the same person at all visits. If it is not feasible to evaluate the patient "in person" at study visits, telephone/telehealth visits may be performed under the circumstances described in Section 11.5.1. Metastatic foci/septic emboli should be evaluated during the telephone/telehealth visits by detailed questioning and a complete medical review of systems. Medical records* may be used to supplement the telephone/telehealth evaluation for metastatic foci/septic emboli.

In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records* alone may be used for metastatic foci/septic emboli assessments after contacting the Medical Monitor or designee.

* When medical records are used alone or to supplement information collected during the telephone/telehealth visit, the metastatic foci/septic emboli assessments extracted from the medical record will be recorded in the site's source documents and entered in the relevant eCRFs. The Investigator/Sub-Investigator (or other delegated medically qualified person

listed on the FDA Form 1572 and trained on the protocol) is expected to review, sign, and date the metastatic foci/septic emboli assessments extracted from the medical record and recorded in the site's source documents. The eCRFs will be verified by the site monitor using these source documents.

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) and the AC will consider the development of new metastatic foci or septic emboli, and timing for metastatic foci (i.e., before/on Day 7 or after Day 7), when evaluating clinical outcome (Section 12.18). Metastatic foci identified through Day 7 are considered part of the patient's baseline *S. aureus* BSI/IE; new metastatic foci identified after Day 7 or new septic emboli after study drug dosing are considered complications of *S. aureus* BSI/IE for the purpose of assessing clinical outcome. New septic emboli are defined as an acute presentation of septic emboli after dosing and are a reason for failure for clinical outcome; septic emboli that are incidentally found on imaging are considered part of the patient's baseline *S. aureus* BSI/IE if found before Day 7.

## 12.13. Signs and Symptoms of Infection

Signs and symptoms will be evaluated during screening and at the Day 7, 14, 30, and 60 visits. Additionally, if SoCA is changed after study drug dosing due to lack of clinical response, signs and symptoms will be assessed on the day of the SoCA change and entered into the eCRF. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the 1572 and trained on the protocol) will assess whether each sign or symptom is attributable to *S. aureus* BSI/IE or provide an alternative attribution and will assess the symptom severity per the definitions in Table 9.

Per inclusion criterion 3, each patient is required to have at least 2 signs or symptoms attributable to *S. aureus* BSI/IE at screening (within approximately 24 hours before randomization) in order to be enrolled in the study. If more than one measurement is taken within the approximately 24 hours before randomization, the most abnormal value is used for inclusion. The signs and symptoms that will be assessed at each visit are described in the inclusion criteria (Section 10.1) and include:

- Shortness of breath
- Sweating
- Chills and/or rigors
- Fatigue
- Confusion
- Pain associated with metastatic foci
- Fever (oral temperature equivalent ≥38.0°C [≥100.4°F]) or hypothermia (oral temperature equivalent <35°C [<95°F])

- Leukocytosis (white blood cell [WBC] count >10,000/µL) [CTCAE 2017], leukopenia (WBC <4000/µL), or bandemia (>10% immature neutrophils [bands] regardless of total peripheral WBC)
- Tachycardia (heart rate >100 bpm)
- Tachypnea (respiratory rate >20 breaths/min)
- Hypotension (systolic blood pressure <90 mmHg)

Leukocytosis, leukopenia, or bandemia are assessed when blood tests are performed as part of standard medical practice.

Select symptoms (shortness of breath, fatigue, confusion) will also be evaluated at pre-BSI/IE. Pre-BSI/IE is the patient's "usual state of health" before the BSI/IE started. Pre-BSI/IE is established by asking the patient or legally acceptable representative about these symptoms and severity (using Table 9) prior to onset of the BSI/IE. The medical record may also be used.

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the 1572 and trained on the protocol) will assess the severity of specific symptoms attributable to *S. aureus* as absent, mild, moderate, or severe, as defined in Table 9. The definition of "absent" for shortness of breath, fatigue, and confusion takes into account the pre-BSI (i.e., absent is defined as return to pre-BSI or absence). Symptoms of sweating and chills/rigors and signs attributable to *S. aureus* will be assessed as present or absent. Some symptoms may be considered 'medically not evaluable' due to certain medical circumstances or treatments, such as a patient in a medically induced coma or after surgery to remove a metastatic focus.

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) and the AC will assess the resolution of or persistence, worsening, or recurrence of signs and symptoms attributable to *S. aureus* BSI/IE which were present at screening, or any new signs or symptoms attributable to *S. aureus* BSI/IE, when evaluating clinical outcome, according to the clinical outcome definitions in Table 10 in Section 12.18. All signs and symptoms attributable to *S. aureus* that were present at screening must be absent or improve by 2 grades (i.e., from severe to mild) in order to be considered as resolved. Symptoms attributable to *S. aureus* that were present at screening and only improve by 1 grade (i.e., from severe to moderate or from moderate to mild) are considered persistent.

**Table 9: Severity Definitions for Symptoms Attributable to *S. aureus***

| Symptom | Absent | Mild | Moderate | Severe |
|---|---|---|---|---|
| Shortness of breath (SOB)[1] | Resolution (to pre-BSI/IE) or absence of SOB | SOB with moderate exertion (e.g., climbing stairs) | SOB with minimal exertion (e.g., normal/ routine activities (e.g., walking on flat surface, performing usual daily activities [i.e., instrumental ADL]) | SOB at rest and/or requiring oxygen (or increase in oxygen requirement in patients who required oxygen pre-BSI/IE); limits ability to perform self-care ADL |
| Fatigue[1] | Resolution (to pre-BSI/IE) or absence of fatigue | Transient, relieved by rest; does not interfere with usual activities | Frequent, interferes with usual daily activities (i.e., instrumental ADL) | Fatigue not relieved by rest; limits ability to perform self-care ADL |
| Confusion[1,2] | Resolution (to pre-BSI/IE) or absence of confusion (e.g., disorientation) | Transient confusion (e.g., mild disorientation that does not interfere with usual activities). | Moderate disorientation; interferes with ability to do usual activities (i.e., instrumental ADL) | Severe, continuous confusion state (e.g., delirium) disorientation limiting ability to perform self-care ADL |
| Pain assoc. with metastatic foci | Absence of pain from metastatic foci | Transient mild pain; does not interfere with usual activities or sleep | Frequent pain; interferes with usual activities or sleep | Constant pain interferes with usual activities or sleep and/or ability to perform self-care ADL |

Reference: Adapted from NIH Common Terminology Criteria for Adverse Events (CTCAE)
Abbreviation: ADL=activities of daily living; assoc.=associated; BSI=blood-stream infection; IE=infective endocarditis; SOB=shortness of breath
Note: Some symptoms may be considered 'medically not evaluable' due to certain medical circumstances or treatments, such as a patient in a medically induced coma or after surgery to remove a metastatic focus.

1. A pre-BSI/IE assessment will be done for shortness of breath, fatigue, and confusion. Pre-BSI/IE is the patient's "usual state of health" before the BSI/IE started.
2. Confusion is defined as a disorder characterized by a lack of clear and orderly thought and behavior. Confusion may include disorientation, illusions, movement changes, inattentiveness, agitation, and/or hallucinations.

Every effort should be made to perform study visits "in person" by the Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the 1572 and trained on the protocol), and preferably by the same person at all visits. If it is not feasible to evaluate the patient "in person" at study visits, telephone/telehealth visits may be performed under the circumstances described in Section 11.5.1. Signs and symptoms should be evaluated during the telephone/telehealth visits by detailed questioning and a complete medical review of systems. Medical records* may be used to supplement the telephone/telehealth evaluation for signs and symptoms.

In rare instances in which it is not feasible to conduct study visits "in person" or by telephone/telehealth, medical records* alone may be used for signs/symptoms assessments after contacting the Medical Monitor or designee.

* When medical records are used alone or to supplement information collected during the telephone/telehealth visit, the signs/symptoms assessments extracted from the medical record will be recorded in the site's source documents and entered in the relevant eCRFs. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) is expected to review, sign, and date the signs/symptoms assessments extracted from the medical record and recorded in the site's source documents. The eCRFs will be verified by the site monitor using these source documents.

  It is understood that symptoms that are not present may not be specifically documented as "absent" in the medical record. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will use their medical judgement in evaluating physical examination, signs/symptoms, and metastatic foci/septic emboli data extracted from the medical record to determine whether symptoms not specifically mentioned in the medical record can be considered to be absent with a reasonable degree of medical certainty. If so, such symptoms should be recorded in the source document as "absent". If this is not the case, and the Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) cannot make the determination that a symptom not specifically mentioned in the medical record is absent (e.g., due to insufficient information in the medical record), the symptom should then be recorded as "not assessed".

  For example, if the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) reviews the progress notes, nursing notes, consult notes, and other parts of the medical record, and there is no specific mention of a symptom, for example sweating, and there is no reasonable medical reason to expect that the patient had sweating attributable to the *S. aureus* BSI (e.g., blood cultures are negative and patient's condition is clinically improved), the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) may assess the symptom as "absent" based on their medical review of the medical record. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will make a notation of their medical assessment in the source document.

## 12.14. Echocardiography

Echocardiograms will be performed as follows:

- All adult patients (≥18 years of age) will have a TTE or TEE within 3 days before or after randomization. All efforts will be made to perform the TTE or TEE before randomization.
  - Where possible, a TEE will be performed [Baddour 2015, Habib 2010, Habib 2015] and is recommended in patients with BMI >30 kg/m$^2$; the TEE may be performed within 3 days before or after randomization unless the TEE is performed due to clinical suspicion of L-IE (see below).
  - In patients that have clinical findings suggestive of L-IE (new murmur, worsening cardiac function, and/or peripheral or central nervous embolic phenomenon), a TEE will be performed before randomization to rule out mitral and/or aortic valve vegetation(s) or the patient will be excluded from the study per exclusion criterion #2 (Section 10.2). In cases where there is an alternative cause of new heart failure or cerebral emboli, a patient with a negative TTE for L-IE may be discussed with the Medical Monitor for potential enrollment.
  - In patients with persistent bacteremia for ≥3 days (i.e., blood cultures positive for *S. aureus* for ≥3 days), an echocardiogram will be performed before randomization to rule out L-IE. A TTE may be performed with permission of the Medical Monitor. If this echocardiogram is not performed or L-IE is not ruled out by this echocardiogram, the patient should not be randomized.
- In adolescents (12 to <18 years of age), echocardiograms (TTE or TEE) will be performed as clinically indicated taking into consideration risk factors for endocarditis (e.g., structurally abnormal heart [including pacemakers]), clinical features suggestive of endocarditis (e.g., new murmur), or persistent bacteremia [McMullan 2020].
- If the patient had an echocardiogram performed prior to the study that was intended to evaluate the current infection, it will be sent to the central echocardiography laboratory as directed by the Sponsor and an additional TTE or TEE is not required unless as indicated above, but should be discussed with the Medical Monitor if obtained ≥3 days prior to randomization.
- Follow-up echocardiograms will be performed as clinically indicated.

The results of all echocardiograms from the initial echocardiogram performed to evaluate the current infection through the Day 60 visit will be entered in the eCRF. The images from all echocardiograms from the initial echocardiogram performed to evaluate the current infection through the Day 60 visit will be provided to the central echocardiography laboratory as directed by the Sponsor. In addition, the results of any prior echocardiograms that are part of the patient's medical history (i.e., from the 1 year prior to screening) will be recorded in the eCRF.

## 12.15. Management of IV Catheters

If not already done prior to the study, intravenous catheters known or suspected to be infected must be removed, and as clinically needed replaced, preferably at a different site, as soon as possible within approximately 72 hours after randomization. Other hemodialysis access types (i.e., AV fistulas or AV grafts) that are known or suspected to be infected will be evaluated for removal/replacement, if clinically feasible. If removal/debridement is not feasible based on standard medical practice, the patient should be discussed with the Medical Monitor for potential enrollment. As described in Section 12.8.2.6, cultures from catheter tips will be performed to determine the source of *S. aureus* BSI/IE and as clinically indicated.

## 12.16. Ultrasounds of Central Venous Catheter Site

In patients with CVCs, ultrasounds to evaluate clots in the vein should be performed within approximately 48 hours after randomization, unless the clot in the vein has been detected within this timeframe via other method (e.g., imaging such as CT scan or MRI or direct visualization during surgery).

## 12.17. Vital Status

Vital status (whether the patient is alive or dead, or last known date alive if vital status is unknown) will be obtained at Days 14, 30, and 60 for all patients, including patients that discontinue the study or withdraw consent/assent (as described in the informed consent/assent form). All efforts must be made to obtain vital status on all patients through Day 60. Vital status data are important for both the safety analysis (to have an accurate accounting of patients who died) and the efficacy analysis ("death due to any cause" is a reason for failure for clinical outcome). The patient's vital status will be determined using available sources (e.g., the patient, patient's contacts, hospital and other medical records, and public records, such as social media, obituaries, social security death index), as described in the informed consent/assent form and FDA guidance described below.

The FDA issued a guidance entitled "Data retention when subjects withdraw from FDA-regulated clinical trials" [FDA 2008], in which FDA provided the following policy:

"Following are key points regarding FDA's policy on the withdrawal of subjects from a clinical investigation, whether the subject elects to discontinue further interventions or the clinical Investigator terminates the subject's participation in further interventions:

- According to FDA regulations, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
- An Investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated

clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

- If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the Investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100).
- If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the Investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an Investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status."

## 12.18. Clinical Outcome

Clinical outcome will be assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) and the AC at Days 14, 30, and 60 according to the definitions in Table 10. The signs and symptoms attributable to *S. aureus* BSI/IE that are evaluated for clinical outcome assessments are described in Section 12.12.

**Table 10: Clinical Outcome Definitions at Days 14, 30, and 60**

| Clinical Outcome | Definition |
|---|---|
| Responder | All of the following criteria are met:<br>• Resolution of signs and symptoms attributable to *S. aureus* BSI/IE which were present at screening[1],<br>• No new signs or symptoms attributable to *S. aureus* BSI/IE,<br>• No complications of *S. aureus* BSI/IE, including:<br>▪ No development of a new metastatic focus of *S. aureus* infection (e.g., deep tissue abscess, septic arthritis) after Day 7[2],<br>▪ No development of new septic emboli (e.g., to the brain, lung, etc.) after study drug dosing[3],<br>• No change in the SoCA after study drug dosing due to persistence, worsening, or recurrence or new signs/symptoms of *S. aureus* BSI/IE[4],<br>• Blood culture(s) negative for *S. aureus* by Day14[5], **and**<br>• The patient is alive. |
| Failure | At least 1 of the following criteria is met:<br>• Persistence, worsening, or recurrence of signs or symptoms attributable to *S. aureus* BSI/IE which were present at screening,[1]<br>• New signs or symptoms attributable to *S. aureus* BSI/IE,<br>• Complications of *S. aureus* BSI/IE, including:<br>▪ Development of a new metastatic focus of *S. aureus* infection (e.g., deep tissue abscess, septic arthritis) after Day 7[2],<br>▪ Development of new septic emboli (e.g., to the brain, lung, etc.) after study drug dosing[3],<br>• SoCA was changed after study drug dosing due to persistence, worsening, or recurrence or new signs/symptoms of *S. aureus* BSI/IE[4],<br>• Failure to clear blood cultures by Day14[5], **or**<br>• Death due to any cause. |
| Indeterminate | The patient is not available for the evaluation of clinical outcome for any reason including:<br>• Lost to follow-up<br>• Withdrawal of consent/assent<br>• Other reason for not performing assessment |

Note: Visit windows are as follows: Day 14 (±1 day), Day 30 (±4 days), Day 60 (±7 days).

1. Specific symptoms attributable to *S. aureus* will be assessed as absent, mild, moderate, and severe according to the definitions in Table 9. Sweating and chills/rigors and signs attributable to *S. aureus* will be assessed as present or absent. All signs and symptoms attributable to *S. aureus* that were present at screening must be absent or improve by 2 grades (i.e., from severe to mild) in order to be considered as resolved. Symptoms attributable to *S. aureus* that were present at screening and only improve by 1 grade (i.e., from severe to moderate or from moderate to mild) are considered persistence.
2. Metastatic foci identified through Day 7 are considered part of the patient's baseline *S. aureus* BSI/IE; new metastatic foci identified after Day 7 are considered complications of *S. aureus* BSI/IE for the purpose of assessing clinical outcome.
3. New septic emboli are defined as an acute presentation of septic emboli after dosing and are a reason for failure for clinical outcome; septic emboli that are incidentally found on imaging are considered part of the patient's baseline *S. aureus* BSI/IE if found before Day 7.
4. Patients may be treated empirically and SoCA may be changed after susceptibility data become available. A change in SoCA based on susceptibility data from the blood culture collected within approximately 72 hours before randomization does not count as "failure".
5. Failure to attain negative blood cultures on or before Day 14. Only applies to Day 14 assessment.

## 12.19. Microbiological Outcome

Microbiological outcome will be determined programmatically at Days 4 and 7 according to the definitions in Table 11.

**Table 11: Microbiological Outcome Definitions at Days 4 and 7**

| Microbiological Outcome | Definitions |
|---|---|
| Clearance of bacteremia[1] | Two consecutive blood cultures collected on 2 different days on or prior to assessment were negative for *S. aureus*. |
| Ongoing bacteremia[1] | Blood culture on the day of assessment or the most recent blood culture prior to the day of assessment was positive for *S. aureus*. |
| If the patient does not meet the criteria for clearance or ongoing bacteremia, including because follow-up blood cultures were not done, microbiological outcome is presumed from clinical outcome as follows: | |
| Presumed clearance of bacteremia[1] | The patient is a responder at Day 14 (per the adjudicated clinical outcome, as defined in Table 10). |
| Presumed ongoing bacteremia[1] | The patient is a failure at Day 14 (per the adjudicated clinical outcome, as defined in Table 10). |
| Indeterminate | The patient is indeterminate for clinical outcome at Day 14 (per the adjudicated clinical outcome, as defined in Table 10). |

1. For the analysis, clearance of bacteremia will include both clearance and presumed clearance of bacteremia, and ongoing bacteremia will include both ongoing and presumed ongoing bacteremia.

## 12.20. Health Resource Utilization

Health resource utilization information will be collected through Day 60.

The hospital admission and discharge dates for the initial hospitalization, and whether the admission was for *S. aureus* BSI/IE, will be entered on the eCRF. For patients who die while in the hospital, the date of death should be entered as the hospital discharge date. The admission and discharge dates will be used for determining the hospital length-of-stay and in-hospital mortality. Additionally, information on intensive care unit (ICU) admission(s) and discharge(s) during the initial hospital admission will be entered in the eCRF for determining the ICU length-of-stay.

The location to which the patient is discharged (e.g., home, nursing home and skilled nursing facility/long-term acute care, rehabilitation, palliative care/hospice) and whether the patient is receiving SoCA in an outpatient facility or via home health care will also be collected in the eCRF.

The eCRF will collect hospital readmissions for any cause and for *S. aureus* BSI/IE or complication of *S. aureus* BSI/IE (e.g., metastatic foci, septic emboli) through Day 60.

## 12.21. Discharge Summaries

Redacted discharge summaries from the initial hospitalization when the patient started in the study will be collected; if discharge summaries are not able to be provided, a patient narrative will be provided by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) (this narrative will be collected in the Investigator's Narrative eCRF).

Discharge summaries and autopsy reports will be collected for SAEs, when feasible/applicable. An Investigator's narrative of the SAE will be entered into the SAE eCRF.

## 12.22. DSMB

An independent DSMB will review accruing safety and tolerability data in an unblinded manner throughout the study. All fatal SAEs and SUSARs will be provided to the DSMB on an ongoing basis allowing the DSMB to monitor fatal and unexpected serious events in a timely manner. The DSMB will also review results from a futility analysis of the primary efficacy parameter in the MRSA population in the mITT analysis set when approximately 60% of patients have primary (Day 14) adjudicated clinical outcome data available. Details of the roles and responsibilities of the DSMB, timing of data reviews, and the futility stopping threshold will be documented in the DSMB charter. The Sponsor and study staff will remain blinded throughout the study. The DSMB will monitor the overall safety of patients in order to minimize unacceptable risk to patients. As a result, the DSMB may recommend changes to study conduct on the basis of emerging safety information to protect the safety and welfare of clinical study patients. Enrollment will continue during the DSMB reviews.

## 12.23. Adjudication Committee

An independent, blinded clinical endpoint AC will adjudicate study eligibility, diagnosis, primary source of BSI/IE, adequacy of source control, and clinical outcomes at Days 14, 30, and 60. The adjudicated diagnosis and primary source of BSI/IE will be considered the final diagnosis and the primary source of BSI/IE to be used for the analysis. The efficacy analysis of clinical outcome will be based on the AC's assessment. The role of the AC and procedures for adjudication will be described in the AC charter.

# 13. TREATMENT OF PATIENTS

## 13.1. Description of Study Drugs

The study drugs, exebacase and placebo, are described in Table 12. Exebacase and placebo will be provided as frozen, sterile, injectable solution for dilution. The placebo formulation is equivalent to the drug product formulation minus the active pharmaceutical ingredient (exebacase). Placebo is similar in appearance to exebacase. Study drug will be labeled in accordance with regulatory requirements. Additional information is provided in the Pharmacy Manual.

**Table 12: Description of Study Drugs (Exebacase and Placebo)**

| Study Drug | Exebacase | Placebo |
|---|---|---|
| **Dosage form** | Sterile injectable solution for dilution | Sterile injectable solution for dilution |
| **Route of administration** | Intravenous infusion over approximately 2 hours | Intravenous infusion over approximately 2 hours |
| **Physical description** | Frozen solution | Frozen solution |
| **Manufacturer** | Emergent BioSolutions, Pantheon (Thermo Fisher Scientific) | Emergent BioSolutions, Pantheon (Thermo Fisher Scientific) |
| **Ingredients (function)** | Exebacase (Active Ingredient)<br>Water for injection (Solvent)<br>L-Histidine (Buffer)<br>D-Sorbitol (Stabilizer) | Water for injection (Solvent)<br>L-Histidine (Buffer)<br>D-Sorbitol (Stabilizer) |

## 13.2. Dosage and Dose Regimen

Patients will receive a single infusion of exebacase or placebo as soon as possible after randomization. Study drug will be diluted and administered as approximately a 2-hour IV infusion, as specified in the Pharmacy Manual.

The dosing scheme is as follows:

- Patients with normal renal function or mild renal impairment (CrCl* ≥60 mL/min) will be administered a dose of **18 mg** of exebacase.
- Patients with moderate or severe renal impairment (CrCl* of 15 to <60 mL/min) will be administered a dose of **12 mg** of exebacase.
- Patients with ESRD (CrCl* <15 mL/min), including those on hemodialysis, will be administered a dose of **8 mg** of exebacase. In patients receiving hemodialysis, study drug will be administered either ≥8 hours before the start of hemodialysis or ≥4 hours after the end of hemodialysis.

*Note: CrCl will be calculated by Cockcroft-Gault formula (provided in Section 12.8.1.1) using ideal body weight in patients with BMI ≥30 kg/m$^2$ and serum creatinine result obtained locally as close to the start of study drug dosing as possible (but not more than approximately 24 hours before the start of study drug dosing; see Section 12.8.1).

## 13.3. Study Drug Preparation and Administration

Detailed instructions for study drug preparation and administration are provided in the Pharmacy Manual.

## 13.4. Storage/Stability

The exebacase formulation must be stored at -20 (±5)°C in a controlled temperature monitored and locked area. The exebacase formulation will be monitored for stability at International Conference on Harmonisation (ICH) storage conditions.

## 13.5. Drug Accountability

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign drug accountability duties to an appropriate qualified pharmacist or designee. Inventory and accountability records must be maintained and must be readily available for inspection by ContraFect or designee and open to inspection at any time by applicable regulatory authorities.

The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug as described in the Pharmacy Manual. The Investigator or designee must maintain drug accountability records that document:

- Investigational product delivery to the study site
- The inventory at the site
- Use by each patient, including vial dispensed

These records will include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study patients.

The investigational product must be used only in accordance with the protocol. The Investigator or designee will also maintain records adequately documenting that the patients were provided the study drug specified.

After the completion of the study and final monitoring of drug accountability by ContraFect or designee, the Investigator or designee will oversee shipment of any remaining study drug back to the drug supply vendor or designee or destruction according to institutional standard operating procedures with pre-approval by ContraFect or designee. If drug is destroyed locally, a certificate of destruction will be provided to ContraFect or designee and maintained in the study files.

## 13.6. Prior and Concomitant Medications

Medications taken within 28 days before randomization through the Day 60 visit will be recorded in the eCRF as described in the CRF Completion Guidelines (CCGs).

## 13.7. Prohibited Medications

Patients on the following medications are excluded as described in the exclusion criteria (Section 10.2):

- Patients who received treatment or are planned to receive treatment within the 14 days following randomization with dalbavancin or oritavancin are excluded from the study. Note: Patients who are receiving teicoplanin, linezolid, telavancin, beta-lactam/beta-lactam inhibitors (e.g., piperacillin-tazobactam), carbapenems, fourth- or fifth-generation cephalosporins (e.g., cefepime, ceftaroline fosamil), and/or sulfamethoxazole/trimethoprim are eligible for the study provided that treatment is switched to a protocol-specified appropriate SoCA (appropriate SoCA includes daptomycin and vancomycin for MRSA and semi synthetic penicillins [e.g., nafcillin, oxacillin, cloxacillin, flucloxacillin] and first generation cephalosporins [e.g., cefazolin] for MSSA. Daptomycin or vancomycin may be used for patients with MSSA with a known history of beta-lactam allergy or other reason that beta-lactam cannot be used.
- Patients with persistent *S. aureus* bacteremia for which treatment with ceftaroline fosamil or other non-protocol-recommended antibiotic (e.g., rifampin, gentamicin, other beta lactam) was instituted prior to randomization due to lack of response or intolerance (i.e., added to or switched from a protocol-recommended SoCA) may remain on the non-protocol recommended antibiotic after randomization, if approved by the Medical Monitor
- Vancomycin or daptomycin used in combination with beta-lactams has not been shown to offer benefit and may increase the risk of kidney injury [Tong 2020]; therefore, this combination should not routinely be used in this study as first-line therapy.
- Patients who previously received exebacase are excluded.
- Patients who participated or plan to participate in another interventional investigational drug, device, or diagnostic trial involving administration of an investigational agent within 30 days prior to or during the study are excluded from the study. Note: Patients who have received agents under FDA Emergency Use Authorization (EUA) for COVID-19 prevention (e.g., vaccines or Evusheld or similar agents) or for COVID-19 treatment under FDA EAU are not excluded.

Treatment with oral step-down antibiotics for the *S. aureus* BSI/IE is not permitted, except in adolescents.

The manufacturer's prescribing information for SoCA will be consulted for information regarding any concomitant medication restrictions.

## 13.8. Treatment Compliance

Study drug will be administered to hospitalized patients by study site personnel.

## 13.9. Randomization and Blinding

*Randomization:*

Patients will be assigned to receive exebacase or placebo in a 2:1 ratio via the IRT system.

The randomization will be stratified by poorly controlled *diabetes* (yes or no) as defined below and susceptibility of the *S. aureus* isolate (MRSA, MSSA, or unknown). For stratification, poorly controlled diabetes is defined as a HgA1C ≥8% within approximately 90 days before randomization. A HgA1C test is not required for patients with no medical history of diabetes and no suspicion of diabetes during the screening period. These patients will be stratified to "no" for poorly controlled diabetes. A HgA1C test should be performed in patients with medical history of diabetes or suspicion of diabetes during screening for whom a HgA1C test result within the approximately 90 days prior to randomization is not available. If a HgA1C is unavailable and testing cannot be performed for these patients prior to randomization, contact the Medical Monitor to determine how the patient should be stratified based on available clinical information. All efforts will be made to obtain susceptibility results from blood cultures before randomization to enable stratification by MRSA or MSSA. If a blood culture was performed for the current *S. aureus* infection prior to the qualifying blood culture, susceptibility results from the prior blood culture may be used. If the patient has a concomitant *S. aureus* infection at another body site from which susceptibility results are available (e.g., skin, abscess), the susceptibility results from this other culture may be used. If the patient is known to be colonized with MRSA, MRSA may be selected for the stratification factor (Section 12.8.2.5).

Patients randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum from the computer-generated randomization schedule. A patient is considered randomized when the IRT randomization transaction is recorded regardless of whether the patient actually receives study drug.

*Blinding:*

This is a double-blind study. The Investigator, study site personnel, and patients will be blinded to treatment group and will not make any effort to determine which study drug treatment is being received (except in the case of emergency unblinding by the Investigator/Sub-Investigator or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol). A pharmacist or study staff member not associated with the operational conduct of the study will prepare the study medication for infusion, as described in the Pharmacy Manual.

An independent DSMB will review data in an unblinded manner, as described in Section 12.22 and the DSMB charter. An independent unblinded statistician will provide unblinded data to the DSMB for the interim analyses of safety and futility as detailed in the DSMB Charter. The Sponsor, study staff, and AC will be blinded to treatment group. The blinded PK staff responsible for study drug concentration assessment will not be involved in any other study procedures or assessments.

*Emergency Unblinding:*

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) may unblind a patient's treatment assignment only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific patient. Prior to any unblinding, the Investigator/ Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the patient's study treatment assignment (unless important to the safety of patients in the study), the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) must notify the Sponsor if the blind is broken for any reason and the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) was unable to contact the Sponsor prior to unblinding. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will record in source documentation the date and reason for revealing the blinded treatment assignment for that patient. The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will be responsible for reporting the emergency unblinding to the local IRB/IEC in accordance with its regulations and guidelines.

Unblinding in the setting of a SUSAR is detailed in a separate Safety Management Plan and Unblinding Plan.

# 14. ADVERSE AND SERIOUS ADVERSE EVENTS

## 14.1. Timeframe for Collecting Adverse Events

All AEs and SAE will be collected from the time of consent/assent through the Day 60 visit.

## 14.2. Reporting of Serious Adverse Events

All SAEs will be reported within 24 hours of the site becoming aware of the SAE. SAEs will be reported through the electronic data capture (EDC) system or on the backup paper SAE report form. The SAE report will provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE:

- SAE description,
- Patient identification,
- Reporter/site,
- Investigator causality assessment.

Additional procedural and contact details on SAE reporting will be provided separately to the Investigator.

Follow-up of SAEs is described in Section 14.12.

## 14.3. Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of AEs are as follows:

- Changes in the general condition of the patient*
- Subjective symptoms offered by or elicited from the patient*
- Objective signs observed by the Investigator or other study personnel*
- All diseases that occur after the start of the study including a change in severity or frequency of preexisting disease*

* Note: Manifestations of the disease under study or clinical outcome of failure for the disease under study should not be reported as AEs except if the event results in re-admission to the hospital and/or death (see Section 14.5 for additional details).

Hospitalization refers to an overnight admission into the hospital for the purpose of investigating and/or treating an acute illness or other AE. Hospitalizations not intended to treat an acute illness or AE, such as hospitalizations for social reasons, should not be reported as SAEs.

Planned hospital admissions and/or surgical operations for an elective procedure or an illness or disease that existed at screening and did not aggravate during the study should not be reported as SAEs. These elective procedures should be recorded in the Surgery and Other Procedures eCRF and these pre-existing illnesses or diseases should be recorded in the Medical History eCRF.

All clinically relevant new abnormalities in laboratory values or clinically relevant physical findings that occur during the study. Note: Laboratory values that are abnormal but not of clinical significance are not to be reported as AEs.

## 14.4. Definition of Serious Adverse Event

A SAE is an AE that fulfills one or more of the following:

- Results in death
- Is immediately life-threatening (i.e., an event in which the patient was at risk of death at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Note: Manifestations of the disease under study or clinical outcome of failure for the disease under study should not be reported as SAEs except if the event results in re-admission to the hospital and/or death (see Section 14.5 for additional details).

Hospitalization refers to an overnight admission into the hospital for the purpose of investigating and/or treating an acute illness or other AE. Hospitalizations not intended to treat an acute illness or AE, such as hospitalizations for social reasons, should not be reported as SAEs.

Planned hospital admissions and/or surgical operations for an elective procedure or an illness or disease that existed at screening and did not aggravate during the study should not be reported as SAEs. These elective procedures should be recorded in the Surgery and Other Procedures eCRF and these pre-existing illnesses or diseases should be recorded in the Medical History eCRF.

## 14.5. Study Endpoints

Study endpoints refer to outcomes that the Sponsor is measuring to evaluate clinical efficacy. Clinical outcome of the disease under study is collected as an efficacy endpoint, and a clinical outcome of "failure" or individual components of the clinical failure definition (as defined in Table 10 in Section 12.18) or other manifestations of the disease under study that do not meet the clinical failure definition (e.g., metastatic foci of *S. aureus* through Day 7) will not be reported as AEs or SAEs, except if the event:

- Results in re-admission to the hospital, and/or
- Results in death

For example:

- Recurrence of *S. aureus* BSI or IE will be reported as an SAE only if it results in re-admission to the hospital and/or results in death.
- Development of a new metastatic focus of *S. aureus* BSI/IE will be reported as an SAE only if it results in re-admission to the hospital and/or results in death.

Information on the individual components of clinical failure definition and other manifestations of the disease under study are collected on other eCRFs (e.g., eCRFs to collect signs/symptoms of BSI/IE, metastatic foci/septic emboli, cultures, clinical outcome, etc.).

## 14.6. Pre-Existing Conditions

Planned hospital admissions and/or surgical operations for an elective procedure or an illness or disease that existed at screening and did not aggravate during the study should not be reported as SAEs. These elective procedures should be recorded in the Surgery and Other Procedure eCRF and these pre-existing illnesses or diseases should be recorded in the Medical History eCRF.

## 14.7. Relationship to Study Drug

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) must make the determination of relationship to the investigational product for each AE (unrelated or unrelated) and record the assessment on the SAE eCRF or paper backup SAE form.

Related: Based on the Investigator's/Sub-Investigator's (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) medical judgment, there is a reasonable medical possibility that the event may have been caused by the investigational product. There is evidence to suggest a causal relationship between the investigational product and the AE.

Unrelated: Based on the Investigator's/Sub-Investigator's (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) medical judgment, there is no medically plausible reason that suggests a relationship between the event and the investigational product.

## 14.8. Grading of Adverse Events

The severity (or intensity) of each AE will be assessed by the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) according to the following scale:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Interferes with normal activities and may require minimal intervention
- Severe: Incapacitating, with inability to work or perform normal activities and/or requires significant medical intervention

***Clarification of the Difference in Meaning Between "Severe" and "Serious"***

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning (as defined in Section 14.4 above). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

## 14.9. Adverse Events of Clinical Interest

An AECI is an AE (serious or non-serious) of scientific and medical interest specific to the sponsor's product or program. Ongoing monitoring and rapid communication to the sponsor is requested as such an event might warrant further investigation in order to further characterize it.

An AECI in this study is any AE that results in discontinuation (i.e., withdrawal) of the study drug infusion and must be reported within 24 hours through the EDC system on the SAE eCRF or backup paper SAE form, as described in Section 14.2.

## 14.10. Overdose

An overdose is defined as the receipt of more than one dose of study drug by a patient during this study. If an overdose is associated with an SAE, the SAE must be reported within 24 hours of the site becoming aware of the SAE, as described in Section 14.2. The actual dose of study drug administered will be recorded in the Study Drug Administration eCRF.

## 14.11. Pregnancy

Female patients who become pregnant during the study will be followed to determine the outcome of the pregnancy. Since this is a single-dose study, female patients who become pregnant during the study after study drug dosing may remain in the study to complete subsequent study visits and assessment of efficacy endpoints. The pregnancy must be reported to the Sponsor within 24 hours of the site becoming aware of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will notify the Sponsor. At the completion of the pregnancy, the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will follow the procedures for reporting an SAE.

## 14.12. AE and SAE Follow-up

All AEs and SAEs will be followed to resolution (the patient's health has returned to his or her baseline status or all variables have returned to normal), or until an outcome is reached, or until deemed to be stable by the Investigator/Sub-Investigator or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol, or the event is otherwise explained, regardless of whether the patient is still participating in the study. All appropriate therapeutic measures will be undertaken and recorded. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

Any updated information on a SAE will be submitted within 24 hours of receipt of the information. Supporting documents (discharge summaries, imaging reports, culture reports, autopsy reports, etc.) will be provided for all SAEs. For SAEs that result in death, the Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will provide a copy of any post-mortem findings including histopathology.

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will provide a narrative for the SAE, which is entered in the SAE eCRF.

## 14.13. Regulatory Reporting Requirements for SAEs

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements for safety reporting to the regulatory authority, IRBs/IECs, and investigators.

A SAE may qualify for expedited reporting to regulatory authorities if it is determined to be a SUSAR. A SUSAR is an AE associated with the use of the study drug which is serious, unexpected, and study-drug related. Expectedness of SAEs is determined by the Sponsor based on the Reference Safety Information of the Investigator's Brochure.

The Sponsor or its designee is responsible for submitting expedited safety reports to the appropriate regulatory agency for all confirmed SUSARs in accordance with national regulatory laws and regulations. In the case of a fatal or life-threatening SUSAR, the Sponsor or its designee notifies the appropriate regulatory agency as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. For a non-fatal, non-life-threatening SUSAR, the report is to be submitted no later than 15 calendar days after the Sponsor is made aware of the event.

Investigators will be notified of all serious, unexpected, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB/IEC of these SAEs in accordance with its regulations and guidelines.

## 14.14. Expectedness Determination

An AE is considered "unexpected" if the nature of the AE is not consistent with what is listed in the Reference Safety Information of the Investigator's Brochure. Reports that add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. The Sponsor will be responsible for determining whether a SAE is expected or unexpected for the purpose of regulatory reporting.

# 15. STATISTICS

A Statistical Analysis Plan (SAP) will be prepared and finalized before the interim analysis for futility. Any changes to the SAP after it has been signed but prior to final database lock and unblinding will be documented in an amendment. Descriptive statistics, including numbers and percentages for categorical variables, and numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided by treatment group. Treatment groups will be referred to as "exebacase + SoCA" and "SoCA alone" for patients randomly assigned to exebacase and placebo, respectively. Additional analyses may also be performed. Listings of individual patient data will be produced.

## 15.1. Populations

Three populations will be used for presentation and analysis of the data: the overall population which includes patients with MRSA and/or MSSA, the MRSA population, and the MSSA population. If a patient has both MRSA and MSSA, the patient will be included in the MRSA population. The determination of MRSA and MSSA will be based on the central laboratory determination of genus and species and susceptibility results based on cefoxitin disk diffusion unless no central result is available. In this case, the local laboratory susceptibility result will be used, and MRSA will be defined as the *S. aureus* isolate that is resistant to cefoxitin or in the absence of a cefoxitin susceptibility result, is resistant to oxacillin.

## 15.2. Analysis Sets

The analysis sets are as follows:

- Intent-to-treat (ITT) analysis set: all randomized patients
- Safety analysis set: all randomized patients who receive any amount of study drug
- Microbiological ITT (mITT) analysis set: all randomized patients who receive any amount of study drug and had documented *S. aureus* BSI/IE based on a blood culture prior to administration of study drug. Determination of *S. aureus* is based on the central laboratory determination of genus and species unless no central result is available. In this case, the local laboratory result will be used.
- Per-Protocol (PP) analysis set: all randomized patients who have no confounding factors (as defined in the SAP) potentially affecting the evaluation of efficacy
- PK analysis set: all randomized patients receiving exebacase with PK samples valid for exebacase assay

## 15.3. Sample Size

The study is designed to have sufficient power for the primary efficacy outcome in patients with MRSA (clinical outcome at Day 14 in the mITT analysis set) and the first two secondary efficacy outcomes (clinical outcome at Day 14 in the overall population in the mITT analysis set and 30-day all-cause mortality in the MRSA population in the mITT analysis set). Based on data

from the Phase 2 study, assuming a 7% (exebacase + SoCA group) and 24% (SoCA alone group) 30-day all-cause mortality rate in the MRSA population with no censoring (i.e., all patients are followed until 30 days), 80% power, 2:1 randomization ratio, and a 2-sided alpha of 0.05, a total of 135 patients are required in the mITT analysis set in the MRSA population (90 and 45 patients in the exebacase + SoCA and SoCA alone groups, respectively) based on the log rank test. A total of 135 patients in the MRSA population results in 86% power to detect a significant difference between treatment groups assuming a 68% clinical responder rate in the exebacase +SoCA group at Day 14 and 40% in the SoCA alone group, using a 2-sided alpha of 0.05, and a Fisher's exact test. In the overall population (MRSA and MSSA), if 40% of patients have MRSA, a sample size of 339 patients (226 and 113 patients in the exebacase + SoCA and SoCA alone groups, respectively) in the mITT analysis set provides 83% power to show a significant treatment difference based on a 77% clinical responder rate in the exebacase + SoCA group at Day 14 and 61% in the SoCA alone group using a 2-sided alpha of 0.05 and a Fisher's exact test. Table 13 provides a summary of the sample size calculations.

**Table 13: Sample Size Calculations (2:1 Randomization Ratio, 2-sided Alpha=0.05)**

| | **Primary Outcome Clinical Responder Day 14 (MRSA Population)** | | **Secondary Outcome Clinical Responder Day 14 (Overall Population)** | | **Secondary Outcome 30-Day All-Cause Mortality (MRSA Population)** | |
|---|---|---|---|---|---|---|
| | **Exebacase + SoCA** | **SoCA Alone** | **Exebacase + SoCA** | **SoCA Alone** | **Exebacase + SoCA** | **SoCA Alone** |
| Outcome Rate | 68% | 40% | 77% | 61% | 7% | 24% |
| Power | 86% | | 83% | | 80% | |
| Sample Size (mITT analysis set) | 90 | 45 | 226 | 113 | 90 | 45 |

If approximately 97% of randomized patients are in the overall population mITT analysis set, a total of 348 patients will be required.

## 15.4. Patient Population and Characteristics

Patient enrollment, protocol deviations, and discontinuations from the study drug and the study will be summarized by treatment group. The number and percentage of patients who discontinued the study due to a coronavirus-related reason, such as unwillingness to attend study visits and development of COVID-19, will also be presented. Demographics, medical and surgical history, baseline assessment of signs and symptoms attributable to *S. aureus* BSI/IE, risk factors for complicated *S. aureus* BSI, diagnosis, source of *S. aureus* BSI/IE, APACHE II score, microbiological assessment, and study drug administration will be summarized by treatment group.

## 15.5. Efficacy Analyses

For efficacy analyses, patient data will be analyzed in the treatment group and stratum (unless otherwise specified) to which the patient was randomized.

For analysis of clinical outcome, once a patient is assessed as a clinical failure due to any of the reasons listed below, the patient is considered a clinical failure for all subsequent visits through Day 60 (i.e., the failure is carried forward):

- Complications of *S. aureus* BSI/IE, including:
  - Development of a new metastatic focus of *S. aureus* infection (e.g., deep tissue abscess, septic arthritis) after Day 7,
  - Development of new septic emboli (e.g., to the brain, lung, etc.) after study drug dosing,
- SoCA for *S. aureus* BSI/IE was changed after study drug dosing due to persistence, worsening, or recurrence or new signs/symptoms of *S. aureus* BSI/IE, **or**
- Death due to any cause.

The other reasons for failure (persistence, worsening, or recurrence of signs or symptoms attributable to *S. aureus* BSI/IE which were present at screening, new signs or symptoms attributable to *S. aureus* BSI/IE, and failure to clear blood cultures by Day14) do not carry forward to subsequent visits.

### 15.5.1. Primary Efficacy Analyses

The primary efficacy outcome is clinical responder rate at Day 14 in patients with MRSA in the mITT analysis set as assessed by the AC. The determination of MRSA (and MSSA) will be based on the central laboratory susceptibility results unless no central result is available. In this case, the local laboratory susceptibility result will be used. Estimand attributes and intercurrent events of interest are described in the SAP. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group.

The null and alternative hypotheses are the following:

H0: $P1 - P2 = 0$

H1: $P1 - P2 \neq 0$

Where:

P1 = the primary efficacy outcome in the exebacase + SoCA group

P2 = the primary efficacy outcome in the SoCA alone group

The clinical responder rate will be compared between the treatment groups using Fisher's exact test. Statistical significance and rejection of the null hypothesis will be based on a 2-sided alpha=0.05. A summary of the reasons for failure and indeterminate (including a separate reason for a missed visit due to coronavirus) will also be provided.

Additional analyses of the primary efficacy outcome in patients with MRSA will be conducted. Clinical outcome at Day 14 will be assessed separately across the randomization stratification factor of poorly controlled diabetes (yes or no). For each subgroup, the number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group in the mITT analysis set. Other subgroup analyses, including age (≥65 and <65 years; if the number of adolescents is not too small, a subgroup of adolescents will be defined as 12 to <18 years of age; age groups of elderly patients will also be examined depending on the number of elderly patients enrolled, final diagnosis (and the final diagnosis categories of BSI/R-IE and complicated BSI/R-IE), SoCA received, and renal function category, will be conducted for exploratory purposes. Additional subgroups of interest will be defined in the SAP. If the number of adolescents is small, primary efficacy results will be provided only in a listing. The primary efficacy outcome will also be assessed in the PP analysis set.

Sensitivity analyses of the primary outcome will also be conducted. The first sensitivity analysis will calculate an adjusted p-value (for the randomization stratification factor of poorly controlled diabetes) using the Cochran-Mantel-Haenszel methodology. The second sensitivity analysis will use multiple imputation methods, as detailed in the SAP, for patients with an indeterminate outcome at Day 14.

### 15.5.2. Secondary Efficacy Analyses

Key secondary efficacy outcomes include clinical outcome at Day 14 in the overall population in the mITT analysis set as assessed by the AC, survival through Day 30 in the MRSA population in the mITT analysis set, and clinical outcome at Day 60 in the MRSA and overall populations in the mITT analysis set as assessed by the AC.

To control for the inflation of the overall type I error rate, a hierarchical testing procedure will be used. If statistical significance is declared for the primary efficacy outcome, testing will be done for the secondary efficacy outcomes in the order listed below. Testing will proceed to the next secondary outcome only if statistical significance (2-sided alpha=0.05) is declared for the preceding secondary outcome being tested.

- Clinical responder rate at Day 14 in the overall population (MRSA and MSSA) in the mITT analysis set. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group. The clinical responder rate will be compared between the treatment groups using Fisher's exact test. A summary of the reasons for failure and indeterminate (including a separate reason for a missed visit due to coronavirus) will also be provided.
- 30-day survival in the MRSA population in the mITT analysis set. Time to death through Day 30 will be analyzed using Kaplan-Meier methods. Patients who are lost to follow-up prior to Day 30 or have not died by Day 30 will be censored at the date last known alive on or prior to Day 30. Survival curves will be provided. The median, 25$^{th}$ and 75$^{th}$ percentiles,

and the probability of survival at Day 30 will be determined by treatment group. Differences between treatment groups will be determined using the log-rank test.

- Clinical responder rate at Day 60 in the MRSA population in the mITT analysis set. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group. The clinical responder rate will be compared between the treatment groups using Fisher's exact test. A summary of the reasons for failure and indeterminate (including a separate reason for a missed visit due to coronavirus) will also be provided.
- Clinical responder rate at Day 60 in the overall population (MRSA and MSSA) in the mITT analysis set. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group. The clinical responder rate will be compared between the treatment groups using Fisher's exact test. A summary of the reasons for failure and indeterminate (including a separate reason for a missed visit due to coronavirus) will also be provided.

Additional analyses of the key secondary efficacy outcomes will be conducted. Clinical outcome at Day 14 in the overall population and Day 60 in the MRSA and overall populations will be assessed separately across the randomization stratification factor of poorly controlled diabetes (yes or no). For each subgroup, the number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group in the mITT analysis set. Other subgroup analyses, as detailed above for the primary efficacy outcome will be conducted for exploratory purposes. If the number of adolescents is small, secondary efficacy results will be provided only in a listing. The key secondary efficacy outcomes will also be assessed in the PP analysis set.

Sensitivity analyses of the key secondary outcomes will also be conducted. If the outcome is found to be statistically significant, a sensitivity analysis will calculate an adjusted p-value (for the randomization stratification factors) using the Cochran-Mantel-Haenszel methodology (for clinical outcome at Day 14 and 60) or a stratified log-rank test (for 30-day survival). In addition, sensitivity analyses will use multiple imputation methods for missing data, as detailed in the SAP, for patients with an indeterminate response at Day 14 and Day 60.

Clinical response at Day 60 in patients with R-IE will be summarized in the mITT analysis set in the overall population and in patients with MRSA. The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group.

### 15.5.3. Additional Efficacy Analyses

Analyses of additional efficacy outcomes will be conducted to support the findings of the primary and secondary efficacy outcomes.

- Survival time (mITT analysis set) through Day 60 in the overall, MRSA and MSSA populations: Survival time will be analyzed using Kaplan-Meier methods. Patients who do not die by Day 60 or who are lost to follow-up will be censored at date last known alive. Survival curves will be provided. The median, 25$^{th}$ and 75$^{th}$ percentiles, and the probability of survival at Day 14, Day 30 and Day 60 will be determined by treatment group.
- Clinical responder rate at Day 14 in the overall R-IE and MRSA R-IE (based on final diagnosis by the AC) populations (mITT analysis set): The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group.
- Clinical responder rate at Day 30 in the overall and MRSA populations, and overall R-IE and MRSA R-IE populations (mITT analysis set): The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group.
- Clinical responder rate at Day 14 by source of *S. aureus* infection as determined by the AC in the overall and MRSA populations (mITT analysis set): The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group and source of infection in the overall and MRSA populations.
- Bacteremia on Day 4 and Day 7 in the overall, MRSA and MSSA populations (mITT analysis set): The number and percentage of patients classified with clearance of bacteremia/presumed clearance of bacteremia, ongoing bacteremia/presumed ongoing bacteremia, and indeterminate by Day 4 and Day 7 will be determined by treatment group in the overall and MRSA populations.
- Clinical responder rate at Day 14, Day 30, and Day 60 in the MSSA population (mITT analysis set): The number and percentage of patients classified as responder, failure, and indeterminate will be determined by treatment group.

## 15.6. Safety Analyses

All safety analyses will be conducted in the safety analysis set and will be summarized by study drug actually received.

Safety will be evaluated by presenting summaries of treatment-emergent AEs (TEAEs), clinical laboratory evaluations (biochemistry, hematology, and coagulation), vital signs (blood pressure, respiratory rate, heart rate, and temperature), and ECG parameters. A TEAE is one that occurs on or after the administration of study drug through the Day 60 visit (Day 60 ± 7 days).

Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). Deaths obtained only through vital status information will be coded as "Death NOS" and analyzed as an AE/SAE with outcome of fatal. An overall summary of AEs will be provided by treatment group. The incidence of TEAEs will be presented by system organ class (SOC) and preferred term (PT) through Day 7 and Day 60, by SOC, PT and relationship to study drug, and by SOC, PT and severity. Serious adverse events, SAEs with an outcome of death, and TEAEs that lead to discontinuation of the study drug will also be presented by SOC and PT. Depending on the number of adolescents (age 12 to <18 years) randomized, the overall summary of AEs and TEAEs by SOC and PT, and/or listings of AEs will be provided for this subgroup.

Descriptive statistics for clinical laboratory results, vital signs, and ECG parameters, including change from baseline, will be presented by timepoint collected and for the overall most abnormal post-baseline value (clinical laboratory results and vital signs only). Incidences of potentially clinically significant clinical laboratory results, vital signs, and ECG parameters, as defined in the SAP, will also be summarized by timepoint collected and the overall most abnormal post-baseline value (clinical laboratory results and vital signs only). Urinalysis results will be presented in a listing.

## 15.7. Interim Analysis

Interim analyses of safety data (unblinded) will be provided to the DSMB throughout the study as defined in the DSMB charter. A futility analysis of the primary efficacy outcome in the MRSA population based on Day 14 clinical outcome data from approximately 60% of patients in the MRSA population in the mITT analysis set will also be reviewed by the DSMB. The futility analysis will be based on conditional power and the threshold for stopping the study due to futility will be provided in the SAP and DSMB charter. The futility boundary is non-binding.

## 15.8. Immunogenicity Analysis

ADA results will be defined as positive and negative based on the confirmatory cut-off point. ADA-positive samples will be further classified as neutralizing (i.e., inhibiting exebacase activity) or non-neutralizing (i.e., having no effect on activity). Baseline and Day 30-60 ADA results will be summarized by result in a shift table and for ADA positive patients, the number and percentage with neutralizing or non-neutralizing ADA will be provided. The number and percentage of patients who had treatment-boosted ADA (defined as increased ADA titers in patients who were positive at baseline) will be summarized. TEAEs by baseline ADA result and clinical outcome at Day 14 by baseline ADA result will also be summarized. IgE results will be presented in a listing.

## 15.9. Health Resource Utilization Analysis

The following with be evaluated in the mITT analysis set for patients enrolled in the US for the overall, MRSA and MSSA population:

- In-hospital mortality: defined as death during the initial hospitalization for *S. aureus* BSI/IE through Day 60
- Hospital length-of-stay (post-study drug administration): for patients that were discharged alive, the length-of-stay from the date of study drug administration to the date of discharge from the initial hospitalization
- ICU length-of-stay (post-study drug administration): for patients that were discharged from the initial hospitalization alive, the total number of days in the ICU from the date of study drug administration to the date of discharge from the initial hospitalization
- Discharged location: where the patient was discharged to from the hospital (e.g., home, nursing home and skilled nursing facility/long-term acute care, rehabilitation, palliative care/hospice)
- Outpatient therapy and home health care: whether or not SoCA was received in an outpatient facility or via home health care, and the number of days that SoCA was received as an outpatient
- 30-day all-cause readmissions: for patients that were discharged alive, readmission for any cause within 30 days of discharge from the initial hospitalization
- 30-day readmissions for *S. aureus* BSI/IE or complication of *S. aureus* BSI/IE: for patients that were discharged alive, readmission for *S. aureus* BSI/IE or complication of *S. aureus* BSI/IE (e.g., metastatic foci, septic emboli) within 30 days of discharge from the initial hospitalization
- Insurance type: private insurance, Medicare, Medicare, other

## 15.10. Pharmacokinetic Analysis

All PK data, dosing, and covariate information collected in this study will be pooled with the data collected from the prior studies to update the previously developed population PK model. The population PK analysis will be described in a separate SAP and a separate report.

The relationship between PK parameters of exebacase (AUC and $C_{max}$), derivative parameters (such as parameter over MIC), and clinical outcome and ADA will be examined.
The relationship between PK parameters and most frequent or most clinically significant AEs may be explored.

## 15.11. Handling of Missing Data

For the primary and secondary efficacy outcomes (with the exception of 30-day survival), patients with missing data are assigned a clinical outcome of indeterminate. In the mITT analysis set, indeterminate outcomes are included in the denominator for the calculation of the responder rate. Thus, a clinical outcome of indeterminate is analyzed the same as a clinical outcome of failure. Sensitivity analyses will be conducted where missing data are imputed using a multiple imputation analysis. For the secondary outcome of 30-day survival, patients who are lost to follow-up prior to Day 30 will be censored at the last known date alive on or prior to Day 30. Handling of other missing data will be described in the SAP.

# 16. DATA MANAGEMENT

## 16.1. Data Collection

The investigative site will be provided eCRFs in which to record all the protocol-specified data for each patient in this study. Entries made in the eCRF must be verifiable against source documents. Data reported in the eCRF will be consistent with the source documents or the discrepancies will be explained.

The Investigator/Sub-Investigator (or other delegated medically qualified person listed on the FDA Form 1572 and trained on the protocol) will be responsible for reviewing all data and eCRF entries and will verify that the information is true and correct.

Patient data will be entered into the eCRF and be ready for review as soon as possible, as outlined in the eCRF completion guidelines.

## 16.2. Access to Source Documents

Study Monitors who are representatives of ContraFect or designee will monitor the study according to a predetermined Monitoring Plan. Monitoring visits provide ContraFect with the opportunity to:

- Evaluate the progress of the study
- Verify the accuracy and completeness of eCRFs
- Assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled
- Resolve any inconsistencies in the study records.

The Investigator must allow the Study Monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records supporting the participation of each patient in the study. The eCRFs and other documentation supporting the study must be kept up-to-date by the Investigator and the

research staff at the investigative site. These study materials must be available for review by the Study Monitor, and/or other qualified representatives of ContraFect, at each monitoring visit.

The Study Monitor will review the various records of the study (eCRFs, patient medical and laboratory records, and other pertinent data). The Study Monitor will verify the eCRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the Investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded. The Study Monitor will ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the Monitoring Plan.

# 17. ADMINISTRATIVE

## 17.1. Statement of Good Clinical Practices

This trial will be conducted in adherence to the study protocol, GCP as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312, and Part 11 as well as ICH E6: Guideline for Good Clinical Practice (ICH E6 GCP) consolidated guidelines and applicable regulatory requirements (http://www.fda.gov/cder/guidance/index.htm).

## 17.2. Protocol Adherence

The Investigator must adhere to the protocol as described in this document. The Investigator is responsible for enrolling patients who have met the protocol inclusion and exclusion criteria. The IRB/IEC responsible for overseeing the conduct of the study must be notified of all changes to the protocol and any deviations from the protocol that may increase risk to the patient and/or that may adversely affect the rights of the patient or validity of the investigation.

## 17.3. Study Termination

ContraFect reserves the right to terminate the study. The Investigator must notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to ContraFect or designee, and retain a copy for the site's study file.

# 18. QUALITY CONTROL AND ASSURANCE

## 18.1. Sponsor Audits

Individuals from ContraFect's Quality Assurance department or designee may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and ContraFect's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by ContraFect or designee to arrange a convenient time for this

visit. The Investigator and staff are expected to cooperate with the auditor(s) and allow access to all patient records supporting the eCRFs and other study-related documents.

## 18.2. Inspection by Regulatory Authorities

During the investigational product's development program, a regulatory authority may visit the Investigator to conduct an inspection of the study and the site. The Investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The Investigator must immediately notify ContraFect when contacted by any regulatory authority for purposes of conducting an inspection.

# 19. ETHICS

## 19.1. Institutional Review Board or Independent Ethics Committee

It is the responsibility of the Investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in ICH E6 GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. Any information supplied to the patient, such as written informed consent/assent form(s) and written information to be provided to patients (e.g., information leaflets), must be reviewed and approved by a qualified IRB/IEC prior to enrollment of participants in the study. Prior to initiation of the study at a site, ContraFect must receive documentation of the IRB/IEC approval, which specifically identifies the study/protocol, and a list of the committee members.

Amendments to the protocol and revisions to the informed consent/assent must also be submitted to and, if required, approved by the IRB/IEC.

Investigators must submit progress reports to the IRB/IEC in accordance with the IRB/IEC requirements. If applicable, annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to ContraFect.

If ContraFect provides the Investigator with a safety report, the Investigator must promptly forward a copy to the IRB/IEC in accordance with its regulations and guidelines.

After completion or termination of the study, the Investigator must notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to ContraFect or designee, and retain a copy for the site's study file.

The Investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB/IEC.

The Investigator is responsible for conducting the study in accordance with the protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

## 19.2. Informed Consent/Assent

Preparation of the informed consent and assent forms is the responsibility of the Investigator and ContraFect or designee and must include all elements required by ICH, GCP, and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Master study-specific informed consent and assent templates will be used to prepare the site-specific informed consent and assent forms. ContraFect or designee must review and approve all changes to site-specific informed consent and assent forms.

The informed consent and assent forms must include a statement that ContraFect or designee and regulatory authorities have direct access to patient records. Prior to initiation of the study at a site, the Investigator must have the IRB/IECs written approval/favorable opinion of the written informed consent and assent forms and any other information to be provided to the patient.

Some patients who will be eligible for this protocol may not be able to give written informed consent or assent themselves due to reasons such as sedation, unconscious state, etc. Therefore, in a situation where a patient is unable to provide written informed consent or assent for themselves, written informed consent may be provided by the patient's legally acceptable representative, as permissible based on local laws and regulations. In such cases, if the patient regains the ability to supply informed consent themselves, they should be reconsented/assented.

For patients 12 to <18 years of age, written informed consent from the patient's parent/guardian or other legally acceptable representative will be obtained according to the site's IRB requirements. For emancipated minors, written informed consent will be obtained according to the site's IRB requirements.

Each patient (or the patient's legally acceptable representative/parent/guardian) must provide written informed consent or assent before any study-specific assessment or procedures are performed and must provide written informed consent or assent on the supplemental consent form before medical health services are provided. The patient (or the patient's legally acceptable representative/parent/guardian) will sign and date the informed consent or assent form. The person rendering consent or assent will also sign and date the informed consent or assent form as the person who obtained the consent or assent of the patient. The original signed informed consent or assent form will be retained with the site's study file. Each patient will be provided a copy of his or her signed informed consent or assent form.

## 19.3. Data Privacy

Applicable data privacy laws and regulations must be adhered to. The study site, Investigator, and ContraFect and their respective designees are responsible for ensuring that the protected health information (as defined under applicable laws) of all patients enrolled in the study is handled in accordance with the US Health Insurance Portability and Accountability Act of 1996 ("HIPAA") Privacy and Security Rules, 45 C.F.R. Parts 160-164, the Health Information

Technology for Economic and Clinical Health Act (HITECH), P.L. No. 111-005, Part I, Title XIII, Subpart D, 13401-13409, the California Consumer Privacy Act ("CCPA"), and any other applicable state and local privacy laws (collectively referred to as the "Applicable Data Privacy Laws").

Appropriate informed consent/assent and authorizations for use and disclosure and/or transfer (if applicable) of protected health information must be obtained from all patients enrolled in the study.

# 20. RECORD KEEPING/RETENTION OF RECORDS

The Investigator must ensure that all records pertaining to the conduct of the clinical study, informed consent/assent forms, drug accountability records, source documents, and other study documentation are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The Investigator must not destroy any records associated with the study without receiving approval from ContraFect. The Investigator must notify ContraFect in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, ContraFect must be contacted to arrange alternative record storage options.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. ContraFect or designee will retain the original eCRF data and audit trail.

## 20.1. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number to maintain patient confidentiality. All computer entry and networking programs will be performed with coded numbers only. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the IRB/IEC, regulatory authorities, or the Sponsor or designees. The patients will be informed that representatives of ContraFect, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with all applicable data protection laws.

# 21. USE OF STUDY RESULTS

By signing the study protocol, the Investigator and his or her institution agree that the results of the study may be used by ContraFect for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. As required, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

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# 23. APPENDICES

## 23.1. Appendix 1: Sequential (Sepsis-Related) Organ Failure Assessment Score (SOFA)

In patients that meet the qSOFA score (as described in Section 12.2.2), a SOFA score will be performed to determine whether the patient meets the criteria for sepsis and/or septic shock. Sepsis and/or septic shock based on the SOFA score are criteria for complicated *S. aureus* BSI according to the inclusion criterion #4 (Section 10.1) and the diagnosis definition in Table 8 (Section 12.5). If the SOFA score is the only criteria for complicated *S. aureus* BSI that is met according to inclusion criterion #4, contact the Medical Monitor prior to randomization. The SOFA score is determined according to the definitions and table below [adapted from Singer 2016]:

- **Sepsis** is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute **change** in total SOFA score of **≥2 points** consequent to the infection. The baseline SOFA score can be assumed to be 0 in patients not known to have preexisting organ dysfunction. A SOFA score of **≥2 points** reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection.
- **Septic shock** is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

| System | Score | | | | |
|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** |
| Respiration: PaO2/FiO2, mmHg (kPa) | ≥400 (53.3) | <400 (53.3) | <300 (40) | <200 (26.7) with respiratory support | <100 (13.3) with respiratory support |
| Coagulation: Platelets, x$10^3$/µL | ≥150 | <150 | <100 | <50 | <20 |
| Liver: Bilirubin, mg/dl (µmol/L) | <1.2 (20) | 1.2-1.9 (20-32) | 2.0-5.9 (33-101) | 6.0-11.9 (102-204) | >12.0 (204) |
| Cardiovascular | MAP ≥70 mmHg | MAP <70 mmHg | Dopamine <5 or dobutamine (any dose)[1] | Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[1] | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[1] |
| CNS: Glasgow Coma Score | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Renal: Creatinine, mg/dL (µmol/L) | <1.2 (110) | 1.2-1.9 (110-170) | 2.0-3.4 (171-299) | 3.5-4.9 (300-440) | >5.0 (440) |
| Renal: Urine output, mL/d | | | | <500 | <200 |

Reference: Adapted from Singer 2016
Abbreviations: FiO2=fraction of inspired oxygen; MAP=mean arterial pressure; PaO2=partial pressure of oxygen
1. Catecholamine doses given as µg/kg/min for at least 1 hour

## 23.2. Appendix 2: APACHE II Score

**APACHE II Score Form**

| | | HIGH ABNORMAL RANGE | | | | | LOW ABNORMAL RANGE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **PHYSIOLOGIC VARIABLE** | **+4** | **+3** | **+2** | **+1** | **0** | **+1** | **+2** | **+3** | **+4** |
| 1 | Temperature core (°C) | >=41 | 39-40.9 | | 38.5-38.9 | 36.0-38.4 | 34-35.9 | 32-33.9 | 30-31.9 | <=29.9 |
| 2 | Mean arterial pressure = (2 x diastolic + systolic)/3 | >=160 | 130-159 | 110-129 | | 70-109 | | 50-69 | | <=49 |
| 3 | Heart rate (ventricular response) | >=180 | 140-179 | 110-139 | | 70-109 | | 55-69 | 40-54 | <=39 |
| 4 | Respiratory rate (non-ventilated or ventilated) | >=50 | 35-49 | | 25-34 | 12-24 | 10-11 | 6-9 | | <5 |
| 5 | Oxygenation<br>A-a$DO_2$ or $PaO_2$(mmHg)<br>a) $FiO_2$>0.5:record A-a$DO_2$ | >=500 | 350-499 | 200-349 | | <200 | | | | |
| | b) $FiO_2$<0.5:record only $PaO_2$ | | | | | >70 | 61-70 | | 55-60 | <55 |
| 6 | Arterial pH<br>If no ABGs see Serum $HCO_3$ below* | >=7.7 | 7.6-7.69 | | 7.5-7.59 | 7.33-7.49 | | 7.25-7.32 | 7.15-7.24 | <7.15 |
| 7 | Serum Sodium | >=180 | 160-179 | 155-159 | 150-154 | 130-149 | | 120-129 | 111-119 | <=110 |
| 8 | Serum Potassium | >=7 | 6-6.9 | | 5.5-5.9 | 3.5-5.4 | 3-3.4 | 2.5-2.9 | | <2.5 |
| 9 | Serum Creatinine (mg/dL)<br>Double point for acute renal failure | >=3.5 | 2-3.4 | 1.5-1.9 | | 0.6-1.4 | | <0.6 | | |
| 10 | Hematocrit (%) | >=60 | | 50-59.9 | 46-49.9 | 30-45.9 | | 20-29.9 | | <20 |
| 11 | White Blood Count | >=40 | | 20-39.9 | 15-19.9 | 3-14.9 | | 1-2.9 | | <1 |
| 12 | Glasgow Coma Scale (see next page)<br>(Score = 15 minus actual GCS) | 15 minus the GCS = | | | | | | | | |
| A | Total Acute Physiology Score (APS) | Sum of the 12 individual variable points = | | | | | | | | |
| * | Serum $HCO_3$(venous-mmol/L) | >=52 | 41-51.9 | | 32-40.9 | 22-31.9 | | 18-21.9 | 15-17.9 | <15 |

Reference: Adapted from Knaus 1985

## APACHE II Score Form (Continued)

<table>
<tr><th colspan="2">Glasgow Coma Scale (Circle appropriate response)</th><th><u>B</u> Age Points</th><th><u>C</u> Chronic Health Points</th><th>APACHE II Score<br>(sum of A+B+C)</th></tr>
<tr>
<td>Eyes open<br>4 - spontaneously<br>3 - to verbal<br>2 - to painful stimuli<br>1 - no response<br><br>Motor response<br>6 - to verbal command<br>5 - localizes to pain<br>4 - withdraws to pain<br>3 - decorticate<br>2 - decerebrate<br>1 - no response</td>
<td>verbal - <u>nonintubated</u><br>5 - oriented and conversant<br>4 - disoriented and talks<br>3 - inappropriate words<br>2 - incomprehensible sounds<br>1 - no response<br><br>verbal - <u>intubated</u><br>5 - seems able to talk<br>3 - questionable ability to talk<br>1 - generally unresponsive</td>
<td>Age Points<br><44 0<br>45-54 2<br>55-64 3<br>65-74 5<br>>75 6<br><br>Age Points =</td>
<td>If any of the 5 CHE categories below is answered with yes, give +5 points for non-operative or emergency postoperative patients or +2 points for elective postoperative patients.<br><br>Liver - Cirrhosis with PHT or encephalopathy<br>Cardiovascular - Class IV angina or at rest or with minimal self-care activities<br>Pulmonary - Chronic hypoxemia or hypercapnia or polycythaemia of PHT >40 mmHg<br>Kidney - Chronic peritoneal or haemodialysis<br>Immune - Immune compromised host<br><br>Chronic Health Points =</td>
<td>A APS points (from prior page)<br>+ B Age points<br>+ C Chronic Health Points<br>_____<br>= Total APACHE II score</td>
</tr>
</table>

Reference: Adapted from Knaus 1985

## 23.3. Appendix 3: Oxygen Conversion Tables

**Table 14: Oxygen Saturation (SpO2) to Partial Pressure of Oxygen (PaO2)**

| SpO2 (%) | PaO2 (mmHg) |
|---|---|
| 80 | 44 |
| 81 | 45 |
| 82 | 46 |
| 83 | 47 |
| 84 | 49 |
| 85 | 50 |
| 86 | 52 |
| 87 | 53 |
| 88 | 55 |
| 89 | 57 |
| 90 | 60 |
| 91 | 62 |
| 92 | 65 |
| 93 | 69 |
| 94 | 73 |
| 95 | 79 |
| 96 | 86 |
| 97 | 96 |
| 98 | 112 |
| 99 | 145 |

**Table 15: Estimation of FiO2**

| Method | $O_2$ flow (L/min) | Estimated FiO2 (%) |
|---|---|---|
| Nasal Cannula | 1 | 24 |
| | 2 | 27 |
| | 3 | 30 |
| | 4 | 33 |
| | 5 | 36 |
| | 6 | 40 |
| | | |
| Nasopharyngeal Catheter | 4 | 40 |
| | 5 | 50 |
| | 6 | 60 |
| | | |
| Face Mask | 5 | 40 |
| | 6-7 | 50 |
| | 7-8 | 60 |
| | | |
| Face Mask with Reservoir | 6 | 60 |
| | 7 | 70 |
| | ≥8 | 80 |

Room air estimated FiO2 (%) = 21.

FiO2 should be decimal (e.g., 0.21) when determining PaO2/FiO2 ratio.

## 23.4. Appendix 4: Common Categories of Immunosuppressive and Myelosuppressive Agents

Inclusion criterion 4.b.vi describes the criterion for complicated *S. aureus* BSI of "On immunosuppressive therapy, such as:

- Biologics such as infliximab, monoclonal antibodies such as daclizumab, methotrexate, cyclophosphamide, or similar agents.
- Patients who have taken ≥10 mg of prednisone or equivalent for 5 days or more."

This section describes the "similar agents" that meet the criterion of immunosuppressive therapy (listed below). This is not an all-inclusive list of all immunosuppressive therapies. Please contact the Medical Monitor if you have questions regarding these immunosuppressive therapies or if a patient is on a potential immunosuppressive therapy that is not listed. Immunosuppressive therapy includes, but is not limited to, the following medications:

**Medications:**

- Methotrexate (Rheumatrex, Trexall) at any dose
- Leflunomide (Arava) / Teriflunomide (Aubagio) at any dose
- Cyclophosphamide (Cyotxan) at any dose
- Cyclosporine A at any dose (not including ophthalmic formulation (Restatis))
- Tacrolimus (FK506) at any dose (not including ophthalmic formulation (Protopic))
- Azathioprine at any dose
- Mycophenolate Mofetil (Cellcept) at any dose
- Sirolimus (Rapamycin, Rapamune) at any dose
- Everolimus (Certican) at any dose
- Temsirolimus (Torisel) at any dose
- Gusperimus at any dose
- Thalidomide at any dose
- Apremilast (Otezla): PDE-4 inhibitor

**Biologics:**

- Anti-tumor Necrosis Factors (TNR Agents)
    - Etanercept (Enbrel)
    - Afelimomab (Fab 2)
    - Infliximab (Remicade)
    - Certolizumab (Cimzia)
    - Golimumab (Simponi)
- IL-1 Receptor Antagonist (IL-1RA) - Kineret (Anakinra)

- CTLA-4 Fusion Protein
    - Abatacept (Orencia)
    - Alefacept (Amevive)
    - Belatacept (Nulojix)
- Anti-CD20
    - Rituximab (Rituxan/MabThera)
    - Obinutuzumab (Gazyva)
    - Ocrelizumab (Ocrevus)
    - Ofatumumab (Arzerra)
    - Anti-CD52 - Alemtuzumab (Campath)
- Anti-Interleukin Antibodies
    - Daclizumab (Anti-Tac, Zenapax)
    - Basiliximab (Simulect)
    - Anti-IL6 - Tocilizumab (Actemra/RoActemra)
    - Anti-IL 12/13 - Ustekinumab (Stelara)
    - Anti-BAFF (B-cell activating factor) - Belimumab
    - Integrin Inhibitor - Natalizumab (Tysarbi)
    - Anti-CTLA 4 – Ipilimumab
    - Ixekizumab (Taltz) or other Anti- IL 17 or Anti-IL 23 antibodies
- Other Interleukins
    - Aldesleukin (Proleukin)
    - Canakinumab (Ilaris)
    - Oprelvekin (Neumega)
    - Anti-PDL1 - Avelumab (Bavencio)
- Other Selective Immunosuppressants
    - Muromonab or OKT-3
    - Efalizumab (Raptiva) - anti-CD11a
    - Fingolimod (Gilenza) - sphingosine 1-phosphatge receptor modulator
    - Eculizumab (Soliris): anti-complement protein C5
    - Tofacitinib (Xeljanz): JAK-STAT inhibitor
- Vedolizumab (Entyvio): Integrin α4β7