Clinical Trial Protocol

CF-301

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

Protocol Number CF-301-102-4
Protocol Amendment #4

Sponsor:
ContraFect Corporation
28 Wells Ave
Yonkers, NY 10701

Original Protocol Date: August 29, 2016

Country-Specific Protocol Amendment #1 for the United States Date: August 17, 2017
Country-Specific Protocol Amendment #2 for the United States Date: December 14, 2017

Administrative Amendment #1 for Latin America Date: October 3, 2017
Country-Specific Protocol Amendment #2 for Latin America Date: December 14, 2017

Country-Specific Protocol Amendment #1 for the EU Date: August 31, 2017
Country-Specific Protocol Amendment #2 for the EU Date: December 18, 2017

Country-Specific Protocol Amendment #1 for Israel Date: June 23, 2017
Country-Specific Protocol Amendment #2 for Israel Date: December 19, 2017

Protocol Amendment #3 Date: April 3, 2018

Protocol Amendment #4 Date: June 22, 2018

IND number: 113473
EudraCT number: 2016-003059-31
Clinicaltrials.gov NCT03163446

CONFIDENTIALITY STATEMENT

Summary of Changes

The primary purpose of this Protocol Amendment is to refine the criteria/risk factors in inclusion criterion #4 to better enable enrollment of patients with severe complicated bacteremia in accordance with recommendations of both the Data Safety Monitoring Board (DSMB) and Adjudication Committee. Consistent with this objective, the exclusion criteria were updated to allow enrollment of patients with osteomyelitis, nosocomial pneumonia due to *S. aureus*, implantable cardioverter defibrillators, permanent pacemakers, prosthetic cardiac values, cardiac value support rings, and other implantable cardiac devices (see revisions to exclusion criteria #6, 7, 9, 11, 12 for all changes).

In addition, the protocol was updated to add an assessment of re-infection by the site investigator and the independent Adjudication Committee between Test-of-Cure (TOC) and Day 180 for patients who meet the definition of response at TOC. The protocol was also revised to collect serious adverse events (SAEs) through the Day 180 visit.

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

Section(s)	Brief Description of Changes
2, 4, 8.3, 11.3, 12.16, 15.4	• Added an assessment of re-infection by the site investigator and Adjudication Committee between TOC and Day 180 for patients who meet the definition of response at TOC.
2, 9.1, 9.4, 11.1	• Added suggested treatment duration for osteomyelitis of 42 to 84 days of standard-of-care antibacterial therapy. Added expected core study duration (through TOC) of 10 to 16 weeks for patients with osteomyelitis.
2, 10.1	• Clarified that the inclusion criteria must be met at the time of Screening (i.e., within 24 hours of randomization), unless otherwise noted, in order for the patient to be eligible for enrollment. • Revised inclusion criterion #3 to require at least **two** signs and symptoms of infection. • Revised the criteria/risk factors in inclusion criterion #4 to better enable enrollment of patients with severe complicated bacteremia.
2, 10.2	• Updated exclusion #6 to exclude patients with presence of a prosthetic cardiac valve, cardiac valve support ring, or other implantable cardiac devices (e.g., left ventricular assist device [LVAD]) **only if** the patient is scheduled for surgical removal of the prosthetic valve, ring, or implantable device during the 24 hours after randomization. Patients with implantable cardioverter defibrillators and permanent pacemakers are eligible for enrollment, and patients with prosthetic cardiac values, cardiac value support rings, or other implantable cardiac devices who are NOT scheduled for surgery during the 24 hours after randomization are eligible for enrollment. • Updated exclusion #7 to exclude endocarditis with severe aortic or mitral valve regurgitation on TEE or TTE, or any paravalvular abscess, **with scheduled surgery** for endocarditis.

	• Updated exclusion #9 so that osteomyelitis is NOT an exclusion. • Updated exclusion #10 to specify that ideal weight should be used in the creatinine clearance calculation by Cockcroft-Gault in patients with BMI ≥ 30 kg/m^2. • Updated exclusion #11 to exclude community acquired pneumonia, and nosocomial pneumonia due to pathogens **other than** *S. aureus*. Patients with nosocomial pneumonia due to *S. aureus* are eligible for enrollment. • Updated exclusion #12 to exclude patients not expected to survive through Day 14 of the study **due to underlying disease** (e.g., end-stage cancer).
2, 4, 10.3.2, 11.3, 12.14	• Added an assessment of vital status (whether the patient is alive or dead, or last known alive date) at Day 180 or when a patient is deemed to be lost to follow-up. The patient's vital status should be determined using available sources (e.g., the patient's relatives, hospital records, and/or public records) as permissible based on local laws and regulations.
2, 4, 11.3, 14.2	• Updated SAE reporting procedures to collect all SAEs occurring during the long-term follow-up period through Day 180.
2, 4, 11.3, 12.16	• Expanded the visit window around the Day 180 visit to ±14 days.
2, 12.16	• Added the following reason for non-response to the clinical outcome assessment: >12 weeks of SOC antibacterial therapy for *S. aureus* BSI and/or related infection (e.g., osteomyelitis).
4, 11.2.1, 12.2, 12.13.2	• Updated the creatinine clearance calculation by Cockcroft-Gault to include the use of ideal body weight in patients with BMI ≥ 30 kg/m^2.
4, 11.2, 11.3, 12.12	• Clarified that all blood cultures performed during the study (from the qualifying blood culture through to Day 180), including blood cultures that are positive or negative for *S. aureus*, should be entered in the eCRF, with all *S. aureus* isolates sent to the central lab.
14.11	• Made minor clarifications to SAE reporting procedures.
23.1 (Appendix 1)	• Revised definition of complicated bacteremia to be consistent with the changes made to the inclusion criteria.
Various	• Made minor editorial changes throughout the document for clarity and consistency.

SPONSOR SIGNATURE PAGE

Protocol CF-301-102-4
Protocol Amendment #4

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Sponsor's Approval

Alena Jandourek, M.D. Executive Director Clinical Development and Medical Affairs ContraFect Corporation	Date

INVESTIGATOR'S AGREEMENT

Protocol CF-301-102-4
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I, the undersigned, have received and reviewed the CF-301-102 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	Alena Jandourek, M.D. Executive Director, Clinical Development and Medical Affairs	ContraFect Corporation 28 Wells Ave, Yonkers, NY 10701 Telephone: 914 207 2300 (Office) 206 384 0182 (Mobile) Email: AJandourek@contrafect.com
Sponsor Project Manager	Nancy Capra Executive Director, Project Management	ContraFect Corporation 28 Wells Ave, Yonkers, NY 10701 Telephone: 215-760-3490 Email: NCapra@contrafect.com
Sponsor Clinical Operations Lead, Global	Susan Ermlich Clinical Operations Consultant	ContraFect Corporation 28 Wells Ave, Yonkers, NY 10701 Telephone: 215-796-0950 Email: SErmlich@contrafect.com
Sponsor Clinical Operations Lead, US	Joy Lipka Clinical Operations Consultant	ContraFect Corporation 28 Wells Ave, Yonkers, NY 10701 Telephone: 215-872-3791 Email: JLipka@contrafect.com
Sponsor Clinical Operations Lead, Latin America	Maureen Chapnick Clinical Operations Consultant	ContraFect Corporation 28 Wells Ave, Yonkers, NY 10701 Telephone: 908-868-4719 Email: MChapnick@contrafect.com
CRO Project Manager, US	Kimberly Lumpkin Clinical Trial Manager	SynteractHCR 5759 Fleet Street, Suite 100 Carlsbad, CA 92008 Telephone: 760 277 5220 Email: Kimberly.Lumpkin@synteractHCR.com
CRO Project Manager, Latin America	Veronica Prado Project Manager	CIDAL 4 Avenida 21-63 zona 14, Guatemala City, Guatemala Telephone (+502) 2375 8300 International Calls: (1-786) 314-7083 Email: vprado@cidal.net
CRO Project Manager, Europe, Russia, and Israel	Ute Doerge-Baischew Global Project Manager	PSI CRO Deutschland GmbH PSI Pharma Support Behringstr. 7 | 82152 Planegg/Munich | Germany Telephone: +49 151 5514 6051 Email: ute.doerge-baischew@psi-cro.com
Lead Study Medical Monitor and US Medical Monitor	Alena Jandourek, M.D. Executive Director, Clinical Development and Medical Affairs	ContraFect Corporation 28 Wells Ave, Yonkers, NY 10701 Telephone: 914-207-2300 (Office) 206-384-0182 (Mobile) Email: AJandourek@contrafect.com
Medical Monitor, Latin America	Jacobo Sabbaj, MD, FACP, FIDSA Advisor and Consultant	CIDAL 4 Avenida 21-63 zona 14, Guatemala City, Guatemala Telephone (+502) 2375-8300 International Calls: (1-732) 428-5502 or (1-786) 338-9580 Email: jsabbaj@cidal.net

Contact Information continued on the next page

Table 1: Contact Information (continued)

Role in Study	Name	Contact Information
Medical Monitor, Europe	Liga Ulmane, M.D. Medical Affairs Manager	PSI CRO Latvia SIA 21 Kr. Valdemara, Riga, LV 1010, Latvia Telephone: +37129492424 Email: Liga.Ulmane@psi-cro.com
Medical Monitor, Backup	John Riefler, M.D. Director of Medical Monitoring & Consulting	PSI Pharma Support America Inc. 875 First Avenue, King of Prussia, PA 19404 Telephone: 267-464-2520, x 2120 Email: John.Riefler@psi-cro.com

2. SYNOPSIS

Name of Sponsor/Company: ContraFect Corporation

Investigational Product: CF-301

Active Ingredient: $C_{1149}H_{1768}N_{324}O_{357}S_3$

Title of Study: 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

Protocol number: CF-301-102-4 (Protocol Amendment #4)

Phase of development: 2

Study centers: Up to approximately 100 study centers will participate in this global study

Objectives:

Primary:

- To describe the safety and tolerability of CF-301 vs. placebo in addition to standard-of-care (SOC) antibacterial therapy for the treatment of patients with *Staphylococcus aureus* bloodstream infections (BSIs) including endocarditis.
- To estimate clinical outcome at Day 14 after CF-301/placebo administration.
- To describe the pharmacokinetic (PK) parameters of CF-301.

Secondary:

- To estimate clinical outcome at Day 7 after CF-301/placebo administration, at the end of SOC antibacterial therapy (EOT), and at test-of-cure (TOC) 28 days after the EOT.
- To estimate microbiological response at Days 7 and 14 after CF-301/placebo administration.
- To estimate microbiological outcome at EOT and at TOC.

Exploratory:

- To describe the time to clearance of *S. aureus* bacteremia (defined as blood cultures negative for 2 consecutive days).
- To describe the time to defervesence (defined as the highest oral temperature equivalent on day of assessment < 38.0°C [< 100.4°F]).
- To describe all-cause mortality.
- To explore the relationship between CF-301 exposures and safety and efficacy endpoints.
- To describe post-dose immunologic response to CF-301.
- To explore the relationship between baseline and post-dose immunologic parameters and safety and efficacy endpoints.
- To describe clinical and microbiological outcomes in the subset of patients with methicillin-resistant *S. aureus* (MRSA) infections.
- To describe clinical and microbiological outcomes by diagnosis.
- To describe relapse and re-infection rates.
- To describe changes in cardiac valve vegetations, valvular function, and cardiac tissue in patients with endocarditis.

- To describe the occurrence of clinical evidence of septic emboli and metastatic *S. aureus* infections.
- To explore health resource utilization, including total length of hospital stay, days in the intensive care unit (ICU), 30-day readmission for *S. aureus* BSI/endocarditis, and surgery for treatment of *S. aureus* BSI/endocarditis.

Study Design:

This is a randomized, multicenter, multinational, double-blind, study to evaluate the safety, tolerability, efficacy, and PK of CF-301 vs. placebo in addition to SOC antibacterial therapy for the treatment of adult patients with *S. aureus* BSI including endocarditis. Patients who meet all screening criteria and have blood culture positive for *S. aureus* determined by rapid diagnostic or conventional method or Gram stain showing Gram-positive cocci in clusters plus positive tube coagulase test from blood culture specimens collected within 72 hours prior to randomization are eligible for the study.

Approximately 115 patients will be randomized in a 3:2 ratio to one of two treatment groups:

- Group 1: CF-301 in addition to SOC antibacterial therapy (70 patients)
- Group 2: Placebo in addition to SOC antibacterial therapy (45 patients)

Patients who are randomized will receive a single dose of CF-301 or placebo over a 2-hour infusion in addition to appropriate SOC antibacterial therapy.

Standard-of-care antibacterial therapy will be selected by the investigator based on standard practice at the site, treatment guidelines (Liu et al., 2011; Baddour et al., 2015), and other local guidelines. Standard-of-care agents include daptomycin and vancomycin for MRSA and semi-synthetic penicillins (e.g., nafcillin, oxacillin, cloxicillin, flucloxacillin) and first-generation cephalosporins (e.g., cefazolin) for methicillin-susceptible *S. aureus* (MSSA). If susceptibility is not known at the time of randomization, the patient should 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, SOC may be changed at the investigator's discretion based on susceptibility results to one of the SOC options described above. Standard-of-care should be administered at the doses and durations specified in the manufacturer's prescribing information, treatment guidelines (Liu et al., 2011; Baddour et al., 2015), other local guidelines, and clinical practice. The suggested duration of SOC treatment is 28 to 42 days for complicated bacteremia and/or endocarditis and 42 to 84 days for osteomyelitis. Patients with known or suspected uncomplicated bacteremia are not eligible for the study; however, if a randomized patient is subsequently determined to have uncomplicated bacteremia, the suggested duration of SOC treatment is approximately 14 days. The investigator will determine diagnosis at screening and during the study to determine treatment duration.

An overall clinical assessment, including a detailed evaluation of signs and symptoms of *S. aureus* BSI, will occur at screening. Intravenous catheters known or suspected to be infected must be removed or changed and replaced at a different site as soon as possible within 72 hours after randomization. In patients with central venous catheters (CVCs), ultrasounds to evaluate clots in the vein are recommended within 48 hours after randomization. Two aerobic blood cultures preferably from 2 different sites will be collected at screening at least 30 minutes apart and as close to the start of study drug dosing as possible, and at least one aerobic blood culture will be collected daily during the study until negative for 2 consecutive days and at Days 7 and 14 after CF-301/placebo administration. Additional blood cultures will be performed as clinically indicated. Blood cultures should be collected from a peripheral venipuncture site when possible.

Physical examinations will be performed at screening, daily through Day 7 and on Day 14 after CF-301/placebo administration, at EOT, and at TOC. The physical examinations will include a close

evaluation for any new areas of pain or signs of metastases; new signs should trigger diagnostic testing for metastatic foci.

All patients should have a transthoracic echocardiogram (TTE) within 3 days of randomization. All efforts should be made to perform this TTE before administration of study drug. 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 and the TTE within 3 days of randomization does not need to be performed. Patients with endocarditis should have a follow-up TTE between Days 7 and 14; where possible, a transesophageal echocardiogram (TEE) should also be performed (Baddour et al., 2015; Habib et al., 2010; Habib et al., 2015). TEEs are strongly recommended in patients with body mass index (BMI) > 30 kg/m^2. The site will provide all echocardiograms to the central echocardiography laboratory.

Safety monitoring will include adverse event (AE) monitoring, physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical safety laboratory tests, and immunological monitoring. Safety monitoring will be performed during the core study from screening through TOC, and a long-term follow-up will occur at Day 180 after CF-301/placebo administration. An independent Data Safety Monitoring Board (DSMB) will review unblinded safety data throughout the core study as defined in the DSMB charter.

Blood samples for PK will be collected as described in the "**Pharmacokinetics**" section below.

Clinical response will be assessed by the investigator. The Adjudication Committee will assess clinical response at predefined intervals. The efficacy analysis of clinical response will be based on the Adjudication Committee's assessment.

Number of patients (planned): Approximately 115 patients with *S. aureus* BSI will be randomized (3:2) to receive a single dose of CF-301 or placebo.

A sample size of approximately 70 patients in the CF-301 treatment group and 45 patients in the placebo group will provide at least 80% power to detect a treatment difference of 25% in clinical response rate at Day 14 after CF-301/placebo, based on expected clinical improvement or response rates of 60% and 85% in the placebo and CF-301 treatment groups, respectively, using a two-sided target alpha level of 0.05 and Fisher's exact test.

Inclusion Criteria:

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

1. Male or female, 18 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 positive tube coagulase test from blood culture specimens. (Note: the 72-hour time period starts at the time the specimen is **collected** for blood culture).
3. At least two of the following signs or symptoms:
    a. Shortness of breath
    b. Sweating
    c. Fatigue
    d. Confusion
    e. Pain associated with metastatic foci
    f. Fever (oral temperature equivalent ≥ 38.0°C [≥ 100.4°F])
    g. Leukocytosis (white blood cell [WBC] count > 10,000/µL), leukopenia (WBC < 4000/µL), or bandemia (> 10% immature neutrophils [bands] regardless of total peripheral WBC)
    h. Tachycardia (heart rate > 100 bpm)
    i. Tachypnea (respiratory rate > 20 breaths/min)

j. Hypotension (systolic blood pressure < 90 mmHg)

4. Patients must have:
   a. Known or suspected right- and/or left-sided endocarditis by Modified Duke Criteria (see protocol appendix)

      and/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. Signs or symptoms of catheter-related infection with clots in the vein at the catheter site seen on ultrasound
      iii. Signs or symptoms of metastatic foci of *S. aureus* infection (e.g., deep tissue abscess, septic pulmonary emboli) or hematogenous seeding (e.g., septic arthritis) confirmed by physical examination, imaging, or culture
      iv. *S. aureus* isolated from sterile body site other than blood
      v. Persistent fever (oral temperature equivalent ≥ 38.0°C [≥ 100.4°F]) at 72 hours or more after the initial blood culture
      vi. Skin examination findings suggesting the presence of acute systemic infection (e.g., presence of ecchymosis, infarcts, petechiae, pustules, or vasculitis)
      vii. Met criteria for severe sepsis or septic shock during the time of diagnosis/presumptive diagnosis of bacteremia
         - Severe sepsis defined as documented or presumed infection associated with either organ dysfunction, hypoperfusion, or hypotension (systolic blood pressure < 90 mm Hg or a decrease of > 4 mm Hg from baseline systolic measure in the absence of other causes of hypotension) AND the presence of systemic inflammatory response syndrome (SIRS), defined by at least 2 of the following:
            - Temperature (oral, rectal, tympanic, or core) > 38.5°C (> 101.3°F) or < 35.0°C (< 95.0°F)
            - Heart rate > 90 beats/minute
            - Respiratory rate > 20 breaths/minute or partial pressure of arterial carbon dioxide (PaCO2) < 32 mmHg or on a ventilator
            - Leukocytosis (> 12,000 WBC/µL), leukopenia (< 4000 WBC/µL), or bandemia (> 10% immature neutrophils [bands] regardless of total peripheral WBC)
         - Septic shock defined as persistent hypotension and perfusion abnormalities despite adequate fluid resuscitation or organ function not capable of maintaining homeostasis
      viii. Significantly immunocompromised:
         - AIDS (HIV positive with an AIDS-defining condition or a CD4 count < 200 cells/mm³)
         - Severe leukopenia defined as ANC <500 cells/mL for ≥ 3 days in the 7 days prior to the qualifying blood culture
         - Post organ-transplantation including autologous bone marrow transplantation
         - On treatment for active graft vs. host disease

- On immunosuppressive therapy (e.g., ≥ 15 mg of prednisone or equivalent for more than 5 days, biologics such as infliximab, monoclonal antibodies such as daclizumab, methotrexate, cyclophosphamide, or similar agents)
- On chemotherapy treatment

or

c. At least one of the following risk factors:
   i. Preexisting valvular heart disease
   ii. Surgery within the previous 30 days that puts the patient at risk for nosocomial bacteremia (e.g., orthopedic, cardiothoracic, or intraabdominal surgery)
   iii. Extravascular foreign material (Note: removal of extravascular foreign material known or suspected to be infected is required within 72 hours after randomization)
   iv. Hemodialysis

5. Patient is not pregnant or breastfeeding and meets one of the following criteria:
   a. A female patient who is not of reproductive potential is eligible without requiring the use of contraception. This includes females 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 and male patients of reproductive 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 should 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. If the patient is not able to provide informed consent, he/she can be enrolled according to local regulatory requirements.

Exclusion Criteria:

1. Patient previously received CF-301.
2. Treatment with any potentially effective (anti-staphylococcal) systemic antibiotic for more than 72 hours within 7 days before randomization.
   EXCEPTION: Documented resistance to the prior systemic antibacterial therapy.
3. Treatment with dalbavancin or oritavancin for the current infection.
   Note: patients who are receiving teicoplanin, linezolid, telavancin, ceftaroline fosamil, and/or sulfamethoxazole/trimethoprim are eligible for the study provided that treatment is switched to an appropriate SOC antibacterial agent (SOC agents include daptomycin and vancomycin for MRSA and semi-synthetic penicillins [e.g., nafcillin, oxacillin, cloxicillin, flucloxacillin] and first-generation cephalosporins [e.g., cefazolin] for MSSA.
4. MRSA isolate is known or suspected to have intermediate susceptibility or resistance to vancomycin or daptomycin.

5. Presence of any removable infection source (e.g., intravascular line, abscess, dialysis graft) that will not be removed or debrided within 72 hours after randomization.
6. Presence of an infected prosthetic joint, or presence of a prosthetic cardiac valve, cardiac valve support ring, or other implantable cardiac device (e.g., left ventricular assist device [LVAD]) **if** the patient is scheduled for surgical removal of the prosthetic valve, ring, or implantable device during the 24 hours after randomization. Note: patients with implantable cardioverter defibrillators and permanent pacemakers are eligible for enrollment, and patients with prosthetic cardiac values, cardiac value support rings, or other implantable cardiac devices who are NOT scheduled for surgery during the 24 hours after randomization are eligible for enrollment.
7. Endocarditis with severe aortic or mitral valve regurgitation on TEE or TTE, or any paravalvular abscess, with scheduled surgery for endocarditis.
8. Known or suspected brain abscess.
9. Known or suspected meningitis. Note: Evidence of metastatic complications related to the primary infection such as septic arthritis and septic pulmonary infarcts are permitted.
10. Asplenia in patients with creatinine clearance < 60 mL/min by Cockcroft-Gault using ideal body weight in patients with BMI ≥ 30 kg/m^2 or on dialysis.
11. Community acquired pneumonia, nosocomial pneumonia due to pathogens **other than** *S. aureus*, or known polymicrobial bacteremia (i.e., more than one pathogen in the blood). Note: patients with nosocomial pneumonia due to *S. aureus* are eligible for enrollment.
12. Patient is not expected to survive through Day 14 of the study due to underlying disease (e.g., end-stage cancer).
13. Patient participated or plans to participate in an interventional investigational drug, device, or diagnostic trial within 30 days or 5 half-lives of investigational drug, whichever is longer, prior to or during the study.
14. Other comorbid condition or laboratory abnormality that would, in opinion of investigator, pose safety risk for patient to participate or pose risk to patient's ability to complete the study.
15. Patient is employed by the sponsor or investigational site or is a first degree relative of a person employed by the sponsor or investigational site. Patient is institutionalized by administrative or court order.

Investigational product, dosage and mode of administration:

- CF-301 will be administered at a dose of 0.25 mg/kg, with a maximum dose of 30 mg for patients who weigh ≥ 120 kg.
- Patients with creatinine clearance of < 60 mL/min (including patients on dialysis) will receive a dose of 0.12 mg/kg, with a maximum dose of 15 mg for patients in this subset who weigh ≥ 125 kg. In patients on hemodialysis, CF-301/placebo will be administered either ≥ 8 hours prior to hemodialysis or ≥ 4 hours after the end of hemodialysis.
- Patients who are > 50 years of age will receive a dose of 0.12 mg/kg, with a maximum dose of 15 mg for patients in this subset who weigh ≥ 125 kg.

If analyses by the DSMB support further dose reductions or dose increases up to 0.4 mg/kg based on accrued PK exposure data in specific patient demographic groups, these will be described in Administrative Amendments or Clarification Letters to the protocol. If the accrued PK data suggest the need for an increase in dose above the 0.4 mg/kg dose defined in the original protocol, then a protocol amendment will be issued.

CF-301 will be provided as a sterile injectable solution in 10 mL vials. Each vial will contain 4.0 mL of CF-301 (10 mg/mL). CF-301 will be diluted as specified in the Pharmacy Manual and

administered as a 2-hour IV infusion using an IV set with an in-line filter (0.2 or 0.22 μm) with corresponding pump.
Reference therapy, dosage and mode of administration: Placebo (vehicle control) will be provided as a sterile injectable solution in 10 mL vials. Each vial will contain 4.0 mL of placebo. Placebo will be administered diluted as specified in the Pharmacy Manual and administered as a 2-hour IV infusion using an IV set with an in-line filter (0.2 or 0.22 μm) with corresponding pump.
Duration of treatment: Patients will receive a single dose of CF-301 or placebo in addition to SOC antibacterial therapy. The duration of SOC will generally be from 28 to 84 days based on the patient's diagnosis (28 to 42 days for complicated bacteremia/endocarditis and 42 to 84 days for osteomyelitis), the investigator's discretion, treatment guidelines, and standard practice.
Duration of study (for each patient): Each patient is expected to complete the core study (through TOC) in approximately 6 to 10 weeks, including screening, randomization, an estimated duration of approximately 28 to 42 days SOC, EOT visit, and TOC at 28-days after the end of SOC treatment. Patients with osteomyelitis are expected to complete the core study (through TOC) in approximately 10 to 16 weeks, since estimated duration of SOC is 42 to 84 days. The study includes a long-term follow-up visit at Day 180 after CF-301/placebo administration for collection of an immunogenicity sample and assessment of SAEs and re-infection. The ability of the patient to return for the Day 180 visit is not required for enrollment in the study, but the visit is highly encouraged. With the long-term follow-up through Day 180 after CF 301/placebo administration, the total study duration is approximately 25 weeks.
Criteria for evaluation: **Safety and Immunogenicity:** Adverse events will be monitored during the core study, from the time of consent through TOC. Patients must be directly observed during CF-301/placebo infusion, and vital signs (blood pressure, respiratory rate, and heart rate) will be performed approximately every 30 to 40 minutes during the infusion and at approximately 30 to 40 minutes after the infusion. In patients who have clinical signs and symptoms of allergic reactions to CF-301, the infusion should 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. If a patient experiences signs and symptoms consistent with anaphylaxis (Simons, et al., 2011), blood samples for serum tryptase and CF-301-specific IgE will be collected as soon as possible within 2 hours. If the serum tryptase sample is positive or equivocal, the sample may also be tested for β-tryptase. Another blood sample for serum tryptase will be collected 2 weeks later. Safety laboratory tests (biochemistry, hematology, coagulation, and urinalysis) will be performed at randomization (pre-dose), at approximately 2 to 4 hours after the start of CF-301/placebo infusion (for the first 17 patients randomized), on Day 2, weekly during SOC, at EOT, and at TOC. Safety laboratory tests will be performed by a central laboratory. A 12-lead ECG will be performed at screening, at approximately 2 to 4 hours after the start of CF-301/placebo infusion (for the first 17 patients randomized), on Day 2, at EOT, and at TOC. Physical examination will be performed at screening, daily through Day 7 and on Day 14 after CF-301/placebo administration, at EOT, and at TOC. Complete physical examinations will be performed at screening, Day 14, EOT, and TOC. The physical examinations performed daily through Day 7 will be targeted physical examinations to evaluate for complications of BSI and will include assessments of head, eye, ear, nose, throat (HEENT), lungs, heart, skin for any evidence of emboli, and palpation for signs of pain. Pain on physical examinations should trigger diagnostic testing for metastatic foci.

Vital signs will be performed at screening, approximately every 30 to 40 minutes during CF-301/placebo infusion and at approximately 30 to 40 minutes after the infusion, daily during SOC for inpatients (and at weekly scheduled visits for patients who are discharged [i.e., at the Day 7 and Day 14 visits, and weekly thereafter]), at EOT, and at TOC. Vital signs will include blood pressure, respiratory rate, and heart rate during infusion and blood pressure, respiratory rate, heart rate, and temperature at all other time points.

Blood samples will be collected for CF 301-specific anti-drug antibody (ADA) and IgE at randomization (pre-dose), Day 14, at EOT, at TOC, and on Day 180 after CF 301/placebo administration. All testing will be performed at central laboratories, as described in the laboratory manual.

If the patient agrees in the informed consent to have blood stored for optional future research (e.g., cytokine and chemokine assays and/or biomarker evaluation), 2 samples (1 serum and 1 plasma) will be collected at randomization (pre-dose), 12 to 24 hours after CF-301/placebo dosing, on Day 7, and at EOT and TOC. Note: future use samples will NOT be collected from patients in Israel.

An independent DSMB will review accruing safety, tolerability, immunogenicity, and PK data in an unblinded manner throughout the study, as detailed in the DSMB charter. The Sponsor and study staff will remain blinded throughout the study. The DSMB will conduct an initial unblinded review of safety, tolerability, and PK data after approximately 17 patients have PK data available (approximately 10 patients on CF-301 and approximately 7 patients on placebo). The DSMB will also assess whether the PK target for the 0.25 mg/kg dose has been attained as predicted from the population PK data from the Phase 1 study. If the mean exposure to CF-301 is significantly lower (e.g., by > 25%) or higher than the mean exposure in healthy volunteers in Study CF-301-101 dosed at 0.25 mg/kg (i.e., the target safe and efficacious exposure), then to achieve the planned exposure target the DSMB may recommend dose adjustment. Enrollment will not be halted during the conduct of this review.

After completion of the core study, all serious adverse events (SAEs) will be collected during the long-term follow-up through Day 180.

Vital status (whether the patient is alive or dead, or last known alive date) will be obtained at Day 180 or when a patient is deemed to be lost to follow-up. The patient's vital status should be determined using available sources (e.g., the patient's relatives, hospital records, and/or public records) as permissible based on local laws and regulations.

Efficacy:

Signs and symptoms of *S. aureus* BSI/endocarditis will be evaluated at screening, daily during SOC for inpatients (and at weekly scheduled visits for patients who are discharged [i.e., at the Day 7 and Day 14 visits, and weekly thereafter]), at EOT, and at TOC.

Two aerobic blood cultures preferably from 2 different sites will be collected at screening at least 30 minutes apart and as close to the start of study drug dosing as possible, and at least one aerobic blood culture will be collected daily during the study until negative for 2 consecutive days and at Days 7 and 14 after CF-301/placebo administration. Additional blood cultures will be performed as clinically indicated. Blood cultures should be collected from a peripheral venipuncture site when possible.

In patients with CVCs, ultrasounds to evaluate clots in the vein are recommended within 48 hours after randomization.

Physical examinations will be performed at the time points described above under the "**Safety**" subsection and will include a close evaluation for any new areas of pain or signs of metastases; new signs should trigger diagnostic testing for metastatic foci. Metastatic foci identified through Day 7 post-randomization are considered related to the patient's baseline *S. aureus* infection; new metastatic foci identified after Day 7 post-randomization are considered progression of the *S. aureus* infection.

All patients should have a TTE within 3 days of randomization. All efforts should be made to perform this echocardiogram before administration of study drug. 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 and the echocardiogram within 3 days of randomization does not need to be performed. Patients with endocarditis should have a follow-up TTE between Days 7 and 14; where possible, a TEE should also be performed (Baddour et al., 2015; Habib et al., 2010; Habib et al., 2015). TEEs are strongly recommended in patients with BMI > 30 kg/m^2. The site will provide all echocardiograms to the central echocardiography laboratory.

Clinical and microbiological outcome will be assessed at Days 7 and 14 after CF-301/placebo administration, at EOT, and at TOC.

Clinical outcome will be assessed by the investigator and the independent Adjudication Committee. The signs and symptoms evaluated for clinical outcome assessments are presence of shortness of breath, sweating, fatigue, confusion, pain associated with metastatic foci, fever, leukocytosis, leukopenia, bandemia, tachycardia, tachypnea, and hypotension.

Re-infection will be assessed at Day 180 after CF-301/placebo administration for patients who meet the definition of response at TOC. Re-infection will be assessed by the investigator and the independent Adjudication Committee.

Definitions for clinical outcomes and re-infection are provided in Table 1 and Table 2, respectively.

Table 1: Clinical Outcome Definitions at Day 7 (± 1 day), Day 14 (± 1 day), EOT (+ 2 days), and at TOC (±4 days)

Clinical Outcome	Definition
Improvement ***(Days 7 and 14 only)***	• Improvement in all attributable signs and symptoms of *S. aureus* BSI which were present at baseline[a], • No new, worsening, or persistent signs and symptoms attributable to *S. aureus* BSI, • No development of a new foci of *S. aureus* infection after Day 7[b] • SOC for *S. aureus* BSI is ongoing with no need to[c]: ▪ add a SOC antibacterial agent due to persistent or worsening *S. aureus* BSI, ▪ switch to a different SOC antibacterial agent due to persistent or worsening *S. aureus* BSI, or ▪ increase SOC dose due to persistent or worsening *S. aureus* BSI, • No further surgery or medical intervention for *S. aureus* BSI is necessary, and • The patient is alive.
Response[d]	• Complete resolution of attributable signs and symptoms of *S. aureus* BSI which were present at baseline, • No new signs and symptoms attributable to *S. aureus* BSI, • No development of a new foci of *S. aureus* infection after Day 7[b] • No further antibacterial therapy for *S. aureus* BSI is necessary, • No further surgery or medical intervention for *S. aureus* BSI is necessary, and • The patient is alive.
Non-response[d]	• Persistence, worsening, or recurrence of attributable signs and symptoms of *S. aureus* BSI which were present at baseline, • New signs and symptoms attributable to *S. aureus* BSI, • Development of a new foci of *S. aureus* infection after Day 7[b], • Complications of *S. aureus* BSI, • SOC for *S. aureus* BSI was changed to[c]: ▪ add a SOC antibacterial agent due to persistence, worsening, or recurrence of *S. aureus* BSI, ▪ switch to a different SOC antibacterial agent due to persistence, worsening, or recurrence of *S. aureus* BSI, or ▪ increase the dose of SOC due to persistence, worsening, or recurrence of *S. aureus* BSI, • >12 weeks of SOC antibacterial therapy for *S. aureus* BSI and/or related infection (e.g., osteomyelitis), • Further surgery or medical intervention for *S. aureus* BSI is necessary (e.g., valvular surgery for progressive *S. aureus* BSI), or • Death due to any cause.
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow up • Withdrawal of consent • Extenuating circumstances that preclude the classification of clinical response

a. Symptoms will be assessed as absent, mild, moderate, and severe. All symptoms present at baseline must improve by one category (e.g., from moderate to mild) in order for a patient to be considered as having improvement.
b. Does not apply at Day 7 assessment. Metastatic foci identified through Day 7 post-randomization are considered baseline; new metastatic foci identified after Day 7 post-randomization are considered progression of the *S. aureus* infection.
c. Per protocol, patients may be treated empirically and SOC may be changed once susceptibly data become available, as described in the "Study Design" section. A change in SOC based on susceptibility data from the blood culture collected within 72 hours prior to randomization does not count as "non-response".
d. At Test-of-Cure, response = cure and non-response = failure.

Table 2: Clinical Re-Infection Definitions at Day 180 (±14 days)

Clinical Outcome[a]	Definition
No re-infection	Between TOC and Day 180, the patient did **not** have *S. aureus* BSI/endocarditis or *S. aureus* infection at any body site (this includes infections that the investigator considers to be relapses as well as those that the investigator considers to be new *S. aureus* infections).
Re-infection	Between TOC and Day 180, the patient had *S. aureus* BSI/endocarditis and/or developed a *S. aureus* infection at any body site documented by a positive culture for *S. aureus* (this includes infections that the investigator considers to be relapses as well as those that the investigator considers to be new *S. aureus* infections).
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow up • Withdrawal of consent • Extenuating circumstances that preclude the classification of clinical response

a. Patients who meet the definition of response at TOC will be assessed for re-infection.

Definitions for microbiological response (Days 7 and 14) and microbiological outcome (End of SOC and TOC) are provided in Table 3 and Table 4, respectively.

Table 3: Microbiological Response Definitions at Day 7 (± 1 day) and Day 14 (± 1 day)

Microbiological Response	Definitions
Clearance of bacteremia	Blood cultures collected on or prior to assessment were negative for *S. aureus* on 2 consecutive days.
Ongoing bacteremia	Blood cultures collected on or prior to assessment continue to be positive for *S. aureus*
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow up • Withdrawal of consent • Extenuating circumstances that preclude the classification of microbiological response

Table 4: Microbiological Outcome Definitions at EOT (+ 2 days) and at TOC (±4 days)

Microbiological Outcome	Definitions
Eradication	Blood cultures were negative for *S. aureus* on 2 consecutive days.
Presumptive Eradication	Follow-up blood cultures were not done and the patient has responded clinically, as defined in Table 1.
Persistence	Blood cultures continue to be positive for *S. aureus*
Presumed Persistence	Follow-up blood cultures were not done and the patient has not responded clinically, as defined in Table 1.
Relapse	Patient was previously classified as having "clearance of bacteremia", "eradication", or "presumptive eradication", and subsequently a blood culture was positive for *S. aureus*.
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow up • Withdrawal of consent • Extenuating circumstances that preclude the classification of microbiological response

Pharmacokinetics (PK):

Blood samples will be collected for PK assessment of CF-301 in 3 subsets of patients as listed below. Pharmacokinetic samples will be collected from patients in both the CF-301 group and the placebo group to maintain the blind.

- ***PK Subset 1*:** A minimum of approximately 17 patients and up to approximately 34 patients (30%) will give serial PK samples at the following time points: pre-dose, 0.5 (30 minutes), 1.5 (1 hour 30 minutes), 2, 2.25 (2 hours 15 minutes), 3, 4, 8, 14, 24, and 48 hours after the start of study drug infusion. The sponsor will determine if additional patients will give serial PK samples in Subset 1 based on ongoing review of accrued PK data, and the number of patients giving limited PK samples (Subsets 2 and 3 below) will be reduced accordingly. Note: PK Subset 1 will not be conducted in Israel.
- ***PK Subset 2*:** Approximately 40 patients (35%) will give limited PK samples at the following time points: 2.25 (2 hours 15 minutes), 3, 8, and 24 hours after the start of study drug infusion.
- ***PK Subset 3*:** Approximately 40 patients (35%) will give limited PK samples at the following time points: 2.25 (2 hours 15 minutes), 4, 8, and 24 hours after the start of study drug infusion.

Permitted time windows are as follows:

- ± 10 minutes around the samples at 0.5 and 1.5 hours after the start of infusion
- - 10 minutes before the sample at the end of infusion (the sample is to be drawn before the infusion is complete and can be obtained up to 10 minutes before the end of the infusion. Note that if the sample is drawn after the infusion is complete in error, it is still to be collected and the exact clock time should be recorded).
- ± 10 minutes around the samples at 2.25, 3, and 4 hours after the start of infusion
- ± 1 hour around the sample at 8 hours after the start of infusion
- ± 2 hours around the samples at 14 and 24 hours after the start of infusion.
- ± 4 hours around the sample at 48 hours after the start of infusion.

PK parameters of CF-301 will be assessed from patients with serial PK sampling, including maximum plasma concentrations (C_{max}), time to C_{max} (T_{max}), elimination half-life ($T_{1/2}$), clearance (CL), volume of distribution (Vz), and area under the curve (AUC_{0-t} and $AUC_{0-\infty}$).

Pharmacodynamics (PD):

The pharmacokinetic/pharmacodynamic (PK/PD) parameters include AUC_{0-24hr}/minimum inhibitory concentration (MIC), C_{max}/MIC, and %Time > MIC over a 24-hour period. PK/PD parameters will be calculated for patients who have MICs available.

Statistical methods:

A Statistical Analysis Plan (SAP) will be prepared and finalized before database lock and analyses of data. Summary data will be tabulated and presented by treatment group.

Safety:

Safety will be evaluated by presenting summaries of treatment emergent AEs (TEAEs), clinical laboratory evaluations (biochemistry, hematology, coagulation, and urinalysis), vital signs (blood pressure, respiratory rate, heart rate, and temperature) and ECGs. Abnormal physical examination results will be recorded as AEs. A treatment emergent AE is one that occurs on or after the first dose of study drug through TOC.

Adverse events will be coded using the Medical Dictionary of Regulatory Activities. The incidence of TEAEs will be presented by system organ class (SOC) and preferred term (PT), by SOC, PT and relationship to study drug, and by SOC, PT and severity. Serious AEs and TEAEs that lead to discontinuation of the study drug will also be presented by SOC and PT. Descriptive statistics for clinical laboratory, vital signs and ECG parameters, including change from baseline, will be presented by time point collected and for the overall most abnormal post-baseline value. Incidences of potentially clinically significant clinical laboratory results, vital signs and ECG parameters, as defined in the SAP, will also be summarized by time point collected and the overall most abnormal post-baseline value.

Efficacy:

The primary efficacy outcome is clinical improvement or response at Day 14 after CF-301/placebo administration in the microbiological intent-to-treat (mITT) population. The number and percentage of patients with an improvement/response, no response, and indeterminate will be determined by treatment group. Exact 2-sided 95% confidence intervals for the point estimates of the clinical improvement/response rates in each treatment group will be determined using the Clopper-Pearson method. The clinical improvement/response rate will be compared between the treatment groups using Fisher's exact test. Statistical significance will be based on a two-sided alpha level of 0.05.

The number and percentage of patients with a clinical outcome of improvement/response, no response, and indeterminate will be determined by treatment group at Day 7 after CF-301/placebo administration, at EOT, and at TOC in the mITT population. Exact 2-sided 95% confidence intervals for the point estimates of the clinical improvement/response rates in each treatment group will be determined using the Clopper-Pearson method. Statistical comparisons between the treatment groups will be conducted using Fisher's exact test and p-values will be provided as explorative statistics.

The number and percentage of patients with a microbiological response of clearance of bacteremia, ongoing bacteremia, and indeterminate will be determined by treatment group at Days 7 and 14 after CF-301/placebo administration in the mITT population. The number and percentage of patients with a microbiological outcome of eradication/presumptive eradication, persistence/presumptive persistence, and indeterminate will be determined by treatment group at EOT and TOC in the mITT population. Exact 2-sided 95% confidence intervals for the point estimates of the clearance of bacteremia or microbiological eradication/presumptive eradication rates in each treatment group will be determined using the Clopper-Pearson method. Statistical comparisons between the treatment groups will be conducted using Fisher's exact test and p-values will be provided as explorative statistics.

Kaplan-Meier methods will be utilized to determine the time to clearance of bacteremia in the mITT population. Time to clearance of bacteremia will be defined as the date/time from study drug administration to the date/time of the first negative blood culture of the two negative blood cultures taken on 2 consecutive days. Patients whose SOC for BSI was changed by adding a SOC antibacterial agent, switching to a different SOC antibacterial agent, or increasing the dose of SOC due to persistence, worsening, or recurrence of *S. aureus* BSI, died prior to clearance of bacteremia or

withdrew from the study will be censored at the date/time of the SOC change, death or study withdrawal, respectively.

Pharmacokinetics:

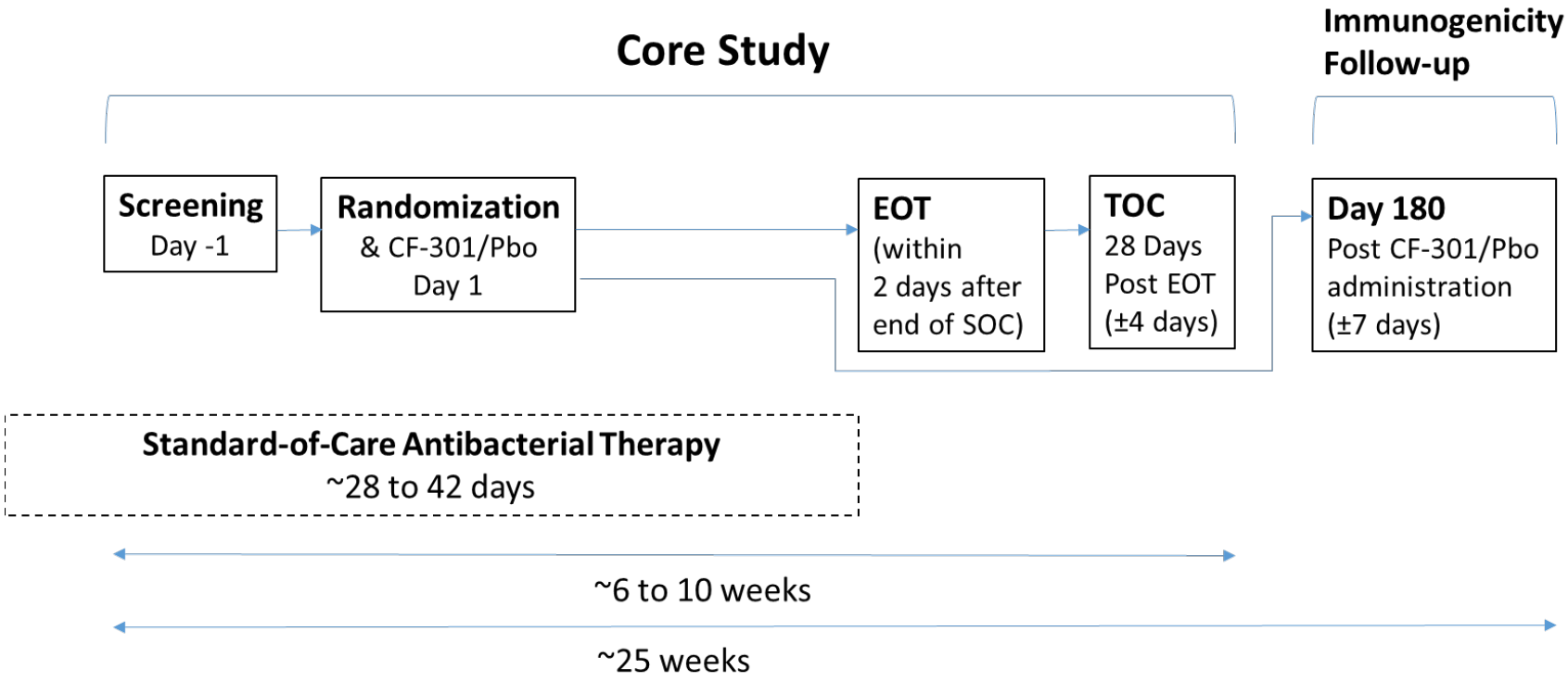
Data collected from Subset 1 will be used to determine the following PK parameters: C_{max}, T_{max}, $T_{1/2}$, CL, Vz, AUC_{0-t}, and $AUC_{0-\infty}$. These values along with the listings for plasma concentrations from all 3 subsets (Subsets 1 to 3) will be reported in the Clinical Study Report (CSR).

All PK data collected in this study (Subsets 1, 2, and 3) will be pooled with the PK data collected from the previous Phase 1 study (Protocol CF-301-101) to update the previously developed population PK model; this will be reported in a separate report, which will include the target attainment analysis. The population PK and target attainment analyses will be described in a separate analysis plan.

Pharmacodynamics:

PK/PD analysis will be conducted to determine the AUC_{0-24hr}/MIC, C_{max}/MIC, and %Time > MIC ratios. PK/PD parameters of CF-301 will be calculated for patients who have MICs available. Exposure response will be evaluated for efficacy and safety endpoints and will be detailed in a separate analysis plan (as described above in the Pharmacokinetics section).

3. STUDY SCHEMATIC



Abbreviations: EOT = End of standard-of-care antibacterial therapy; Pbo = placebo; SOC = standard-of-care antibacterial therapy; TOC = test-of-cure visit 28 days after the EOT.

4. SCHEDULE OF ASSESSMENT / STUDY FLOW CHART

Core Study							Immunogenicity Follow-Up Day 180 Post CF-301/Pbo (±14 days)[c]
Study Procedures	**Screening Day -1 (≤ 24 hours of randomization)[a]**	**Treatment (CF-301/Placebo + SOC)**			**EOT (within 2 days after last dose of SOC)**	**TOC 28 Days Post EOT (±4 days)[c]**	
		Randomization/ Dosing Day 1[a]	**Day 2**	**Subsequent days of SOC[b]**			
Informed consent	X						
I/E criteria	X						
Medical history & risk factors[d]	X						
Apache II score[e]		X					
Diagnosis[f]	X			Day 7			
Safety labs[g]	X	X	X	Weekly	X	X	
12-Lead ECG[h]	X	X	X		X	X	
Physical exam[i]	X	X	X	Daily to D7, D14	X	X	
Weight and height	X						
Vital signs[j]	X	X	X	Daily	X	X	
Symptoms of infection[k]	X	X	X	Daily	X	X	
Blood cultures[l]	X	Daily until negative for 2 days, at D7 & D14, and as clinically indicated					
Pregnancy test[m]	X	X			X	X	
Remove/change IV catheter[n]		Within 72 h after randomization					
Echocardiography[o]		X		X			
Ultrasound of CVC site[p]		Within 48 h after rand.					
PK samples[q]		X	X				
CF-301 ADA & IgE[r]		X		Day 14	X	X	X
Serum tryptase[s]							
Optional future research[t]		X	X	Day 7	X	X	
CF-301 or placebo dosing[u]		X					
AE assessment[v]	X	X	X	X	X	X	SAEs
Prior/concomitant meds[w]	X	X	X	X	X	X	
Outcome assessment				Days 7 & 14	X	X	X[x]
Vital status							X[y]

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BSI = bloodstream infection; CRF = case report form; DR = drug related; EOT = end of standard-of-care treatment; FSH = follicle stimulating hormone; h = hour; HEENT = head, eyes, ears, nose, throat; I/E = inclusion/exclusion; Pbo = placebo; PE = physical examination; PK = pharmacokinetic; rand. = randomization; SOC = standard-of-care; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram; TOC = test of cure.

a. Patients should be randomized as soon as possible after confirmation of study eligibility. However, to provide flexibility, screening assessments may be performed within 24 hours before randomization. Dosing should occur as soon as possible after randomization and within 24 hours of randomization.
b. When a specific "Day" or "D" is noted (e.g., Day 7, D7), the days are relative to CF-301/placebo administration unless otherwise noted. There is a ±1-day window around the procedures performed on Days 7 and 14.
c. The core study ends at TOC performed 28 days after the end of SOC. A long-term follow-up visit occurs at Day 180 after CF-301/placebo for collection of an immunogenicity sample and assessment of SAEs and re-infection. The ability of the patient to return for the Day 180 visit is not required for enrollment in the study, but the visit is highly encouraged.
d. Medical history for 1 year prior to screening.
e. Certain components of the Apache II score will be determined locally (including oxygenation, Glasgow Coma Scale, and chronic health points) and other components will be obtained from central laboratory data.
f. The investigator will determine diagnosis at screening and on Day 7 to determine treatment duration.
g. *Local Laboratory*: Limited safety laboratory tests may need to be performed locally at screening for study eligibility determination (e.g., serum creatinine to calculate creatinine clearance by Cockcroft-Gault formula using ideal body weight in patients with BMI ≥ 30 kg/m^2 (Section 12.2) to determine the dose of study drug, FSH as applicable). If local laboratory results are available within the 72 hours prior to screening, these may be used to support eligibility. *Central Laboratory*: Samples for safety laboratory tests (biochemistry, hematology, coagulation, and urinalysis) collected at randomization (pre-dose), at approximately 2 to 4 hours after the start of CF-301/placebo infusion (for the first 17 patients randomized), on Day 2, weekly during SOC, at EOT, and at TOC. Samples are sent to a central lab.
h. 12-lead ECG at screening, at approximately 2 to 4 hours after the start of CF-301/placebo infusion (for the first 17 patients randomized), on Day 2, at EOT, and at TOC.
i. PE at screening, daily through Day 7 and on Day 14, at EOT, and at TOC. Complete PEs will be performed at screening, Day 14, EOT, and TOC and include evaluation of the HEENT, neck, lungs, heart, chest, abdomen, extremities, neurological status, skin for any evidence of emboli, palpation for signs of pain, and any other notable conditions. Targeted PEs will be performed daily through Day 7 and include evaluation for complications of BSI, HEENT, lungs, heart, skin for any evidence of emboli, and palpation for signs of pain. Pain on PEs should trigger diagnostic testing for metastatic foci.
j. Vital signs at screening, approximately every 30 to 40 minutes during CF 301/placebo infusion and at approximately 30 to 40 minutes after the infusion, daily during SOC for inpatients (and at weekly scheduled visits for patients who are discharged [i.e., at the Day 7 and Day 14 visits, and weekly thereafter]), at EOT, and at TOC. Vital signs will include blood pressure, respiratory rate, and heart rate during/after infusion and blood pressure, respiratory rate, heart rate, and temperature at all other time points. If more than one measurement is taken on a given day, record the highest value for temperature and most abnormal value for other vital signs in the CRF.
k. Symptoms of infection at screening, daily during SOC for inpatients (and at weekly scheduled visits for patients who are discharged [i.e., at the Day 7 and Day 14 visits, and weekly thereafter]), at EOT, and at TOC.
l. For study eligibility, patients have blood culture positive for *S. aureus* by rapid diagnostic or conventional method or Gram stain showing Gram-positive cocci in clusters plus positive tube coagulase test from blood culture collected within 72 hours prior to randomization; this qualifying blood culture will be collected in the eCRF. Additionally, two aerobic blood cultures preferably from 2 different sites will be collected at screening at least 30 minutes apart and as close to the start of study drug dosing as possible, and at least one aerobic blood culture daily during the study until negative for 2 consecutive days and at Days 7 and 14 and as clinically indicated. Blood cultures should be collected from a peripheral venipuncture site when possible. All blood cultures performed during the study (from the qualifying blood culture through to Day 180), including blood cultures that are positive or negative for *S. aureus*, should be entered in the eCRF. *S. aureus* isolates, including the isolate from the qualifying blood culture, are sent to the central lab.
m. For females of reproductive potential only: Urine or serum pregnancy test performed locally at screening for eligibility determination; blood sample collected for serum pregnancy test performed by the central lab at randomization, EOT, and TOC.
n. IV catheters known or suspected to be infected must be removed or changed as soon as possible within 72 hours after randomization.
o. All patients should have a TTE within 3 days of randomization. All efforts should be made to perform this TTE before administration of study drug. 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 and the TTE within 3 days of randomization does not need to be performed. Patients with endocarditis should have a follow-up TTE between Days 7 and 14; where possible, a TEE should also be performed. TEEs are strongly recommended in patients with BMI > 30 kg/m^2. The site will provide all echocardiograms to the central echocardiography laboratory.

p. In patients with central venous catheters (CVCs), ultrasounds to evaluate clots in the vein are recommended within 48 hours after randomization.
q. *PK Subset 1*: pre-dose, 0.5 (30 minutes), 1.5 (1 hour 30 minutes), 2, 2.25 (2 hours 15 minutes), 3, 4, 8, 14, 24, and 48 hours after the start of study drug infusion. Note: PK Subset 1 will not be conducted in Israel.
PK Subset 2: 2.25 (2 hours 15 minutes), 3, 8, and 24 hours after the start of study drug infusion.
PK Subset 3: 2.25 (2 hours 15 minutes), 4, 8, and 24 hours after the start of study drug infusion.
r. Blood samples for CF 301-specific ADA and IgE at randomization (pre-dose), Day 14, EOT, TOC, and Day 180; samples are sent to the central lab.
s. If a patient experiences signs and symptoms consistent with anaphylaxis (Simons, et al., 2011; Section 11.2.3.1), blood samples for serum tryptase and CF-301-specific IgE will be collected as soon as possible within 2 hours. If the serum tryptase sample is positive or equivocal, the sample may also be tested for β-tryptase. Another blood sample for serum tryptase will be collected 2 weeks later. Samples are sent to a central lab.
t. If patient consents to optional future research, two samples (1 serum and 1 plasma) for cytokine and IgE will be collected at randomization (pre-dose), 12 to 24 hours after dosing, on Day 7, and at EOT and TOC. Samples are sent to a central lab. Note: future use samples will NOT be collected in Israel.
u. Patients must be directly observed during CF-301/placebo infusion, and vital signs (blood pressure, respiratory rate, and heart rate) will be performed during/after infusion as described above. CF-301 will be administered at a dose of 0.25 mg/kg, with a maximum dose of 30 mg for patients who weigh ≥ 120 kg. Patients with creatinine clearance of < 60 mL/min (including patients on dialysis) will receive 0.12 mg/kg, with a maximum dose of 15 mg for patients in this subset who weigh ≥ 125 kg. In patients on hemodialysis, CF-301/placebo will be administered either ≥ 8 hours prior to hemodialysis or ≥ 4 hours after end of hemodialysis. Patients who are > 50 years of age will receive a dose of 0.12 mg/kg, with a maximum dose of 15 mg for patients in this subset who weigh ≥ 125 kg.
v. AEs will be collected from the time of consent through TOC. After completion of the core study, all SAEs will be collected during the long-term follow-up through Day 180. For patients who are unable to return for the Day 180 visit, this information may be obtained via phone or email.
w. All medications taken within 28 days before randomization and through the EOT will be recorded, and only antibacterial medications or medications to treat AEs will be recorded after EOT through TOC.
x. Re-infection between TOC and Day 180 will be assessed for patients who meet the definition of response at TOC.
y. Vital status (whether the patient is alive or dead, or last known alive date) will be obtained at Day 180 or when a patient is deemed to be lost to follow-up. The patient's vital status should be determined using available sources (e.g., the patient's relatives, hospital records, and/or public records) as permissible based on local laws and regulations.

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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
ADA	Anti-drug antibody
AE	Adverse event
Apache II	Acute Physiology and Chronic Health Evaluation II Score
AR	Authorized representative
$AUC_{0-\infty}$	Area under the concentration-time curve to infinity
AUC_{0-t}	Area under the concentration time curve
BAT	Basophil activation test
BSI	Blood stream infection
CF-301	Bacteriophage-derived lysin
CFR	Case Fatality Rate
CL	Clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
CRO	Contract Research Organization
CVC	Central Venous Catheter
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
Echo	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
FSH	Follicle stimulating hormone
GM	Geometric Mean
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IRB	Institutional Review Board
IWRS	Interactive web response system
LAR	Legally authorized representative
LR	Legal representative
MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant *S. aureus*
MSSA	Methicillin susceptible *S. aureus*
PI	Principal Investigator
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SIRS	Systemic Inflammatory Response Syndrome
SOC	Standard-of-care (antibacterial agent) or system organ class (for statistical analysis)
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
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

CF-301, a recombinantly-produced bacteriophage-derived lysin, is the first of a new class of highly targeted, protein-based therapies to enter clinical development. Lysins are a new class of antimicrobials consistent of bacteriophage-derived cell-wall hydrolases. CF-301 represents a novel, highly potent and targeted therapeutic for *Staphylococcus aureus* (*S. aureus)* blood steam infections (BSIs) to augment conventional antibiotics which are the current standard of care.

S. aureus, a virulent pathogen in humans, is a leading cause of bacteremia and endocarditis. *S. aureus* BSIs including endocarditis are associated with substantial morbidity and mortality. For example, in 2011, the United States Centers for Disease Control (CDC) estimated that there were 80,461 serious methicillin-resistant *S. aureus* (MRSA) infection cases in the United States, all of which required hospitalization, resulting in up to 11,285 deaths (Dantes 2013). *S. aureus* BSI is often associated with complications, including metastatic bone and soft tissue infections, endocarditis, and recurrent infections. Complicated *S. aureus* BSI requires extended duration treatment with antibiotic therapy, 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, standard-of-care (SOC) antibiotics are unable to penetrate. The availability of a new, highly effective treatment of *S. aureus* BSI remains an area of high unmet medical need due to the high degree of morbidity and mortality, potentially lengthy treatment burden, and the increasing prevalence of multidrug resistant strains.

In *in vitro* experiments, CF-301 exhibits potent activity against all strains of *S. aureus*, including those that demonstrate resistance to currently available therapies such as vancomycin, daptomycin, and linezolid. *In vitro* and *in vivo* studies have demonstrated CF-301 to have a very rapid onset of bactericidal action and synergistic effect when administered in combination with SOC antibiotic treatments for *S. aureus* BSI (e.g. daptomycin). Importantly, while biofilm formation limits the efficacy of SOC antibiotics in the treatment of complicated *S. aureus* bacteremia (including endocarditis), CF-301 demonstrates potent ability to clear biofilms in *in vivo* and *in vitro* models. In vitro, CF-301 exhibits low potential to develop resistance and can reduce the propensity for the development of resistance to SOC antibiotics when co-administered.

ContraFect considers these nonclinical data to be highly predictive of human response, and as such, considers CF-301 to offer significant potential to improve patient outcomes when administered in combination with SOC antibiotics for the treatment of *S. aureus* bacteremia.

7.1.2. Overview of *S. aureus* Blood Stream Infections

S. aureus is a leading cause of bacteremia 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., endocarditis; Fowler et al, 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 infective endocarditis. The incidence of infective endocarditis in the setting of *S. aureus* BSI has been estimated to be 10-15% (Fowler et al, 2003; Chang et al, 2003; Valente et al, 2005), although incidence as high as 21% has been reported (Chang et al, 2003). Risk factors for infective endocarditis 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 et al, 2003; El-Ahdhab et al, 2005; Hill et al, 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 et al, 2005). 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 et al, 2006; Snygg-Martin et al, 2008; García-Cabrera et al, 2013). Silent cerebrovascular complications (including ischemia and microhemorrhage) may occur in up to 80% of patients (Snygg-Martin et al, 2008; Cooper et al, 2009). The in-hospital mortality rate for infective endocarditis is estimated to be 18 to 23% and the six-month mortality rate has been estimated to be between 22 to 27% (Wallace et al, 2002; Chu et al, 2004; Hasbun et al, 2003; Hill et al, 2007; Wang et al, 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 intravascular catheters and/or surgical drainage of abscess if present; López-Cortès et al, 2013). Empiric treatment with antibiotic therapy that has activity against both MRSA and methicillin-susceptible *S. aureus* (MSSA) is generally indicated when blood cultures with Gram-positive cocci are observed (Kim et al, 2008; McConeghy et al, 2013). Treatment failure is fairly common in patients with *S. aureus* BSI, particularly among those patients with infection due to MRSA (Lodise et al, 2008). Drug-resistance, toxicity related to high dose/long duration therapy, and biofilm formation that cannot be cleared by standard of care antibiotics 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 20-40% (Anantha et al, 2014; Van Hal et al, 2012).

The threat of antibiotic resistance among bloodstream *S. aureus* isolates, and in particular, the increasing prevalence of methicillin resistance and the emergence of multi-drug resistance are of concern. Among 24,000 nosocomial bloodstream infections in the United States between 1995 and 2002, the proportion of MRSA isolates increased from 22% to 57% (Wisplinghoff et al, 2004). Mortality associated with MRSA bacteremia has been reported to be higher than mortality associated with MSSA bacteremia (Shurland et al, 2007; Cosgrove et al, 2003). Both the CDC and the World Health Organization (WHO) regard

antibiotic resistance as one of the greatest threats to human health worldwide, with *S. aureus* bloodstream infections, especially MRSA, categorized as a "serious threat" by the CDC.

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., MRSA with vancomycin minimum inhibitory concentration [MIC] >1.5 μg/mL), intermediate vancomycin resistance (VISA), and high-level vancomycin resistance (VRSA) are associated with worse clinical outcomes (Bayer, 2013). Use of daptomycin, an alternative to vancomycin, has grown over the past decade. Risk factors for the emergence of daptomycin resistance include previous exposure to vancomycin, infection with a MRSA strain with a vancomycin MIC of 2 μg/mL or greater, and treatment with insufficient doses of vancomycin (Moise et al, 2008; Rose et al, 2007; Fowler et al, 2006).

As noted by Fowler et al (2005), while the introduction of penicillin to treat *S. aureus* BSI drastically decreased the case fatality rate (CFR) of *S. aureus* BSI from ~80% in the pre-antibiotic era, CFRs reported over recent decades have plateaued in the ~15-50% range (Fowler et al, 2005). This continued high mortality rate may be, at least in part, reflective of a relative plateau in antibiotic efficacy. Hence, there is a medical need for novel, highly effective, targeted new treatments for *S. aureus* BSI, with limited propensity for resistance and with the potential for synergistic efficacy and reduced resistance when used in combination with existing agents. A treatment that would target all forms of *S. aureus* BSI would offer advantages over a treatment specific for specific strains (e.g., MRSA) by potentially enabling faster initiation of treatment, without the need to first determine the susceptibility of the *S. aureus* strain. Thus, a therapeutic agent, such as CF-301 would afford the opportunity to address a wider range of resistant strains quickly, potentially helping to prevent or slow the spread of resistant strains.

7.1.4. CF-301 for the Treatment of *S. aureus*

CF-301, a novel, targeted, antibacterial therapy for the treatment of *S. aureus* BSI, represents the first of a new field of protein-based therapies called bacteriophage-derived lysins. In nature, lysins are highly specific enzymes produced by bacteriophages that digest the bacterial cell wall to allow phage progeny release. CF-301 is a purified recombinant lysin that is fundamentally distinct from conventional antibiotics. When added externally to *S. aureus* bacteria, CF-301 creates immediate lysis upon contact with the cell wall, causing log-fold death of the target bacterium. Whereas most conventional antibiotics target a broad spectrum of bacteria, including pathogenic and normal flora, lysins are highly targeted to specific bacterial species. CF-301 specifically targets staphylococci, including MSSA and MRSA as well as strains that are non-susceptible to vancomycin and daptomycin. The highly targeted nature of CF-301 reduces the potential for biological toxicity associated with negative effects of broad-spectrum antibiotics on the human microbiome including the killing of beneficial normal flora.

CF-301 is distinct from current standard of care antibiotics due to: (1) its novel mechanism of action; (2) bactericidal activity against antibiotic-resistant *S. aureus*; (3) rapid onset of antibacterial activity both i*n vitro* and *in vivo*; (4) narrow lytic spectrum of action; (5) potent

activity against biofilms; (6) synergistic activity with standard of care antibiotics (oxacillin, vancomycin, and daptomycin; (7) low propensity to develop bacterial resistance; and (8) ability to protect against the emergence of resistance to standard of care antibiotic therapies when used in combination. CF-301 activity has been evaluated in multiple preclinical disease models that indicate its ability to address the limitations of these current standard of care antibiotics against *S. aureus.*

Full details of the background and development of CF-301 are available in the Investigator's Brochure.

7.1.5. Preclinical Studies

The efficacy of CF-301 was tested in two murine *S. aureus* bacteremia models. CF-301 was administered as a single or multiple doses, either alone or in combination with SOC antibiotics (daptomycin, vancomycin or oxacillin). Results from these studies demonstrated that:

- CF-301 was effective in mouse bacteremia and neutropenic thigh infection models either as a single-agent or in combination with daptomycin, vancomycin, or oxacillin. In a rat endocarditis model, CF-301 was effective in combination with daptomycin.
- CF-301 performed synergistically against *S. aureus* isolates in combination with daptomycin, vancomycin, and oxacillin, and significantly improves the clearance of bacterial burden in tissues and the survival of mice in models of *S. aureus* bacteremia (including infections with a biofilm component), compared with antibiotic monotherapy.
- CF-301 demonstrated *in vivo* activity against *S. aureus* biofilm in a mouse *S. aureus* infected catheter implant model alone and in combination with daptomycin.
- AUC/MIC is the PK-PD index most predictive of efficacy in the murine neutropenic thigh infection model. AUC/MIC values $\geq$1.5 and $\geq$0.5 are supportive of efficacy as a single-agent and in combination with daptomycin, vancomycin, and oxacillin.

Using the mouse neutropenic thigh infection model, AUC/MIC was determined to be the PK/PD index most predictive of efficacy of CF-301 administered either alone or in combination with daptomycin, vancomycin or oxacillin.

- The minimal AUC/MIC ratios required to achieve bactericidal efficacy for CF-301 as a single-agent was ≥1.5 and CF-301 in combination with daptomycin was ≥0.3 and with vancomycin or oxacillin was ≥0.5. In the mouse neutropenic thigh infection model with a catheter biofilm implant, a similar AUC/MIC value of ≥ 0.5 was determined to be correlated with efficacy.

Target Attainment analysis utilizing population PK modeling for the purpose of supporting CF-301 dose selection for Phase 2 clinical evaluation was performed and demonstrates that in patients with *S. aureus* BSIs, doses of 0.25 mg/kg and 0.4 mg/kg, given as a 2-hour infusion (in the presence of SOC antibacterial therapy (e.g., daptomycin), are predicted to be efficacious. Nonclinical studies have been conducted to support clinical development: (1.) Pharmacokinetic and distribution studies; (2.) Safety pharmacology studies were conducted under GLP in rats and

dogs to assess the effects of CF-301 on the central nervous system (CNS) as well as cardiovascular or respiratory function; (3.) single-dose and repeat-dose GLP toxicology studies conducted in rats and dogs; (2) genotoxicity study (Ames); (4.) special toxicity studies; and (5.) exploratory studies to determine the key PK parameter (AUC or C_{max}) most correlated with toxicity. The proposed route of administration and dosing regimen in human clinical trials is a single 2-hour IV infusion. Therefore, the GLP *in vivo* rat and dog nonclinical toxicology studies utilized 2-hour IV infusions. The rat was identified as the more sensitive toxicity species. A summary of these studies is provided below.

- CF-301 is a therapeutic protein, which like other proteins undergoes catabolism by multiple tissues to small peptides and individual amino acids, without the need for metabolic enzymes, such as cytochromes and are not actively transported across membranes. Therefore, the potential for drug-drug interactions with CF-301 is low. Further, because CF-301 undergoes catabolism in multiple organ, excretion in urine is not a route of elimination and was not found and is not expected in humans.

- The half-life of CF-301 was short (< 1 hour in rats and 1.2-2.93 hours in dogs) and clearance was higher than the GFR in both species. CF-301 distributed over total body water in both rats and dogs, indicating that CF-301 is distributed outside of the vascular space. There was no accumulation of CF-301 following 7 consecutive days of IV QD dosing via 2-hour infusion.

- CF-301 has no direct pharmacological effects on the 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 three doses administered one week apart and was shown to be secondary to ADA formation. A similar response was not observed after a single administration, even at a high dose.

- Following single doses of CF-301 in rats up to 25 mg/kg, anti-CF-301 antibodies were detected 14 days after dosing, with increasing numbers of positive samples identified with increasing doses. Following 7 daily repeated doses of up to 50 mg/kg/day in rats and dogs, titers of anti-CF-301 antibodies were detectable in a few animals on Day 8 (following last dose) and increased in incidence and titer by days 15 and 29 post dose, but the presence of anti-CF-301 antibodies did not affect the clearance of or exposure to CF-301. The results were consistent with a typical immune response with regard to the timeline of appearance of ADA.

- Data from a GLP single-dose rat toxicity study. The following key observations were made:

    - Perivascular/adventitial findings surrounding the pulmonary arteries, the primary toxicological observation following a single 2-hour IV infusion, occurred at a low incidence and minimal severity at 10 and 25 mg/kg and resolved during a 14-day recovery period.

    - The no observed effect level (NOEL) was 2.5 mg/kg following a single dose in the rat (the most sensitive species) and translates to a human dose of 0.4 mg/kg.

  - The no observed adverse effect level (NOAEL) was 25 mg/kg following a single dose in the rat.

- In 7-day GLP repeat-dose toxicity studies, dose-dependent adventitial findings in both rats and dogs were the dose-limiting toxicity observations. Compared to a single dose of CF-301 where the adventitial finding was of low incidence, minimal severity, and reversible at dose of ≤ 25 mg/kg, following repeated doses of CF-301, the adventitial finding increased in incidence, severity, and tissue distribution in medium to larger blood vessels of multiple tissues. There was evidence of reversibility of the lesions as well as progression to chronicity of the lesions at higher doses of ≥ 10 mg/kg/day in rats and dogs, following a 21 days post-infusion treatment-free recovery period.

- A series of special toxicity studies was conducted and demonstrated that:

  - Enzymatically-active CF-301 produced the adventitial vascular reactions whereas enzymatically-inactive CF-301 did not; and

  - CF-301 produced signs and symptoms of hypersensitization response in 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). See information on clinical immunogenicity in Sections 7.1.6 and 7.2 and the IB.

- A series of exploratory studies in the rat was 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. The goal of these investigations was to support the dose rationale for the Phase 2 clinical study by correlating the observation of arterial adventitial findings with either C_{max} or AUC experimentally and by an unbiased Neural Network modeling. Overall, the exploratory studies and Neural Network analyses concluded that AUC is the PK parameter most associated with an observation of an arterial adventitial/ perivascular finding in the pulmonary arteries.

- The exposure limit at the stopping rules for the first in human Phase 1 study was based on the NOEL dose of 2.5 mg/kg in the rat that showed a C_{max} value of 1940 ng/mL. The associated AUC_{0-24} was 2520 ng•h/mL. These values were derived from a single rat TK study with only 18 rats. Along with the FIH Phase 1 study, several more toxicology studies were conducted that brought up the total number of rats to 270 and dogs to 78. Cross-species PK modeling of the totality if the TK data was performed to better define the exposure levels at the Cmax and AUC at the rat NOEL dose of 2.5 mg/kg:

  - Based on this collective analysis, the predicted mean AUC_{0-24} was 3596 ng•h/mL and the predicted mean C_{max} was 1754 ng/mL following a single 2.5 mg/kg 2-hour infusion of CF-301 (the rat NOEL dose).

In summary, the efficacy and safety of CF-301 has been evaluated nonclinical. Based on data from standard mouse models of efficacy, target attainment simulations were performed. These

showed that in patients with *S. aureus* BSIs, doses of 0.25 mg/kg and 0.4 mg/kg, given as a 2-hour infusion (in the presence of SOC antibacterial therapy (e.g., daptomycin, vancomycin, or oxacillin), are predicted to be efficacious. The toxicity of CF-301 has been characterized and the dose-responsiveness evaluated. Based on the current understanding of the nature of the adventitial findings and the absence of any clinical signs, body weight changes, clinical pathology changes or other parameters that could be easily monitored, the proposed clinical doses have been shown to provide exposure below the predicted C_{max} and AUC values at the rat NOEL dose of 2.5 mg/kg.

Additional detail on the preclinical studies can be found in the CF-301 Investigator's Brochure.

7.1.6. Clinical Studies

CF-301 has been evaluated in one Phase 1 clinical study, CF-301-101, which was a double-blind, randomized, study to evaluate the safety, tolerability, and pharmacokinetics (PK) of single, escalating IV doses of CF-301 in healthy male and female subjects. Pre-defined stopping rules were included in the protocol and an independent Data Safety Monitoring Board (DSMB) reviewed safety and PK data at pre-specified time points 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 CF-301-specific antidrug antibody [ADA], CF-301-specific immunoglobulin E [IgE], and ex vivo CF-301-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 active drug CF-301 (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.

CF-301 was generally safe and well tolerated during study CF-301-101. There were no deaths, no serious adverse events (SAEs), and no discontinuations due to adverse events (AEs) during the study. There were no infusion reactions or adverse events of hypersensitivity related to CF-301 reported. A total of 5 non-serious AEs were reported by 4 subjects: 2 subjects who received CF-301 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 treatment emergent adverse event (TEAE) (headache in the CF-301 group) was considered related to study drug. The number of TEAEs observed in the placebo and CF-301 groups was similar and the incidence of AEs among subjects who received CF-301 was not dose-dependent.

Pharmacokinetic parameters of CF-301 are summarized in Table 3. After IV infusion of CF-301, 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 (GM) $t_{½}$ ranged from 4.37 to 6.58 hours for the first 3 cohorts, independent of dose, and was 11.3 hours for the 1 subject in Cohort 4 with individual subject values ranging from 4.33 to 14.7 hours across the 4 cohorts with no apparent relationship to dose.

Table 3: Phase 1 Pharmacokinetic Parameters for CF-301 (Study CF-301-101)

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) [1.00 – 2.00]	2.00 (4) [1.88 – 2.02]	2.00 (4) [1.48 – 2.00]	2.00 (1) [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%) dosed with CF-301 developed CF-301-specific ADA (7 by Day 28 and 2 by Day 90). 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 CF-301 were reported. No subjects tested positive for CF-301-specific basophil activation test (BAT). Consideration of this single, transient low-level signal for CF-301-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, CF-301 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 CF-301 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% of subjects developed CF-301-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 CF-301 in urine.

Additional detail on Study CF-301-101 can be found in the CF-301 Investigator's Brochure.

7.2. Risks and Benefits

Pre-clinical pharmacology and toxicity studies (Section 7.1.5) indicate that a single dose of CF-301 at 0.25mg/kg administered to patients with *S. aureus* BSIs including endocarditis is anticipated to be an efficacious dose with exposures well below the levels which were associated with toxicity in animal models. Animal infection model results are considered to be highly predictive of human efficacy in antibacterials. Furthermore, the Phase 1, single ascending dose clinical study of CF-301 demonstrated CF-301 to be well tolerated, with no adverse clinical safety signals, with a linear PK profile at the intended dose for use in this Phase 2 (0.25 mg/kg).

The Phase 2 study will evaluate the safety, tolerability, efficacy and PK of CF-301 in addition to SOC antibacterial therapy in patients with complicated *S. aureus* BSIs (bacteremia) including

endocarditis. As previously described (Sections 7.1.2 and 7.1.3), *S. aureus* BSIs including endocarditis are highly morbid conditions, which result in substantial morbidity and mortality despite currently available, SOC antistaphylococcal antibiotics. An important objective of the Phase 2 study is to evaluate whether CF-301 in addition to SOC antibacterial therapy improves clinical outcomes in these patients compared to SOC alone. As such, all patients in this study will be treated with SOC antibacterial therapy for *S. aureus* BSI or endocarditis based on current guidelines. The therapeutic benefits and side effects of SOC antibacterial agents are documented in the prescribing information and published literature.

Patients will be randomized to receive a single dose of CF-301 or placebo in addition to SOC antibacterial therapy, and no patients in the study will be treated with the experimental therapy, CF-301, alone. Together with the favorable safety and tolerability profile in Phase 1, a single dose of CF-301 may provide additional clinical benefit over and above the benefit of SOC treatment, which allows for a positive benefit/risk ratio.

Since this is the first time that CF-301 will be studied in patients with *S. aureus* BSIs, a rigorous safety monitoring plan has been put in place. All patients will be dosed in a hospital setting and all patients will be closely monitored for safety and tolerability by repeated assessment of AEs, physical examinations, vital signs, 12 lead electrocardiograms (ECGs), clinical safety laboratory tests, and immunological tests. Patients will be directly observed during CF-301/placebo infusion, and vital signs (blood pressure, respiratory rate, and heart rate) will be performed approximately every 30 to 40 minutes during the infusion and at approximately 30 to 40 minutes after the infusion. An independent DSMB will review unblinded safety data throughout the study as defined in the DSMB charter.

As CF-301 is a protein-based therapeutic, and therefore hypersensitivity is possible, patients will be monitored closely for immunologic responses to CF-301 both clinically and by laboratory measurement of CF-301- specific ADA and CF-301-specific IgE. Importantly, in the Phase 1 study, no hypersensitivity related to CF-301 was observed. Furthermore, the incidence and magnitude of pre-existing (pre-dose) CF-301-specitic-IgE in CF-301-naïve healthy subjects and patients with *S. aureus* bacteremia has been evaluated and found to be low. Taken together, this provides strong evidence to support the conclusion that the risk of immediate, IgE-mediated, allergic reaction to CF-301 in the present Phase 2 study is low.

Although some CF-301-naïve healthy subjects and patients with *S. aureus* bacteremia have been found to have measurable pre-existing (pre-dose) CF-301-specific ADAs, the clinical relevance of these findings is unknown. The current study consists of only a single dose of CF-301. Patients will be dosed in a hospital setting and directly observed during CF-301/placebo infusion, and vital signs (blood pressure, respiratory rate, and heart rate) will be performed approximately every 30 to 40 minutes during the infusion and at approximately 30 to 40 minutes after the infusion. In patients who have clinical signs and symptoms of allergic reactions to CF-301, the infusion should 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 (Section 11.2.3). Treatments for acute allergic hypersensitivity reactions should be provided in accordance with standard medical practice.

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

7.3. Population to be Studied

Adult patients with *S. aureus* BSI including endocarditis will be included in this study.

7.4. Rationale for Route and Dose

CF-301 will be administered by IV infusion over 2 hours and is not expected to be orally bioavailable.

CF-301 was shown to be effective as a single dose when given in combination with SOC antibacterial therapy in eradicating *S. aureus* in the neutropenic murine thigh infection models (standard models for assessing anti-infective drug PK/PD parameters [Louie et al., 2001]) as well as in other *in vitro* and *in vivo* models of activity. A population PK analysis was performed on the data from the CF-301-101 study in humans, which was also supported by allometric scaling of the animal PK data extrapolated to humans. The simulations predict that the majority of patients in Study CF-301-102 who would receive a single dose of 0.25 mg/kg CF-301 as a 2-hour IV infusion in combination with SOC antibacterial therapy are expected to achieve AUC/MIC ratios that are equal to or greater than the efficacious AUC/MIC ratios of 0.5 (i.e., the ratio established in a neutropenic thigh model to be efficacious when CF-301 was given with daptomycin). PK/PD modeling of the available animal and human data support a target efficacious dose in humans to be between 0.1 to 0.2 mg/kg. Therefore, a single dose of 0.25 mg/kg CF-301 administered as a 2-hour infusion in combination with SOC antibacterial therapy is anticipated to achieve the desired AUC/MIC ratio of 0.5 or greater in >80% of patients for isolates with an MIC of ≤ 2 μg/ml.

The GLP single-dose toxicity study in rats (Study CF-301-054) established a 2.5 mg/kg dose given as a 2-hour IV infusion in rats as the NOEL. Initially at the IND application, the only available TK/toxicity data was from Study CF-301-052 which was a single daily dose in 72 rats that determined an $AUC_{0\text{-}inf}$ of 2270 ng•h/mL and a C_{max} of 1900 ng/mL associated with this NOEL dose of 2.5 mg/kg. Additional TK and toxicity studies have been performed in order to refine the understanding of the critical C_{max} and AUC exposures associated with adventitial findings that were observed in pulmonary arteries of rats following single 2-hour IV infusion at doses above the NOEL dose.

Cross-species population PK modeling on pooled data from available TK and toxicity studies in both the rats (n=27) and dogs (n=78). The analysis support that a CF-301 NOEL dose of 2.5 mg/kg in rats is associated with an $AUC_{0\text{-}24}$ of 3600 ng•h/mL and a C_{max} of 1750 ng/mL. Further, interrogation of all rat and dog toxicity data by both conventional statistical analysis and Neural Network analysis indicate that total dose and AUC exposures are the most relevant predictors of an adventitial reaction observation in rats administered a 2-hour IV infusion of CF-301 at doses above the 2.5 mg/kg NOEL. Neural Network analysis provides a method for analyzing data with minimal assumption about the nature and type of relationships between variables and allow inclusion of all available variables in one analysis without the need for user selection and provide an additional level assessment compared to conventional statistical analysis.

The population PK modeling data (animal and human) support that a single dose of CF-301 ≤ 0.4 mg/kg administered as a 2-hour IV infusion would not exceed the AUC and C_{max} limits associated with NOEL dose of 2.5 mg/kg 2-hour infusion in rats and would, therefore, be

expected to be well tolerated and not associated with adverse clinical effects. Single doses of CF-301 at 0.25 mg/kg and 0.4 mg/kg administered as 2-hour IV infusions were assessed in study CF-301-101 and were well tolerated, although the 0.4 mg/kg dose was only administered to one subject. Interpretive criteria indicate that the majority of contemporary clinical *S. aureus* isolates have an MIC ≤ 2 µg/ml, and are predicted to be susceptible to CF-301 at 0.25 mg/kg and 0.4 mg/kg doses in humans.

From a benefit/risk perspective, the selected dose of 0.25 mg/kg for the current study is expected to maintain AUC/MIC ratios of > 0.5, which is well above the expected efficacious threshold established in animal efficacy studies, and is expected to result in exposures in humans (AUC and C_{max}) that are approximately two-fold lower than the exposures associated with the NOEL in rats.

Therefore, based on the safety, efficacy, and PK results of study CF-301-101 and cross-species population PK modeling, the clinical efficacy and safety of the CF-301 0.25 mg/kg dose in the current study is predicted to be efficacious by PK/PD target attainment modeling and is predicted to be well within the safety limit of exposure based on PK/TK modeling.

The modeling of the data described in the paragraphs above demonstrates that a single dose of 0.25 mg/kg in humans may be needed to achieve target AUC:MIC ratios of ≥ 0.5 in > 80% patients for isolates with an MIC of > 2 µg/mL. Modeling of the PK data supports that a single dose of 0.4 mg/kg of CF-301 administered as a 2-hour IV infusion would not exceed the modeled $AUC_{0\text{-}24}$ of 3600 ng•h/mL or C_{max} 1750 ng/mL exposure limits associated with the NOEL dose of 2.5 mg/kg established in the rat following a 2-hour IV infusion, as described above.

Following a review of the 0.25 mg/kg dose data from the Phase 2 study by the DSMB (based on predefined criteria described in a DSMB charter), if the observed $AUC_{0\text{-}24}$ turn out to be significantly lower (by >25%) or higher than the target AUCs predicted from the study CF-301-101, the DSMB may recommend that the dose of CF-301 may be adjusted in order to achieve exposure targets.

7.5. Rationale for Inclusion of Patients with Renal Impairment

Patients with renal insufficiency are at high risk for infection with complicated *S. aureus* BSI; therefore, it is anticipated that patients with renal insufficiency may derive benefit from a new therapeutic agent that may provide additional benefit above SOC alone. Therefore, patients with renal insufficiency are an important patient population in which to study the safety, efficacy, and PK of CF-301 on a background on SOC antibacterial therapy.

CF-301 is a recombinant protein with a molecular mass of approximate 26 kDa. Measurement of CF-301 levels in urine of healthy subjects in Study CF-301-101 determined a negligible amount (<0.1% the dose) of CF-301 excreted in urine. The lack of urinary excretion of CF-301 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 CF-301 in mice, IV administration of ^{131}-I-CF-301, resulted in detection of CF-301 in multiple tissues (CF-301-023). The kidneys had

the highest level of CF-301, followed by the liver, spleen, stomach, lung, and blood that was rapidly decreased in the level of CF-301 in the majority of organs, including the kidney, suggesting rapid clearance of CF-301 from the blood and catabolism by multiple tissues. This is consistent with normal catabolism of protein and peptides (Meibohm and Zhou, 2012; Czock et al, 2012; Maack, 1979; Meier et al, 2004; lshimitsu et al, 1994). 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).

Based on the collective CF-301 nonclinical and clinical data and published literature, the main route of elimination for CF-301 is understood to be catabolism and not urinary excretion. Also, even patients with severe renal impairment, retain substantial capacity for protein catabolism (Meibohm and Zhou, 2012; Czock et al, 2012; Maack, 1979; Meier et al, 2004; lshimitsu et al, 1994). Thus, CF-301 dosing in patients with mild and moderate renal impairment (defined as creatinine clearance 30 to 80 mL/min) was not expected to substantially impact CF-301 plasma levels.

Given the single-dose administration paradigm of CF-301, and the potential benefit of CF-301 to patients with renal insufficiency who are at risk for complicated *S. aureus* BSIs, inclusion of patients with mild or moderate renal insufficiency including patients undergoing dialysis was initially planned at a single-dose level of 0.25 mg/kg. Based on the DSMB's review of PK exposure data, patients with creatinine clearance < 60 mL/min (including patients on dialysis) will receive a dose of 0.12 mg/kg. In view of the spleen's role as a major organ for CF-301 catabolism, subjects with creatinine clearance <30 mL/min who are asplenic were excluded from the study under prior versions of the protocol and subjects with creatinine clearance <60 mL/min who are asplenic will be excluded under this amendment. Enrollment and subsequent tolerability and clinical outcome of these patients will be closely monitored as a component of DSMB activities, as described in the DSMB charter. In patients on hemodialysis, CF-301/placebo will be administered either ≥ 8 hours prior to dialysis or ≥ 4 hours after end of dialysis.

As patients with renal insufficiency and *S. aureus* BSIs may benefit from treatment with CF-301, this approach will allow for obtaining data in a patient population with severe renal disease, safeguard the safety of patients in this study, and allow for continued evaluation of CF-301 in this important population.

7.6. 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 Objective

- To describe the safety and tolerability of CF-301 vs. placebo in addition to SOC antibacterial therapy for the treatment of patients with *S. aureus* BSIs including endocarditis.
- To estimate clinical outcome at Day 14 after CF 301/placebo administration.
- To describe the PK parameters of CF-301.

8.2. Secondary Objectives

- To estimate clinical outcome at Day 7 after CF 301/placebo administration, at the end of SOC antibacterial therapy (EOT), and at test-of-cure (TOC) 28 days after the EOT.
- To estimate microbiological response at Days 7 and 14 after CF-301/placebo administration.
- To estimate microbiological outcome at EOT and at TOC.

8.3. Exploratory Objectives

- To describe the time to clearance of *S. aureus* bacteremia (defined as blood cultures negative for 2 consecutive days).
- To describe the time to defervesence (defined as the highest oral temperature equivalent on day of assessment < 38.0°C [< 100.4°F]).
- To describe all-cause mortality.
- To explore the relationship between CF-301 exposures and safety and efficacy endpoints.
- To describe post-dose immunologic response to CF-301.
- To explore the relationship between baseline and post-dose immunologic parameters and safety and efficacy endpoints.
- To describe clinical and microbiological outcomes in the subset of patients with MRSA infections.
- To describe clinical and microbiological outcomes by diagnosis.
- To describe relapse and reinfection rates.
- To describe changes in cardiac valve vegetations, valvular function, and cardiac tissue in patients with endocarditis.
- To describe the occurrence of clinical evidence of septic emboli and metastatic *S. aureus* infections.
- To explore health resource utilization, including total length of hospital stay, days in the intensive care unit (ICU), 30-day readmission for *S. aureus* BSI/endocarditis, and surgery for treatment of *S. aureus* BSI/endocarditis

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design

This is a randomized, multicenter, multinational, double-blind, study to evaluate the safety, tolerability, efficacy, and PK of CF-301 vs. placebo in addition to SOC antibacterial therapy for the treatment of adult patients with *S. aureus* BSI including endocarditis. Patients who meet all screening criteria and have blood culture positive for *S. aureus* determined by rapid diagnostic or conventional method or Gram stain showing Gram-positive cocci in clusters plus positive tube coagulase test from blood culture specimens collected within 72 hours prior to randomization are eligible for the study.

Approximately 115 patients will be randomized in a 3:2 ratio to one of two treatment groups:

- Group 1: CF-301 in addition to SOC antibacterial therapy (70 patients)
- Group 2: Placebo in addition to SOC antibacterial therapy (45 patients)

Patients who are randomized will receive a single dose of CF-301 or placebo (at the doses described in Section 9.4) over a 2-hour infusion in addition to appropriate SOC antibacterial therapy.

Standard-of-care antibacterial therapy will be selected by the investigator based on standard practice at the site, treatment guidelines (Liu et al., 2011; Baddour et al., 2015), and other local guidelines. Standard-of-care agents include daptomycin and vancomycin for MRSA and semi-synthetic penicillins (e.g., nafcillin, oxacillin, cloxicillin, flucloxacillin) and first-generation cephalosporins (e.g., cefazolin) for MSSA. If susceptibility is not known at the time of randomization, the patient should 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, SOC may be changed at the investigator's discretion based on susceptibility results to one of the SOC options described above. Standard-of-care should be administered at the doses and durations specified in the manufacturer's prescribing information, treatment guidelines (Liu et al., 2011; Baddour et al., 2015), other local guidelines, and clinical practice. The suggested duration of SOC treatment is 28 to 42 days for complicated bacteremia and/or endocarditis and 42 to 84 days for osteomyelitis. Patients with known or suspected uncomplicated bacteremia are not eligible for the study; however, if a randomized patient is subsequently determined to have uncomplicated bacteremia, the suggested duration of SOC treatment is approximately 14 days. The investigator will determine diagnosis at screening and during the study to determine treatment duration.

An overall clinical assessment, including a detailed evaluation of signs and symptoms of *S. aureus* BSI, will occur at screening. Intravenous catheters known or suspected to be infected must be removed or changed and replaced at a different site as soon as possible within 72 hours after randomization. In patients with central venous catheters (CVCs), ultrasounds to evaluate clots in the vein are recommended within 48 hours after randomization. Two aerobic blood cultures preferably from 2 different sites will be collected at screening at least 30 minutes apart and as close to the start of study drug dosing as possible, and at least one aerobic blood culture will be collected daily during the study until negative for 2 consecutive days and at Days 7 and 14 after CF-301/placebo administration. Additional blood cultures will be performed as

clinically indicated. Blood cultures should be collected from a peripheral venipuncture site when possible.

Physical examinations will be performed at screening, daily through Day 7 and on Day 14 after CF-301/placebo administration, at EOT, and at TOC. The physical examinations will include a close evaluation for any new areas of pain or signs of metastases; new signs should trigger diagnostic testing for metastatic foci.

All patients should have a transthoracic echocardiogram (TTE) within 3 days of randomization. All efforts should be made to perform this TTE before administration of study drug. 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 and the TTE within 3 days of randomization does not need to be performed. Patients with endocarditis should have a follow-up TTE between Days 7 and 14; where possible, a transesophageal echocardiogram (TEE) should also be performed (Baddour et al., 2015; Habib et al., 2010; Habib et al., 2015). TEEs are strongly recommended in patients with body mass index (BMI) > 30. The site will provide all echocardiograms to the central echocardiography laboratory.

Safety monitoring will include AE monitoring, physical examinations, vital sign measurements, 12-lead ECGs, clinical safety laboratory tests, and immunological monitoring. Safety monitoring will be performed during the core study from screening through TOC, and a long-term follow-up will occur at Day 180 after CF-301/placebo administration. An independent DSMB will review unblinded safety data throughout the core study as defined in the DSMB charter.

Blood samples for PK will be collected.

Clinical response will be assessed by the investigator. The Adjudication Committee will assess clinical response at predefined intervals. The efficacy analysis of clinical response will be based on the Adjudication Committee's assessment.

9.2. Number of Patients

Approximately 115 patients with *S. aureus* BSI will be randomized (3:2) to receive a single dose of CF-301 or placebo.

In a study of *Staphylococcus aureus* bacteremia and endocarditis, 61.7% and 60.9% of patients receiving daptomycin and standard of care therapy in the modified intent to treat population, respectively, were considered a clinical success at the end of therapy (Fowler et al., 2006). The median duration of therapy was 14 days for the daptomycin group and 15 days for the standard of care group. Thus, it is reasonable to assume an expected clinical improvement or response rate of 60% in placebo group.

A sample size of approximately 70 patients in the CF-301 treatment group and 45 patients in the placebo group will provide at least 80% power to detect a treatment difference of 25% in clinical response rate at Day 14 after CF-301/placebo, based on expected clinical improvement or response rates of 60% and 85% in the placebo and CF-301 treatment groups, respectively, using a two-sided target alpha level of 0.05 and Fisher's exact test.

9.3. Treatment Assignment

Approximately 115 patients will be randomized in a 3:2 ratio to one of two treatment groups:

- Group 1: CF-301 (70 patients)
- Group 2: Placebo (45 patients)

9.4. Dosing and Dose Adjustment Criteria

Study Drug

CF-301 and placebo will be provided as sterile injectable solutions in 10 mL vials. Each vial of CF-301 will contain 4.0 mL of CF-301 (10 mg/mL). Placebo (vehicle control) is similar in appearance to CF-301, but does not contain the active ingredient. CF-301 and placebo will be diluted as specified in the Pharmacy Manual and administered as a 2-hour IV infusion.

The dosing scheme is as follows:

- CF-301 will be administered at a dose of 0.25 mg/kg, with a maximum dose of 30 mg for patients who weigh ≥ 120 kg.
- Patients with creatinine clearance of < 60 mL/min (including patients on dialysis) will receive a dose of 0.12 mg/kg, with a maximum dose of 15 mg for patients in this subset who weigh ≥ 125 kg. In patients on hemodialysis, CF-301/placebo will be administered either ≥ 8 hours prior to hemodialysis or ≥ 4 hours after the end of hemodialysis.
- Patients who are > 50 years of age will receive a dose of 0.12 mg/kg, with a maximum dose of 15 mg for patients in this subset who weigh ≥ 125 kg.

If analyses by the DSMB support further dose reductions or dose increases up to 0.4 mg/kg based on accrued PK exposure data in specific patient demographic groups, these will be described in Administrative Amendments or Clarification Letters to the protocol. If the accrued PK data suggest the need for an increase in dose above the 0.4 mg/kg dose defined in the original protocol, then a protocol amendment will be issued.

Patients must be directly observed during CF-301/placebo infusion, and vital signs (blood pressure, respiratory rate, and heart rate) will be performed approximately every 30 to 40 minutes during the infusion and at approximately 30 to 40 minutes after the infusion. In patients who have clinical signs and symptoms of allergic reactions to CF-301, the infusion should 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. If a patient experiences signs and symptoms consistent with anaphylaxis (Simons, et al., 2011; Table 4), blood samples for serum tryptase and CF-301-specific IgE will be collected as soon as possible within 2 hours. If the serum tryptase sample is positive or equivocal, the sample may also be tested for β-tryptase. Another blood sample for serum tryptase will be collected 2 weeks later.

Standard-of-Care Antibacterial Therapy

Standard-of-care antibacterial therapy will be selected by the investigator based on standard practice at the site, treatment guidelines (Liu et al., 2011; Baddour et al., 2015), and other local

guidelines. Standard-of-care agents include daptomycin and vancomycin for MRSA and semi-synthetic penicillins (e.g., nafcillin, oxacillin, cloxicillin, flucloxacillin) and first-generation cephalosporins (e.g., cefazolin) for MSSA. Note: patients who are receiving teicoplanin, linezolid, telavancin, ceftaroline fosamil, and/or sulfamethoxazole/trimethoprim are eligible for the study provided that treatment is switched to a SOC agent.

If susceptibility is not known at the time of randomization, the patient should 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, SOC may be changed at the investigator's discretion based on susceptibility results to one of the SOC options described above.

Standard-of-care should be administered at the doses and durations specified in the manufacturer's prescribing information, treatment guidelines (Liu et al., 2011; Baddour et al., 2015), other local guidelines, and clinical practice.

The suggested duration of SOC treatment is 28 to 42 days for complicated bacteremia and/or endocarditis and 42 to 84 days for osteomyelitis. Patients with known or suspected uncomplicated bacteremia are not eligible for the study; however, if a randomized patient is subsequently determined to have uncomplicated bacteremia, the suggested duration of SOC treatment is approximately14 days. The investigator will determine diagnosis at screening and during the study to determine treatment duration.

Recommended doses for SOC antibacterial agents are as follows:

- 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 being 10 to 20 µg/mL. 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 collected in the CRF. Since red man syndrome is a known side effect of vancomycin, do not administer vancomycin at the same time as study drug. Study drug should be administered either prior to the start of vancomycin infusion or a minimum of 2 hours after vancomycin infusion is complete.
- Daptomycin: 6 to 8 mg/kg once daily

The manufacturer's prescribing information for the SOC antibacterial agents should be referenced for full dosing information.

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 24 hours of randomization), unless otherwise noted below, in order for the patient to be eligible for enrollment:

1. Male or female, 18 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 plus positive coagulase test from blood culture specimens. A list of acceptable rapid diagnostic tests is provided in Section 23.3. (Note: the 72-hour time period starts at the time the specimen is **collected** for blood culture).
3. At least two of the following signs or symptoms:
    a. Shortness of breath
    b. Sweating
    c. Fatigue
    d. Confusion
    e. Pain associated with metastatic foci
    f. Fever (oral temperature equivalent ≥ 38.0°C [≥ 100.4°F])
    g. Leukocytosis (white blood cell [WBC] count > 10,000/µL), leukopenia (WBC < 4000/µL), or bandemia (> 10% immature neutrophils [bands] regardless of total peripheral WBC)
    h. Tachycardia (heart rate > 100 bpm)
    i. Tachypnea (respiratory rate > 20 breaths/min)
    j. Hypotension (systolic blood pressure < 90 mmHg)
4. Patients must have:
    a. Known or suspected right- and/or left-sided endocarditis by Modified Duke Criteria (Section 23.1)

    and/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. Signs or symptoms of catheter-related infection with clots in the vein at the catheter site seen on ultrasound
        iii. Signs or symptoms of metastatic foci of *S. aureus* infection (e.g., deep tissue abscess, septic pulmonary emboli) or hematogenous seeding (e.g., septic arthritis) confirmed by physical examination, imaging, or culture

iv. *S. aureus* isolated from sterile body site other than blood

v. Persistent fever (oral temperature equivalent ≥ 38.0°C [≥ 100.4°F]) at 72 hours or more after the initial blood culture

vi. Skin examination findings suggesting the presence of acute systemic infection (e.g., presence of ecchymosis, infarcts, petechiae, pustules, or vasculitis)

vii. Met criteria for severe sepsis or septic shock during the time of diagnosis/presumptive diagnosis of bacteremia

- Severe sepsis defined as a documented or presumed infection associated with either organ dysfunction, hypoperfusion, or hypotension (systolic blood pressure < 90 mm Hg or a decrease of > 4 mm Hg from baseline systolic measure in the absence of other causes of hypotension) AND the presence of systemic inflammatory response syndrome (SIRS), defined by at least 2 of the following:
  - Temperature (oral, rectal, tympanic, or core) > 38.5°C (> 101.3°F) or < 35.0°C (< 95.0°F)
  - Heart rate > 90 beats/minute
  - Respiratory rate > 20 breaths/minute or partial pressure of arterial carbon dioxide (PaCO2) < 32 mmHg or on a ventilator
  - Leukocytosis (> 12,000 WBC/µL), leukopenia (< 4000 WBC/µL), or bandemia (> 10% immature neutrophils [bands] regardless of total peripheral WBC)
- Septic shock defined as persistent hypotension and perfusion abnormalities despite adequate fluid resuscitation or organ function not capable of maintaining homeostasis

viii. Significantly immunocompromised:

- AIDS (HIV positive with an AIDS-defining condition or a CD4 count < 200 cells/mm³)
- Severe leukopenia defined as ANC <500 cells/mL for ≥ 3 days in the 7 days prior to the qualifying blood culture
- Post organ-transplantation including autologous bone marrow transplantation
- On treatment for active graft vs. host disease
- On immunosuppressive therapy (e.g., ≥ 15 mg of prednisone or equivalent for more than 5 days, biologics such as infliximab, monoclonal antibodies such as daclizumab, methotrexate, cyclophosphamide, or similar agents)
- On chemotherapy treatment

or

c. At least one of the following risk factors:

i. Preexisting valvular heart disease

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

iii. Extravascular foreign material (Note: removal of extravascular foreign material known or suspected to be infected is required within 72 hours after randomization)

iv. Hemodialysis

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

   a. A female patient who is not of reproductive potential is eligible without requiring the use of contraception. This includes females 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 and male patients of reproductive 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 should 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. If the patient is not able to provide informed consent, he/she can be enrolled according to local regulatory requirements (see Section 12.1).

10.2. Exclusion Criteria

1. Patient previously received CF-301.
2. Treatment with any potentially effective (anti-staphylococcal) systemic antibiotic for more than 72 hours within 7 days before randomization.
   EXCEPTION: Documented resistance to the prior systemic antibacterial therapy.
3. Treatment with dalbavancin or oritavancin for the current infection.
   Note: patients who are receiving teicoplanin, linezolid, telavancin, ceftaroline fosamil, and/or

sulfamethoxazole/trimethoprim are eligible for the study provided that treatment is switched to an appropriate SOC antibacterial agent (SOC agents include daptomycin and vancomycin for MRSA and semi-synthetic penicillins [e.g., nafcillin, oxacillin, cloxicillin, flucloxacillin] and first-generation cephalosporins [e.g., cefazolin] for MSSA.

4. MRSA isolate is known or suspected to have intermediate susceptibility or resistance to vancomycin or daptomycin.
5. Presence of any removable infection source (e.g., intravascular line, abscess, dialysis graft) that will not be removed or debrided within 72 hours after randomization.
6. Presence of an infected prosthetic joint, or presence of a prosthetic cardiac valve, cardiac valve support ring, or other implantable cardiac device (e.g., left ventricular assist device [LVAD]) **if** the patient is scheduled for surgical removal of the prosthetic valve, ring, or implantable device during the 24 hours after randomization. Note: patients with implantable cardioverter defibrillators and permanent pacemakers are eligible for enrollment, and patients with prosthetic cardiac values, cardiac value support rings, or other implantable cardiac devices who are NOT scheduled for surgery during the 24 hours after randomization are eligible for enrollment.
7. Endocarditis with severe aortic or mitral valve regurgitation on TEE or TTE, or any paravalvular abscess, with scheduled surgery for endocarditis.
8. Known or suspected brain abscess.
9. Known or suspected meningitis. Note: Evidence of metastatic complications related to the primary infection such as septic arthritis and septic pulmonary infarcts are permitted.
10. Asplenia in patients with creatinine clearance < 60 mL/min by Cockcroft-Gault using ideal body weight in patients with BMI ≥ 30 kg/m^2 (Section 12.2) or on dialysis.
11. Community acquired pneumonia, nosocomial pneumonia due to pathogens **other than** *S. aureus*, or known polymicrobial bacteremia (i.e., more than one pathogen in the blood). Note: patients with nosocomial pneumonia due to S. aureus are eligible for enrollment.
12. Patient is not expected to survive through Day 14 of the study due to underlying disease (e.g., end-stage cancer).
13. Patient participated or plans to participate in an interventional investigational drug, device, or diagnostic trial within 30 days or 5 half-lives of investigational drug, whichever is longer, prior to or during the study.
14. Other comorbid condition or laboratory abnormality that would, in opinion of investigator, pose safety risk for patient to participate or pose risk to patient's ability to complete the study.
15. Patient is employed by the sponsor or investigational site or is a first degree relative of a person employed by the sponsor or investigational site. Patient is institutionalized by administrative or court order.

10.3. Discontinuation Criteria

10.3.1. Discontinuation from Study Drug

Any AE that results in stopping of the study drug infusion is considered an event of clinical interest and must be reported within 24 hours (Section 14.6). Reasons for study drug discontinuation include any of the following:

- Patient is unable or unwilling to complete the study drug infusion
- Patient withdraws informed consent at any time during study drug infusion
- Clinical signs and symptoms of allergic reaction or anaphylaxis to CF-301 (see Section 11.2.3 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 PI and/or Sponsor
- 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 from study drug (i.e., have the infusion stopped before the full dose is administered) should continue to participate in study visits unless consent was withdrawn.

10.3.2. Discontinuation from the Study

Reasons for discontinuation during the core study or during the long-term follow-up include any of the following:

- Patient is unable or unwilling to adhere to the protocol
- Patient is unable to return for the long-term follow-up (Day 180 only)
- Patient withdraws informed consent
- AE (whether or not related to study drug) that precludes further participation in the study in the judgment of the Investigator and/or Sponsor
- Patient lost to follow-up [Note: vital status (whether the patient is alive or dead, or last known alive date) will be obtained when a patient is deemed to be lost to follow-up (Section 12.14)].
- The Investigator considers that it is in the patient's best interest not to continue participation in the study
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

The reasons for withdraw from the core study and during the long-term follow-up will be collected separately on the CRF. The ability of the patient to return for the Day 180 visit is not required for enrollment in the study, but the visit is highly encouraged; patients who are unable to return for the visit should be contacted by phone or email (Section 11.3). If a patient completes the core study, but does not return for the long-term follow-up, he/she will be considered as having completed the core study.

Patients are encouraged to remain in the study for follow up assessments. Sites should contact the sponsor in advance if the investigator is considering withdrawing the patient from the study. Patients who are withdrawn from the core study or during the long-term follow-up will not participate in further study visits, but any AEs should be followed to resolution, as described in Section 14.11.

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 flow chart is provided in Section 3 and a study schematic is provided in Section 3. The study procedures performed at each visit are described in the subsections below.

11.1. Study Duration

Patients will receive a single dose of CF-301 or placebo in addition to SOC antibacterial therapy. The duration of SOC will generally be from 28 to 84 days based on the patient's diagnosis (28 to 42 days for complicated bacteremia/endocarditis and 42 to 84 days for osteomyelitis), the investigator's discretion, treatment guidelines, and standard practice.

Each patient is expected to complete the core study (through TOC) in approximately 6 to 10 weeks, including screening, randomization, an estimated duration of approximately 28 to 42 days SOC, EOT visit, and TOC at 28-days after the end of SOC treatment. Patients with osteomyelitis are expected to complete the core study (through TOC) in approximately 10 to 16 weeks, since estimated duration of SOC is 42 to 84 days.

The study includes a long-term follow-up visit at Day 180 after CF-301/placebo administration for collection of an immunogenicity sample and assessment of SAEs and re-infection. The ability of the patient to return for the Day 180 visit is not required for enrollment in the study, but the visit is highly encouraged. With the long-term follow-up through Day 180 after CF-301/placebo administration, the total study duration is approximately 25 weeks.

11.2. Core Study

11.2.1. Screening

Patients will be screened to determine whether or not they meet the eligibility criteria for the study. Patients should be randomized as soon as possible after confirmation of study eligibility. However, to provide flexibility, screening assessments may be performed within 24 hours before randomization. For the purposes of the visit schedule, screening is considered Day -1.

The qualifying blood culture collected within 72 hours prior to randomization that supports study eligibility will be collected in the eCRF and the isolate will be sent to the central laboratory whenever possible (Section 12.12). In addition, two aerobic blood cultures are collected at screening, as described below.

If local laboratory test results from the patient's routine care are available from the 72 hours before screening, these may be used to support study eligibility determination (Section 12.13).

If the patient had an echocardiogram performed prior to enrollment in the study for the current infection, this will be provided to the central echocardiography laboratory (Section 12.8).

The following procedures will be performed at the time of Screening:

- Informed consent (see Section 12.1)
- Review of inclusion/exclusion criteria
- Medical history for the prior 1 year
- Risk factors for complicated *S. aureus* BSI

- Diagnosis
- Local laboratory testing, if needed for eligibility determination (see Section 12.13), and to determine serum creatinine to calculate creatinine clearance by Cockcroft-Gault formula using ideal weight for patients with BMI ≥ 30 kg/m^2 (Section 12.2) to determine the dose of study drug.
- 12-lead ECG
- Complete physical examination (Section 12.6), including body weight and height.
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature). If more than one measurement is taken on the day assessment, the highest value for temperature and most abnormal value for other vital signs should be recorded in the eCRF.
- Symptoms attributable to *S. aureus* BSI/endocarditis
- Two aerobic blood cultures preferably from 2 different sites will be collected at least 30 minutes apart and as close to the start of study drug dosing as possible (collected via peripheral venipuncture when possible). Results of all blood cultures (including blood cultures that are positive or negative for *S. aureus*) will be entered in the eCRF and *S. aureus* isolates will be sent to the central laboratory (Section 12.12)
- Urine or serum β-hCG pregnancy test for women of reproductive potential only (performed locally study eligibility; see Section 12.13 and Inclusion Criteria in Section 10.1)
- AE assessment from the time informed consent is obtained
- Medication review

11.2.2. Randomization

Patients who are screened and determined to be eligible for the study will be randomized via an interactive web response system (IWRS). For the purposes of the visit structure, the day of CF-301/placebo dosing considered Day 1 of the study. Dosing should occur as soon as possible after randomization and within 24 hours of randomization. The following procedures will be performed on the day of randomization:

- Collect components of Apache II score. Certain components of the Apache II score will be performed locally and collected on the CRF (including oxygenation, Glasgow Coma Scale, and chronic health points) and other components will be obtained from central laboratory data.
- Blood and urine samples for clinical safety laboratory tests pre-dose and approximately 2 to 4 hours after the start of CF-301/placebo infusion (for the first 17 patients randomized). (sent to the central laboratory; see Section 12.13)
- Blood sample for serum pregnancy test for women of reproductive potential only (sent to the central laboratory; see Section 12.13).
- 12-lead ECG at approximately 2 to 4 hours after the start of CF-301/placebo infusion (for the first 17 patients randomized)
- Targeted physical examination (Section 12.6). Note: if the physical examination at screening was performed within 3 hours of randomization, it does not need to be repeated.
- Vital signs:

  - Temperature. If more than one measurement is taken on the day of randomization, the highest temperature should be recorded in the eCRF.
  - Blood pressure, respiratory rate, and heart rate approximately every 30 to 40 minutes during the infusion and at approximately 30 to 40 minutes after the infusion.
- Symptoms attributable to *S. aureus* BSI/endocarditis
- An aerobic blood culture collected prior to CF-301/placebo dosing (collected via peripheral venipuncture when possible). All blood culture (including blood cultures that are positive or negative for *S. aureus*) will be entered in the eCRF and *S. aureus* isolates will be sent to the central laboratory (Section 12.12)
- Intravenous catheters known or suspected to be infected must be removed or changed and replaced at a different site as soon as possible within 72 hours after randomization
- All patients should have a TTE within 3 days of randomization. All efforts should be made to perform this TTE before administration of study drug. 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 and the TTE within 3 days of randomization does not need to be performed. TEEs are strongly recommended in patients with BMI > 30 kg/m^2. The site will provide all echocardiograms to the central echocardiography laboratory.
- Ultrasounds to evaluate clots in the vein are recommended within 48 hours after randomization in patients with CVCs.
- Blood samples for PK at the time points described in Section 12.16.
- Blood samples for immunogenicity samples (ADA, IgE) and optional future research collected pre-dose (to be sent to the central laboratory (Section 12.13). Note: future use samples will NOT be collected from patients in Israel.
- CF-301/placebo dosing. Patients must be directly observed during CF-301/placebo infusion (see Section 11.2.3).
- AE assessment
- Medication review

11.2.3. Study Drug

Patients will receive a single dose of study drug (CF-301 or placebo) as described in Section 9.4.

11.2.3.1. Allergic Reactions / Anaphylaxis

Patients must be directly observed during CF-301/placebo infusion, and vital signs (blood pressure, respiratory rate, and heart rate) will be performed approximately every 30 to 40 minutes during the infusion and at approximately 30 to 40 minutes after the infusion. In patients who have clinical signs and symptoms of allergic reactions to CF-301, the infusion should 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.

If a patient experiences signs and symptoms consistent with anaphylaxis as described in Table 4, blood samples for serum tryptase and CF-301-specific IgE will be collected as soon as possible

within 2 hours. If the serum tryptase sample is positive or equivocal, the sample may also be tested for β-tryptase. Another blood sample for serum tryptase will be collected 2 weeks later. Collection of these samples is important to further support the diagnosis of anaphylaxis. Anaphylaxis should be reported as an SAE (see Section 14).

Table 4: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

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 ONE OF THE FOLLOWING:

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence) **OR**

2. Two or more of the following that occur rapidly after exposure to *a likely allergen[a] for that patient* (minutes to several hours)

   a. Involvement of the skin-mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

Source: Simons, et al., 2011

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

11.2.4. Standard-of-Care Antibacterial Therapy

Standard-of-care antibacterial therapy will be administered as described in Section 9.4.

The eCRF will collect information on the entire course of SOC antibacterial treatment for the patient's current episode of *S. aureus* BSI/endocarditis, including SOC received prior to patient's entry in the study.

For the purposes of the visit schedule, the day of CF-301/placebo dosing is considered Day 1 of the study and each subsequent day during SOC is considered a sequential study day (i.e., Day 2, Day 3, Day 4, etc.).

There is a ±1-day window around the procedures performed on Days 7 and 14.

The following procedures will be performed during SOC:

- Diagnosis assessment on Day 7
- Blood and urine samples for clinical safety laboratory tests on Day 2 and weekly during SOC (sent to the central laboratory; see Section 12.13)
- 12-lead ECG on Day 2
- Targeted physical examinations (Section 12.6) daily through Day 7.

- Vital signs (blood pressure, respiratory rate, heart rate, and temperature) daily for inpatients (and at weekly scheduled visits for patients who are discharged [i.e., at the Day 7 and Day 14 visits, and weekly thereafter]). If more than one measurement is taken on a given day, the highest value for temperature and most abnormal value for other vital signs should be recorded in the eCRF.
- Symptoms attributable to *S. aureus* BSI/endocarditis assessed daily for inpatients (and at weekly scheduled visits for patients who are discharged [i.e., at the Day 7 and Day 14 visits, and weekly thereafter]).
- An aerobic blood culture collected daily until negative for 2 consecutive days and at Days 7 and 14 after CF-301/placebo administration. Additional blood cultures will be performed as clinically indicated. Blood cultures should be collected from a peripheral venipuncture site when possible. Results of all blood cultures (including blood cultures that are positive or negative for *S. aureus*) will be entered in the eCRF and *S. aureus* isolates will be sent to the central laboratory (Section 12.12)
- If not done at randomization, intravenous catheters known or suspected to be infected must be removed or changed and replaced at a different site as soon as possible within 72 hours after randomization
- If not done at randomization, all patients should have a TTE within 3 days of randomization. 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 and the TTE within 3 days of randomization does not need to be performed. TEEs are strongly recommended in patients with BMI > 30 kg/m^2. The site will provide all echocardiograms to the central echocardiography laboratory.
- If not done at randomization, ultrasounds to evaluate clots in the vein are recommended within 48 hours after randomization in patients with CVCs.
- Blood samples for PK at the time points described in Section 12.16.
- Blood samples for immunogenicity samples (CF-301 ADA & IgE) on Day 14 (to be sent to the central laboratory (Section 12.13).
- Blood samples for optional future research on Day 2 and Day 7 (to be sent to the central laboratory (Section 12.13). Note: future use samples will NOT be collected from patients in Israel.
- AE assessment daily
- Medication review daily
- Clinical outcome assessment on Day 7 and Day 14 (Section 12.15)

11.2.5. End of Standard-of-Care

A visit will be performed on or within 2 days after the end of SOC. For the purposes of the visit schedule, this visit is termed the "EOT" visit.

The following procedures will be performed at the EOT:

- Blood and urine samples for clinical safety laboratory tests (sent to the central laboratory; see Section 12.13)
- 12-lead ECG

- Complete physical examination (Section 12.6)
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature). If more than one measurement is taken on the day assessment, the highest value for temperature and most abnormal value for other vital signs should be recorded in the eCRF.
- Symptoms attributable to *S. aureus* BSI/endocarditis.
- Blood cultures as clinically indicated. Blood cultures should be collected from a peripheral venipuncture site when possible. Results of all blood cultures (including blood cultures that are positive or negative for *S. aureus*) will be entered in the eCRF and *S. aureus* isolates will be sent to the central laboratory (Section 12.12).
- Blood sample for serum pregnancy test for women of reproductive potential only (sent to the central laboratory; see Section 12.13).
- Blood samples for immunogenicity samples (CF-301 ADA & IgE) (to be sent to the central laboratory (Section 12.13).
- Blood samples for optional future research. Note: future use samples will NOT be collected from patients in Israel.
- AE assessment
- Medication review
- Clinical outcome assessment (Section 12.15)

Every attempt must be made to ensure the patient returns for the EOT visit, 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 the EOT visit, **the site must contact the medical monitor** to discuss whether the EOT visit may be conducted over the phone in order to facilitate collection of as much data as possible for the investigator to make the assessment of clinical outcome at EOT. In the event the EOT visit is conducted over the phone, the site should collect information on signs/symptoms of infection, SOC antibacterial therapy, concomitant medications, and AEs. The investigator should make an assessment of clinical outcome based on the data collected. If the patient is at another facility (e.g., nursing home, another hospital), the site should obtain medical records from that facility whenever possible.

11.2.6. Test-of-Cure

A test-of-cure visit will be performed 28 days (± 4 days) after the last day of SOC antibacterial therapy. For the purposes of the visit schedule, this visit is termed the "TOC" visit. The procedures to be performed at TOC are the same as the EOT procedures, listed above in Section 11.2.5.

Every attempt must be made to ensure the patient returns for the TOC visit, 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 the TOC visit, **the site must contact the medical monitor** to discuss whether the TOC visit may be conducted over the phone in order to facilitate collection of as much data as possible for the investigator to make the assessment of clinical outcome at TOC. In the event the TOC visit is conducted over the phone, the site should collect information on signs/symptoms of infection, SOC antibacterial therapy, concomitant medications, and AEs. The investigator should make an assessment of

clinical outcome based on the data collected. If the patient is at another facility (e.g., nursing home, another hospital), the site should obtain medical records from that facility whenever possible.

11.3. Immunogenicity Follow-up

The study includes a long-term follow-up visit at Day 180 (± 14 days) after CF-301/placebo administration for collection of an immunogenicity sample and assessment of SAEs and re-infection. The ability of the patient to return for the Day 180 visit is not required for enrollment in the study, but the visit is highly encouraged and the site may offer support for the patient to facilitate return for the visit (e.g., reimbursement of travel expenses).

The following procedures will be performed at the Day 180 visit:

- Blood samples for CF-301 ADA & IgE will be collected and sent to the central laboratory (Section 12.13).
- Re-infection between TOC and Day 180 will be assessed by the investigator for patients who meet the definition of response at TOC (Section 12.15; Table 6).
- Blood cultures should be performed between TOC and Day 180 as clinically indicated. Results of all blood cultures (including blood cultures that are positive or negative for *S. aureus*) will be entered in the eCRF and *S. aureus* isolates will be sent to the central laboratory (Section 12.12).
- All SAEs will be collected through Day 180.
- Vital status (whether the patient is alive or dead, or last known alive date) will be obtained when a patient is deemed to be lost to follow-up and for all patients at Day 180. The patient's vital status should be determined using available sources (e.g., the patient's relatives, hospital records, and/or public records) as permissible based on local laws and regulations.

For patients who are unable to return for the visit, relapse, SAE information, and vital status may be obtained via phone or email.

12. STUDY ASSESSMENTS

12.1. Informed Consent

Fully informed consent will be obtained before any study specific procedures are performed. The content and process of obtaining informed consent must be in accordance with all applicable ethical and regulatory requirements.

It is anticipated, by the very nature of the study that some patients who will be eligible for this protocol will not be able to give fully informed consent themselves due to various reasons including sedation, unconscious state, etc. Therefore, in a situation where a patient is unable to provide consent for him/herself, informed consent will be obtained by using one of the following possible options, which must comply with an individual country's local laws and ethics committees regulating the enrollment of incapacitated adults into clinical trials.

This process must be expedited to ensure that securing a representative's consent does not lead to delays that may result in increased risk or delayed medical treatment to the patient.

Therefore, the following will be applied as long as local laws allow:

- Consent from a legal (LR) or authorized (AR) or legally authorized representative (LAR) or next of kin or legally appointed individual in person or judge or specifically appointed lawyer for this purpose as required by local regulations;
- In extreme and urgent circumstances when emergent action is required to save the life of the person concerned, restore good health or alleviate suffering, it is understood that the presumed will of the patient will be determined by a physician and documented based on his/her knowledge of the study subject. The physician will follow the process required by local regulations and ethics committee for enrolment of this patient. Note: under the FDA regulations, the type of consent described in this bullet is only allowed when the research is reviewed under the exception from informed consent as emergency research (21 CFR 50.24). Therefore, for enrollment at sites in the United States, informed consent should be given by the patient or a LAR.

When consent is obtained remotely (by fax, scanned copy, etc.) according to local regulations via a LR / LAR / AR / next of kin / legally appointed individual, an original signature must be obtained at the earliest opportunity.

Patients enrolled in the study on the basis of consent by a LR / LAR / AR / next of kin / legally appointed individual / independent physician or by a physician will be given the opportunity to provide written confirmatory consent when and if they become able to do so and if the local regulations allow and/or require this. If the subject declines to confirm consent, he/she will be withdrawn from the study at the point where he/she declines consent.

In addition, where local regulatory and ethics committees allow, advance consent may be obtained prior to study entry in an attempt to obtain personal consent from the patient themselves.

Should a patient who is enrolled in the study on the basis of advance consent subsequently become unable to make medical decisions for him/herself, then the patient's legally acceptable next of kin / LAR / LR / AR should be informed of the patient's participation in the trial.

The above guidelines apply to all areas of the protocol where Informed Consent is referenced.

12.2. Cockcroft-Gault

Estimated creatinine clearance is calculated by Cockcroft-Gault formula as follows:

In patients with BMI < 30 kg/m^2:

Estimated creatinine clearance = [(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 creatinine clearance = [(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

12.3. Medical History

A complete medical history for 1 year prior to screening will be recorded for each patient. Medical history will include previous and current medical diagnoses and major surgical procedures.

12.4. Diagnosis

The investigator will determine diagnosis at screening and during the study to determine treatment duration. Diagnosis definitions are provided in Section 23.1).

12.5. Apache II score

Certain components of the Apache II score will be determined locally (including oxygenation, Glasgow Coma Scale, and chronic health points) on the day of randomization and collected on the eCRF and other components will be obtained from central laboratory data.

12.6. Physical Examination

Physical examination will be performed at screening, daily through Day 7 and on Day 14 after CF-301/placebo administration, at EOT, and at TOC.

Complete physical examinations will be performed at screening, Day 14, EOT, and TOC. Complete physical examinations include, but are not limited to, evaluation of the head, eyes, ears, nose, throat (HEENT), neck, lungs, heart, chest, abdomen, extremities, neurological status, skin for any evidence of emboli, palpation for signs of pain, and any other notable conditions.

Weight and height will be measured at screening. If it is not possible to measure weight and height at screening, a recently available historical weight and height can be used.

Targeted physical examinations will be performed daily through Day 7. Targeted physical examinations include evaluation for complications of BSI, HEENT, lungs, heart, skin for any evidence of emboli, and palpation for signs of pain.

Pain on physical examinations should trigger diagnostic testing for metastatic foci.

12.7. 12-Lead Electrocardiogram

A 12-lead ECG will be performed at screening, at approximately 2 to 4 hours after the start of CF-301/placebo infusion (for the first 17 patients randomized), on Day 2, at EOT, and at TOC.

Heart rate, PR interval, QRS, QT, QTcB, and QTCF values will be recorded on the eCRF. Any clinically relevant abnormality will be recorded as an adverse event and will be followed to resolution/satisfaction.

12.8. Echocardiogram

All patients should have a TTE within 3 days of randomization. All efforts should be made to perform this TTE before administration of study drug. 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 and the TTE within 3 days of randomization does not need to be performed. Patients with endocarditis should have a follow-up TTE between Days 7 and 14; where possible, a TEE should also be performed (Baddour et al., 2015; Habib et al., 2010; Habib et al., 2015). TEEs are strongly recommended in patients with BMI > 30 kg/m^2. The site will provide all echocardiograms to the central echocardiography laboratory. The central echocardiography laboratory will review the echocardiograms for diagnostic evaluation of valvular function and other parameters.

12.9. Vital Signs

Vital signs will be performed at screening, approximately every 30 to 40 minutes during CF-301/placebo infusion and at approximately 30 to 40 minutes after the infusion, daily during SOC for inpatients (and at weekly scheduled visits for patients who are discharged [i.e., at the Day 7 and Day 14 visits, and weekly thereafter]), at EOT, and at TOC. Vital signs will include blood pressure, respiratory rate, and heart rate during infusion and blood pressure, respiratory rate, heart rate, and temperature at all other time points. If more than one measurement is taken on the day assessment, the highest value for temperature and most abnormal value for other vital signs should be recorded in the eCRF.

12.10. Symptoms of Infection

The investigator will assess symptoms (shortness of breath, sweating, fatigue, confusion, and pain associated with metastatic foci) at screening, daily during SOC for inpatients (and at weekly scheduled visits for patients who are discharged [i.e., at the Day 7 and Day 14 visits, and weekly thereafter]), at EOT, and at TOC. The investigator will determine if symptoms are attributable to *S. aureus* BSI/endocarditis. The investigator will assess symptoms as follows:

Absent	
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

12.11. Management of IV Catheters

Intravenous catheters known or suspected to be infected must be removed or changed and replaced at a different site as soon as possible within 72 hours after randomization. In patients with CVCs, ultrasounds to evaluate clots in the vein are recommended within 48 hours after randomization

12.12. Blood Cultures

For study eligibility, patients must have blood culture positive for *S. aureus* determined by rapid diagnostic or conventional method or Gram stain showing Gram-positive cocci in clusters plus positive tube coagulase test from blood culture specimens collected within 72 hours prior to randomization. The site microbiological laboratory is encouraged to use an FDA-cleared or CE-IVD certified rapid diagnostic test to identify *S. aureus* if it is available at the site (Section 23.3).

The qualifying blood culture collected within 72 hours prior to randomization that supports study eligibility will be collected in the eCRF. Wherever possible, the isolate from the initial positive culture for *S. aureus* should be retained and sent for confirmation of identification and susceptibility testing at the central microbiology laboratory.

Two aerobic blood cultures preferably from 2 different sites will be collected at screening at least 30 minutes apart and as close to the start of study drug dosing as possible, and at least one aerobic blood culture will be collected daily during the study until negative for 2 consecutive days and at Days 7 and 14 after CF-301/placebo administration. Additional blood cultures will be performed as clinically indicated. Blood cultures should be collected from a peripheral venipuncture site when possible. Results from all blood cultures performed during the study (from the qualifying blood culture through to Day 180), including blood cultures that are positive or negative for *S. aureus*, should be entered in the eCRF. *S. aureus* isolates, including the isolate from the qualifying blood culture, are sent to the central lab.

The study site's local microbiology laboratory will perform identification and *in vitro* susceptibility testing to SOC antibiotics according to local practices. The investigator should ensure that all *S. aureus* isolates obtained from all cultures performed during the study period (and wherever possible, the isolate from the initial positive culture for *S. aureus*) are sent to the central microbiology laboratory, as described in Section 23.3 and the laboratory manual. The central microbiology laboratory will repeat the identification and perform *in vitro* susceptibility testing of isolates in batches for the purposes of the final study analysis; the central microbiology laboratory will not be providing 'real-time' results. Further evaluation to identify the potential mechanism of resistance may be performed.

The use of FDA-cleared or CE-IVD certified rapid diagnostic tests to identify *S. aureus* may be employed to reduce the amount of prior empiric antibacterial therapy being administered to potential study patients. Patients may be enrolled based on a positive result from a rapid

diagnostic test, but confirmation of *S. aureus* by conventional methods will be the required objective measure for *S. aureus* in the study analyses for efficacy. Patients who are enrolled based on a positive rapid diagnostic test, but have negative result for *S. aureus* or missing blood culture at screening should continue to be followed in the study for safety assessments.

12.13. Laboratory Testing

12.13.1. Central Laboratory

The laboratory tests that will be performed by the central safety laboratory are presented in Section 23.4. The details for sample collection, preparation, and shipping to the central laboratory will be provided in a separate laboratory manual. The following samples will be collected for sending to the central laboratory:

- Blood and urine samples will be collected for safety laboratory tests (biochemistry, hematology, coagulation, and urinalysis) at randomization (pre-dose), at approximately 2 to 4 hours after the start of CF-301/placebo infusion (for the first 17 patients randomized), on Day 2, weekly during SOC, at EOT, and at TOC.
- Blood samples for serum pregnancy testing will be collected at randomization, EOT, and TOC (female patients of reproductive potential). The pregnancy test that qualifies the patient for study eligibility is performed locally, as described under Section 12.13.2.
- Blood samples will be collected for CF 301-specific anti-drug antibody (ADA) and IgE at randomization (pre-dose), Day 14, at EOT, at TOC, and on Day 180 after CF 301/placebo administration.
- If a patient experiences signs and symptoms consistent with anaphylaxis (Simons, et al., 2011; Section 11.2.3.1), blood samples for serum tryptase and CF-301-specific IgE will be collected as soon as possible within 2 hours. If the serum tryptase sample is positive or equivocal, the sample may also be tested for β-tryptase. Another blood sample for serum tryptase will be collected 2 weeks later.
- If the patient agrees in the informed consent to have blood stored for optional future research (e.g., cytokine and chemokine assays and/or biomarker evaluation), 2 samples (1 serum and 1 plasma) will be collected at randomization (pre-dose), 12 to 24 hours after CF-301/placebo dosing, on Day 7, and at EOT and TOC. Note: future use samples will NOT be collected from patients in Israel.

12.13.2. Local Laboratory

Limited safety laboratory tests may need to be performed by the site's local laboratory at screening so that timely results are available for study eligibility determination. If laboratory safety results are already available within the 72 hours prior to screening from standard-of-care/routine testing, these results may be used to support eligibility determination. The laboratory tests that are required to be available locally for eligibility determination are those that are part of the inclusion/exclusion criteria, as follows:

- Serum creatinine to calculate creatinine clearance by Cockcroft-Gault formula using ideal body weight in patients with BMI ≥ 30 kg/m^2 (Section 12.2) to determine the dose of study drug
- Urine or serum pregnancy test (for women of reproductive potential; see inclusion criteria)
- FSH (to confirm postmenopausal status as applicable; see inclusion criteria)

Other safety laboratory tests may be performed locally at the investigator's discretion to assess the patient in general for study eligibility. During the study, additional clinical laboratory safety testing should be performed at the site's local laboratory per the site's standard of care for routine clinical management of the patient.

12.14. Vital Status

Vital status (whether the patient is alive or dead, or last known alive date) will be obtained at Day 180 or when a patient is deemed to be lost to follow-up. The patient's vital status should be determined using available sources (e.g., the patient's relatives, hospital records, and/or public records) as permissible based on local laws and regulations.

12.15. Contraception

Contraception requirements are described in the Inclusion Criteria (Section 10.1).

The manufacturer's prescribing information for the SOC antibacterial agents should be referenced for information related to pregnancy and contraception.

12.16. Efficacy Outcome Assessments

Clinical and microbiological outcome will be assessed at Days 7 and 14 after CF-301/placebo administration, at EOT, and at TOC.

Clinical Outcome: Clinical outcome will be assessed by the investigator and the independent Adjudication Committee and will be based on the definitions in Table 5. The signs and symptoms evaluated for clinical outcome assessments are presence of shortness of breath, sweating, fatigue, confusion, pain associated with metastatic foci, fever, leukocytosis, leukopenia, bandemia, tachycardia, tachypnea, and hypotension.

Re-infection will be assessed at Day 180 after CF-301/placebo administration for patients who meet the definition of response at TOC (Table 5). Re-infection will be assessed by the investigator and the independent Adjudication Committee. The definition of re-infection is provided in Table 6.

Table 5: Clinical Outcome Definitions at Day 7 (± 1 day), Day 14 (± 1 day), EOT (+ 2 days), and at TOC (±4 days)

Clinical Outcome	Definition
Improvement ***(Days 7 and 14 only)***	• Improvement in all attributable signs and symptoms of *S. aureus* BSI which were present at baseline[a], • No new, worsening, or persistent signs and symptoms attributable to *S. aureus* BSI, • No development of a new foci of *S. aureus* infection after Day 7[b] • SOC for *S. aureus* BSI is ongoing with no need to[c]: ▪ add a SOC antibacterial agent due to persistent or worsening *S. aureus* BSI, ▪ switch to a different SOC antibacterial agent due to persistent or worsening *S. aureus* BSI, or ▪ increase SOC dose due to persistent or worsening *S. aureus* BSI, • No surgery or medical intervention for *S. aureus* BSI is necessary, and • The patient is alive.
Response[d]	• Complete resolution of attributable signs and symptoms of *S. aureus* BSI which were present at baseline, • No new signs and symptoms attributable to *S. aureus* BSI, • No development of a new foci of *S. aureus* infection after Day 7[b] • No further antibacterial therapy for *S. aureus* BSI is necessary, • No further surgery or medical intervention for *S. aureus* BSI is necessary, and • The patient is alive.
Non-response[d]	• Persistence, worsening, or recurrence of attributable signs and symptoms of *S. aureus* BSI which were present at baseline, • New signs and symptoms attributable to *S. aureus* BSI, • Development of a new foci of *S. aureus* infection after Day 7[b], • Complications of *S. aureus* BSI, • SOC for *S. aureus* BSI was changed to[c]: ▪ add a SOC antibacterial agent due to persistence, worsening, or recurrence of *S. aureus* BSI, ▪ switch to a different SOC antibacterial agent due to persistence, worsening, or recurrence of *S. aureus* BSI, or ▪ increase the dose of SOC due to persistence, worsening, or recurrence of *S. aureus* BSI, • >12 weeks of SOC antibacterial therapy for *S. aureus* BSI and/or related infection (e.g., osteomyelitis), • Surgery or medical intervention for *S. aureus* BSI is necessary (e.g., valvular surgery for progressive *S. aureus* BSI), or • Death due to any cause.
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow up • Withdrawal of consent • Extenuating circumstances that preclude the classification of clinical response

a. Symptoms will be assessed as absent, mild, moderate, and severe. All symptoms present at baseline must improve by one category (e.g., from moderate to mild) in order for a patient to be considered as having improvement.
b. Does not apply at Day 7 assessment. Metastatic foci identified through Day 7 post-randomization are considered baseline; new metastatic foci identified after Day 7 post-randomization are considered progression of the *S. aureus* infection.
c. Per protocol, patients may be treated empirically and SOC may be changed once susceptibly data become available, as described in the "Study Design" section. A change in SOC based on susceptibility data from the blood culture collected within 72 hours prior to randomization does not count as "non-response".
d. At Test-of-Cure, response = cure and non-response = failure.

Table 6: Clinical Re-Infection Definitions at Day 180 (±14 days)

Clinical Outcome[a]	Definition
No re-infection	Between TOC and Day 180, the patient did **not** have *S. aureus* BSI/endocarditis or *S. aureus* infection at any body site (this includes infections that the investigator considers to be relapses as well as those that the investigator considers to be new *S. aureus* infections).
Re-infection	Between TOC and Day 180, the patient had *S. aureus* BSI/endocarditis and/or developed a *S. aureus* infection at any body site documented by a positive culture for *S. aureus* (this includes infections that the investigator considers to be relapses as well as those that the investigator considers to be new *S. aureus* infections).
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow up • Withdrawal of consent • Extenuating circumstances that preclude the classification of clinical response

a. Patients who meet the definition of response at TOC will be assessed for re-infection.

Microbiological Response/Outcome: Definitions for microbiological response (Days 7 and 14) and microbiological outcome (End of SOC and TOC) are provided in Table 7 and Table 8, respectively. Microbiological outcome will be determined programmatically based on the data from the central microbiology laboratory. In the event an isolate is not sent to the central microbiology laboratory then the local laboratory data collected on the case report form (CRF) will be used.

Table 7: Microbiological Response Definitions at Day 7 (± 1 day) and Day 14 (± 1 day)

Microbiological Response	**Definitions**
Clearance of bacteremia	Blood cultures collected on or prior to assessment were negative for *S. aureus* on 2 consecutive days.
Ongoing bacteremia	Blood cultures collected on or prior to assessment continue to be positive for *S. aureus*
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow up • Withdrawal of consent • Extenuating circumstances that preclude the classification of microbiological response

Table 8: Microbiological Outcome Definitions at EOT (+ 2 days) and at TOC (±4 days)

Microbiological Outcome	**Definitions**
Eradication	Blood cultures were negative for *S. aureus* on 2 consecutive days.
Presumptive Eradication	Follow-up blood cultures were not done and the patient has responded clinically, as defined in Table 5.
Persistence	Blood cultures continue to be positive for *S. aureus*.
Presumed Persistence	Follow-up blood cultures were not done and the patient has not responded clinically, as defined in Table 5.
Relapse	Patient was previously classified as having "clearance of bacteremia", "eradication", or "presumptive eradication", and subsequently a blood culture was positive for *S. aureus*.
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow up • Withdrawal of consent • Extenuating circumstances that preclude the classification of microbiological response

12.17. Pharmacokinetic Assessments

Blood samples will be collected for PK assessment of CF-301 in 3 subsets of patients as listed below. Pharmacokinetic samples will be collected from patients in both the CF-301 group and the placebo group to maintain the blind. Blood samples for PK may be collected by peripheral venipuncture or from a central IV catheter. For samples < 3 hours after start of infusion, the sample must be collected from a different site than the site of infusion. The specific details pertaining to sample collection, processing, and shipping are provided in the laboratory manual.

- ***PK Subset 1*:** A minimum of approximately 17 patients and up to approximately 34 patients (30%) will give serial PK samples at the following time points: pre-dose, 0.5 (30 minutes), 1.5 (1 hour 30 minutes), 2, 2.25 (2 hours 15 minutes), 3, 4, 8, 14, 24, and 48 hours after the start of study drug infusion. The sponsor will determine if additional patients will give serial PK samples in Subset 1 based on ongoing review of accrued PK data, and the number of patients giving limited PK samples (Subsets 2 and 3 below) will be reduced accordingly. Note: PK Subset 1 will not be conducted in Israel.
- ***PK Subset 2*:** Approximately 40 patients (35%) will have limited PK samples collected at the following time points: 2.25 (2 hours 15 minutes), 3, 8, and 24 hours after the start of study drug infusion.
- ***PK Subset 3*:** Approximately 40 patients (35%) will have limited PK samples collected at the following time points: 2.25 (2 hours 15 minutes), 4, 8, and 24 hours after the start of study drug infusion.

Permitted time windows are as follows:

- ± 10 minutes around the samples at 0.5 and 1.5 hours after the start of infusion
- - 10 minutes before the sample at the end of infusion (the sample is to be drawn before the infusion is complete and can be obtained up to 10 minutes before the end of the infusion. Note that if the sample is drawn after the infusion is complete in error, it is still to be collected and the exact clock time should be recorded).
- ± 10 minutes around the samples at 2.25, 3, and 4 hours after the start of infusion
- ± 1 hour around the sample at 8 hours after the start of infusion
- ± 2 hours around the samples at 14 and 24 hours after the start of infusion.
- ± 4 hours around the sample at 48 hours after the start of infusion.

PK parameters of CF-301 will be assessed from patients with serial PK sampling, including maximum plasma concentrations (C_{max}), time to C_{max} (T_{max}), elimination half-life ($T_{1/2}$), clearance (CL), volume of distribution (Vz), and area under the curve (AUC_{0-t} and $AUC_{0-\infty}$).

12.18. Pharmacodynamic Assessments

The PK/PD parameters include AUC_{0-24hr}/minimum inhibitory concentration (MIC), C_{max}/MIC, and %Time > MIC over a 24-hour period. PK/PD parameters will be calculated for patients who have MICs available.

12.19. DSMB

An independent DSMB will review accruing safety, tolerability, immunogenicity, and PK data in an unblinded manner throughout the study, as detailed in the DSMB charter. The Sponsor and study staff will remain blinded throughout the study. The DSMB will conduct an initial unblinded review of safety, tolerability, and PK data after approximately 17 patients have PK data available (approximately 10 patients on CF-301 and approximately 7 patients on placebo). After the first approximately 17 patients have received the CF-301 0.25 mg/kg or placebo single 2-hour infusion and have PK data available, the DSMB will assess the exposures in this initial group of patients, as detailed in the DSMB Charter. If the mean exposure to CF-301 is significantly lower (e.g., by > 25%) or higher than the mean exposure in healthy volunteers in Study CF-301-101 dosed at 0.25 mg/kg (i.e., the target safe and efficacious exposure), then the DSMB may recommend dose adjustment of CF-301 to achieve the planned exposure target that was established to be safe and is expected to be efficacious (refer to Section 7.1.5 for toxicology data and animal PK/PD data). Additional DSMB reviews are described in the DSMB charter. Enrollment will not be halted during the conduct of DSMB reviews. No formal efficacy analyses will be conducted at the time of these reviews; however, descriptive summary tables of key efficacy endpoints may be provided to support assessment of benefit/risk. If analyses by the DSMB support further dose reductions or dose increases up to 0.4 mg/kg based on accrued PK exposure data in specific patient demographic groups, these will be described in Administrative Amendments or Clarification Letters to the protocol. If the accrued PK data suggest the need for an increase in dose above the 0.4 mg/kg dose defined in the original protocol, then a protocol amendment will be issued.

12.20. Adjudication Committee

An independent blinded Adjudication Committee will adjudicate the Day 7 diagnosis, and this adjudicated diagnosis will be considered the final diagnosis to be used for the analysis. In addition, clinical response and re-infection will be assessed by the Adjudication Committee at predefined intervals. The efficacy analysis of clinical response and re-infection will be based on the Adjudication Committee's assessment. The role of the Adjudication Committee and procedures for adjudication are described in the Adjudication Committee Charter.

13. TREATMENT OF PATIENTS

13.1. Description of Study Drugs

CF-301 will be provided as a sterile injectable solution in 10 mL vials. Each vial will contain 4.0 mL of CF-301 (10 mg/mL), as described in Table 9. Study drug will be labeled in accordance with regulatory requirements.

Table 9: CF-301 Description

Product Name:	CF-301
Chemical Name	$C_{1149}H_{1768}N_{324}O_{357}S_3$
Dosage Form:	Sterile injectable solution
Unit Dose:	4.0 mL (10 mg/mL) in 10 mL vials; 0.25 mg/kg dose and 0.12 mg/kg dose (See Section 9.4)
Route of Administration:	Intravenous infusion over 2 hours
Physical Description:	Clear colorless solution
Manufacturer:	Emergent BioSolutions

Material	Function of Component
CF-301	Active Ingredient
Water for Injection	Solvent
L-Histidine	Buffer
D-Sorbitol	Stabilizer

Placebo will be provided as a sterile injectable solution in 10 mL vials. Each vial will contain 4.0 mL of placebo. The composition of the placebo is shown in Table 10. The placebo formulation is equivalent to the drug product formation minus the active pharmaceutical ingredient (CF-301). Placebo is similar in appearance to CF-301.

Table 10: Placebo Description

Material	Function of Component
Water for Injection	Solvent
L-Histidine	Buffer
D-Sorbitol	Stabilizer

13.2. Dosage and Dose Regimen

The dosage and dose regimen for study drug and SOC is described in Section 9.4.

13.3. Study Drug Preparation and Administration

The CF-301 or placebo study drug will be prepared by a pharmacist or study staff designated by the Investigator. CF-301 and placebo are similar in appearance, but the CF-301 study drug and/or prepared infusion may contain small visible particles. Therefore, the pharmacist/study staff responsible for preparing study drug will not be involved in any other study procedures or assessments. Measures will be put into place (e.g., covering the infusion bag) to ensure the study staff administering the study drug are not unblinded. Additional details are provided in a separate Pharmacy Manual.

The specified dose and volume of CF-301 or placebo will be calculated for individual patients and diluted as specified in the Pharmacy Manual. The patient's weight at screening will be used to calculate the mg/kg dose of study drug. If it is not possible to measure weight at screening, a recently available historical weight can be used.

The IV infusion will be administered over 2 hours using an IV set with an in-line filter (0.2 or 0.22 μm) with corresponding pump, as described in the Pharmacy Manual.

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

13.4. Storage/Stability

The CF-301 formulation must be stored at -20 (±5)°C in a controlled temperature monitored and locked area.

The CF-301 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 some of the 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 the Study Monitor and open to inspection at any time by any applicable regulatory authorities.

The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until the end of the study. The Investigator or designee must maintain records that document:

- investigational product delivery to the study site
- the inventory at the site
- use by each patient, including injection vials from each supply dispensed

These records should 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 will also maintain records adequately documenting that the patients were provided the study drug specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to ContraFect or ContraFect's designee or destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from ContraFect. If drug is destroyed locally, a certificate of destruction will be provided to ContraFect or designee.

13.6. Prior and Concomitant Medications

All medications taken within 28 days before randomization and through the EOT will be recorded, and only antibacterial medications or medications to treat adverse events will be recorded after EOT through TOC.

13.7. Prohibited Medications

Patients who received treatment with dalbavancin or oritavancin for the current infection are excluded from the study. Note: patients who are receiving teicoplanin, linezolid, telavancin, ceftaroline fosamil, and/or sulfamethoxazole/trimethoprim are eligible for the study provided that treatment is switched to an appropriate SOC antibacterial agent (SOC agents include daptomycin and vancomycin for MRSA and semi-synthetic penicillins [e.g., nafcillin, oxacillin, cloxicillin, flucloxacillin] and first-generation cephalosporins [e.g., cefazolin] for MSSA.

Patients who participated or plan to participate in an interventional investigational drug, device, or diagnostic trial within 30 days prior to or during the study are excluded from the study. In addition, patients who previously received CF-301 are excluded.

All medications for the health and welfare of the patient are permitted.

The manufacturer's prescribing information for the SOC antibacterial therapy should be consulted for information regarding any concomitant medication restrictions.

13.8. Treatment Compliance

Study drug (CF-301 or placebo) will be administered to hospitalized patients by study site personnel.

13.9. Randomization and Blinding

Patients will be assigned to receive CF-301 or placebo in a 3:2 ratio via the IWRS. Patients randomized into the study will be assigned the treatment corresponding to the next available number in the computer-generated randomization schedule. A patient is considered randomized when the IWRS randomization transaction is recorded regardless of whether the patient actually receives study drug.

This is a double-blind study. Study site personnel will be blinded to treatment group. A pharmacist not associated with the operational conduct of the study will prepare the study medication for infusion, as described in Section 13.3.

An independent DSMB will review data in an unblinded manner, as described in Section 12.18 and the DSMB charter. The Sponsor, study staff, and Adjudication Committee will be blinded to treatment group.

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, may the PI unblind a patient's treatment assignment. Prior to any unblinding, the PI 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 PI must notify the Sponsor if the blind is broken for any reason and the PI was unable to contact the Sponsor prior to unblinding. The PI will record in source documentation the date and reason for revealing the blinded treatment assignment for that patient.

14. ADVERSE AND SERIOUS ADVERSE EVENTS

14.1. Definition of Adverse Events

14.1.1. Adverse Event (AE)

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 adverse event 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: the clinical outcome of the disease under study is collected as an efficacy endpoint and an outcome of non-response is not an AE.
- 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

14.1.2. Serious Adverse Event (SAE)

A serious adverse event 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 in-patient 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.

14.2. Timeframe for Collecting Adverse Events

All AEs and SAEs will be collected during the core study, from the time of consent through TOC. After completion of the core study, all SAEs will be collected during the long-term follow-up through Day 180. For patients who are unable to return for the Day 180 visit, this information may be obtained via phone or email.

14.3. Relationship to Study Drug

The Investigator must make the determination of relationship to the investigational product for each AE (unrelated or related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the

investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

14.4. Study Endpoints

Study endpoints of efficacy non-response would not ordinarily be reported as AEs. Serious AEs with an outcome of death which are a component of a study endpoint (e.g., all-cause mortality) must be reported as SAEs.

14.5. Grading of Adverse Events

The severity (or intensity) of each AE will be assessed 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 14.1.2 above). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.6. Events of Clinical Interest

Any AE that results in stopping of the study drug infusion is considered an event of clinical interest and must be reported within 24 hours.

14.7. Overdose

An overdose occurs if a patient has taken, accidentally or intentionally, study drug in a dose exceeding that prescribed by the protocol. An overdose (and any associated AE) must be reported within 24 hours of the site becoming aware of the overdose.

14.8. Pregnancy

Female patients who become pregnant during the core study should be immediately discontinued from the study and followed to determine the outcome of the pregnancy. 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 should notify the sponsor. At the completion of the pregnancy, the investigator 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 should follow the procedures for reporting an SAE.

14.9. Unexpected Adverse Event

An AE is considered "unexpected" if the nature of the AE is not consistent with what is listed in the Investigator's Brochure (IB). Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events.

EXAMPLES: hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator's brochure listed only cerebral vascular accidents.

14.10. Suspected Unexpected Adverse Drug Reaction (SUSAR)

An AE associated with the use of the study drug which is serious, unexpected, and study drug related.

14.11. SAE Reporting

All SAEs must be reported within 24 hours of the site becoming aware of the SAE. SAEs are reported through the electronic data capture (EDC) system or backup paper SAE report form. The SAE report should provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE: patient identification, reporting source, causality, and an event outcome.

Other procedural and contact details on SAE reporting will be described in the SAE completion guidelines which will be available to the Investigator. Any event that is serious, study drug related, and unexpected as assessed by the medical monitor or the sponsor will be submitted to the regulatory authorities and in accordance with national regulatory laws and regulations. The Investigator will be responsible for reporting all SAEs that require reporting to the local IRB/IEC in accordance with its regulations and guidelines.

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

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, stabilization occurs (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained, regardless of whether the patient is still participating in the study. All appropriate therapeutic measures should be undertaken and recorded. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

15. STATISTICS

A Statistical Analysis Plan (SAP) will be prepared and finalized before database lock and unblinding of the Core Study, and analyses of data. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations (SD), medians, minimums, and maximums for continuous variables will be provided by treatment group. Exploratory analyses may also be performed. Listings of individual patient's data will be produced.

15.1. Analysis Populations

The analysis populations are:

- The Intent-to-Treat (ITT) Population includes all randomized patients regardless of whether or not the patient received study drug (CF-301 or placebo).
- The Safety Population includes all patients who receive any amount of study drug (CF-301 or placebo).
- The Microbiological Intent-to-Treat (mITT) Population includes all patients who:
    1. Had documented *S. aureus* BSI and/or endocarditis based on a blood culture collected within 72 hours of randomization and
    2. Received any amount of study drug.

  The mITT population is the primary analysis population for the efficacy analyses.
- The Clinically Evaluable (CE) Population includes all patients who:
    1. Have confirmed clinical diagnosis of *S. aureus* BSI and/or endocarditis
    2. Received adequate course of antibacterial therapy, as defined in SAP.
    3. Have sufficient information to determine clinical outcome at the visit (i.e., not indeterminate).
    4. Have no additional confounding factors, as described in the SAP.
- The Microbiologically Evaluable (ME) Population includes all patients who are in the mITT and CE Population and:
    1. *For Day 7 and Day 14 only*: Had a culture performed at the visit.
- The PK Population includes all randomized patients who provide PK samples.

15.2. Patient Population and Characteristics

Enrollment, protocol deviations, and discontinuations from the study drug and the study will be summarized by treatment group. Demographics, medical and surgical history, baseline assessment of signs and symptoms of *S. aureus* BSI/endocarditis, BSI risk factors, diagnosis, APACHE II score, microbiological assessment and study drug administration will be summarized by treatment group.

15.3. Safety Analysis

Safety will be evaluated by presenting summaries of treatment emergent AEs (TEAEs), clinical laboratory evaluations (biochemistry, hematology, coagulation, and urinalysis), vital signs (blood pressure, respiratory rate, heart rate, and temperature) and ECGs. Abnormal physical

examination results will be recorded as AEs. A treatment emergent AE is one that occurs on or after the first dose of study drug through TOC. Safety analyses will be conducted in the Safety Population and subjects will be analyzed according to the treatment actually received.

Adverse events will be coded using the Medical Dictionary of Regulatory Activities. The incidence of TEAEs will be presented by system organ class (SOC) and preferred term (PT), by SOC, PT and relationship to study drug, and by SOC, PT and severity. Serious AEs and TEAEs that lead to discontinuation of the study drug will also be presented by SOC and PT.

Descriptive statistics for clinical laboratory, vital signs and ECG parameters, including change from baseline, will be presented by time point collected and for the overall most abnormal post-baseline value. Incidences of potentially clinically significant (meeting predefined criteria specified in the SAP) clinical laboratory results, vital signs and ECG parameters will also be summarized by time point collected and the overall most abnormal post-baseline value.

15.4. Efficacy Analysis

For all efficacy analyses, patient data will be summarized in the group to which the patient was randomized. The primary efficacy outcome is clinical improvement or response at Day 14 after CF-301/placebo administration in the mITT Population. The number and percentage of patients with an improvement/response, no response, and indeterminate will be determined by treatment group. Exact 2-sided 95% confidence intervals for the point estimates of the clinical improvement/response rates in each treatment group will be determined using the Clopper-Pearson method. The clinical improvement/response rate will be compared between the treatment groups using Fisher's exact test. Statistical significance will be based on a two-sided alpha level of 0.05.

The number and percentage of patients with a clinical outcome of improvement/response, no response, and indeterminate will be determined by treatment group at Day 7 after CF-301/placebo administration, at EOT, and at TOC in the mITT Population. Exact 2-sided 95% confidence intervals for the point estimates of the clinical improvement/response rates in each treatment group will be determined using the Clopper-Pearson method. Statistical comparisons between the treatment groups will be conducted using Fisher's exact test and p-values will be provided as explorative statistics.

The number and percentage of patients with a microbiological response of clearance of bacteremia, ongoing bacteremia, and indeterminate will be determined by treatment group at Days 7 and 14 after CF-301/placebo administration in the mITT Population. The number and percentage of patients with a microbiological outcome of eradication/presumptive eradication, persistence/presumptive persistence, and indeterminate will be determined by treatment group at EOT and TOC in the mITT Population. Exact 2-sided 95% confidence intervals for the point estimates of the clearance of bacteremia or microbiological eradication/presumptive eradication rates in each treatment group will be determined using the Clopper-Pearson method. Statistical comparisons between the treatment groups will be conducted using Fisher's exact test and p-values will be provided as explorative statistics.

Additional exploratory efficacy analyses will be conducted to support the efficacy findings for the primary and secondary outcomes. Kaplan-Meier methods will be utilized to determine the time to clearance of bacteremia and time to defervesence in the mITT Population. Time to

clearance of bacteremia will be defined as the date/time from study drug administration to the date/time of the first negative blood culture of the two negative blood cultures taken on 2 consecutive days. Time to defervesence will be determined only in those patients who had a fever at baseline and will be defined as the date/time from study drug administration to the date/time of the first oral temperature equivalent < 38.0°C (< 100.4°F) using the highest temperature value on a given day. For both time to clearance of bacteremia and time to defervesence, patients whose SOC for BSI was changed by adding a SOC antibacterial agent, switching to a different SOC antibacterial agent, or increasing the dose of SOC due to persistence, worsening, or recurrence of *S. aureus* BSI, died prior to clearance of bacteremia/defervesence or withdrew from the study prior to clearance of bacteremia/defervesence will be censored at the date/time of the SOC change, death or study withdrawal, respectively.

All-cause mortality through TOC in the ITT Population and microbiological relapse at EOT, TOC, and Day 180 in the mITT Population will be summarized by treatment group. Exact 2-sided 95% confidence intervals for the point estimates of all-cause mortality and microbiological relapse in each treatment group will be determined using the Clopper-Pearson method.

Clinical improvement (Day 7 and Day 14), clinical response (EOT and TOC), clearance of bacteremia (Day 7 and Day 14) and microbiological eradication/presumed eradication (EOT and TOC) will be summarized separately for patients with MSSA and MRSA in the mITT population. Exact 2-sided 95% confidence intervals for the point estimates will be determined using the Clopper-Pearson method.

Additional exploratory analyses will be described in the SAP.

15.5. Pharmacokinetic Analysis

Data collected from Subset 1 will be used to determine the following PK parameters: C_{max}, T_{max}, $T_{1/2}$, CL, Vz, AUC_{0-t}, and $AUC_{0-\infty}$. These values along with the listings for plasma concentrations from all 3 subsets (Subsets 1 to 3) will be reported in the Clinical Study Report (CSR).

All PK data collected in this study (Subsets 1, 2, and 3) will be pooled with the PK data collected from the previous Phase 1 study (Protocol CF-301-101) to update the previously developed population PK model; this will be reported in a separate report, which will include the target attainment analysis. The population PK and target attainment analyses will be described in a separate analysis plan.

15.6. Pharmacodynamics Analysis

PK/PD analysis will be conducted to determine the AUC_{0-24hr}/MIC, C_{max}/MIC, and %Time > MIC ratios. PK/PD parameters of CF-301 will be calculated for patients who have MICs available. Exposure response will be evaluated for efficacy and safety endpoints and will be detailed in a separate analysis plan (as described above in the Section 15.5).

15.7. Handling of Missing Data

For the primary and secondary efficacy outcomes, patients with missing data are assigned a response of indeterminate. In the mITT population, indeterminate outcomes are included in the denominator for the calculation of the outcome rate. Thus, a response of indeterminate is analyzed the same as a response of non-response or failure for the clinical outcome or ongoing bacteremia or persistence/presumed persistence for microbiological outcome.

Handling of other missing data will be described in the SAP.

16. DATA MANAGEMENT

16.1. Data Collection

The investigative site will be provided electronic case report forms (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 should be consistent with the source documents or the discrepancies should be explained.

The Investigator will be responsible for reviewing all data and eCRF entries and will verify that the information is true and correct.

Patient data should be entered into the eCRF and be ready for review as soon as possible, but no later than 5 days after each visit/time point.

16.2. Access to Source Documents

Qualified representatives of ContraFect designees ("Study Monitors") 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 CRFs
- 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 CRFs and office, hospital, and laboratory records supporting the participation of each patient in the study. The CRFs 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's requirements.

17. ADMINISTRATIVE

17.1. Statement of Good Clinical Practices

This trial will be conducted in adherence to the study protocol, Good Clinical Practices (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 in and 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 is to notify the IRB/IEC in writing of the study's completion or early termination, and send a copy of the notification to ContraFect or CRO and retain one copy for the site study regulatory file, called the On Site Study File (OSF).

18. QUALITY CONTROL AND ASSURANCE

18.1. Sponsor Audits

During the study, individuals from ContraFect's Quality Assurance department and/or their authorized representatives 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 to arrange a convenient time for this visit. The Investigator and staff are expected to cooperate with the auditors and allow access to all patient records supporting the CRFs 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 CRFs 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 the ICH E6 GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The protocol and any information supplied to the patient to obtain informed consent, including written ICF(s), patient recruitment procedures (e.g., advertisements), and written information to be provided to patients (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, 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 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.

When 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 submit a final report to the IRB/IEC and to ContraFect.

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

Preparation of the informed consent form (ICF) is the responsibility of the Investigator and ContraFect or designee and must include all elements required by the 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.

A master study-specific template will be used to prepare the ICF. ContraFect or designee must review and approve all changes to site-specific ICFs.

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

Before undergoing screening, each patient must consent in writing to study participation. If the patient is not able to provide informed consent, he/she can be enrolled according to local regulatory requirements (Section 12.1). The patient (or representative) will sign and date the ICF. The person rendering consent will also sign and date the ICF as the person who obtained

the consent of the patient. The original signed ICF will be retained with the study center's records. Each patient will receive a copy of his or her signed ICF.

19.3. Data Privacy

Applicable data privacy laws and regulations must be adhered to. The Investigator and ContraFect are responsible for ensuring that sensitive information is handled in accordance with local requirements (e.g., Health Insurance Portability and Accountability Act [HIPAA]).

Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

20. RECORD KEEPING/RETENTION OF RECORDS

The Investigator must ensure that all records pertaining to the conduct of the clinical study, ICFs, 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 CRF 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 will retain the original CRF 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 records will be kept in a locked file cabinet. 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 local 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. If necessary, 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: Diagnosis Definitions

The investigator will determine diagnosis at screening and on Day 7 to determine SOC treatment duration. An independent blinded Adjudication Committee will adjudicate the Day 7 diagnosis, and this adjudicated diagnosis will be considered the final diagnosis to be used for the analysis. The diagnosis definitions that will be used by the investigator and Adjudication Committee are provided in the table below.

Diagnosis	Definition
S. aureus endocarditis	Definite or possible endocarditis based on the Modified Duke Criteria (Li, et al. 2000), as defined below. 1. **Definite** diagnosis: presence of 2 major, 1 major and 3 minor, or 5 minor criteria, or 2. **Possible** diagnosis:1 major criterion and 1 minor criterion, or 3 minor criteria Major and minor criteria are as follows: A. Major clinical criteria: 1. Blood cultures positive for endocarditis: a. *S. aureus* (in the absence of a primary focus) identified from 2 separate blood cultures b. Microorganisms consistent with endocarditis 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]) 2. Evidence of endocardial involvement: a. Echocardiogram positive for infective endocarditis with pendulum-like intracardiac mass on valve or supporting structures, or in the path of regurgitant jets b. New valvular regurgitation (worsening or changing of preexisting murmur not a sufficient criterion) when confirmed by echocardiogram B. Minor clinical criteria: 1. Predisposition to endocarditis, such as predisposing heart condition, or intravenous drug use 2. Fever, defined as oral temperature equivalent > 38.0°C (> 100.4°F) 3. Vascular phenomena, such as conjunctival hemorrhage, and Janeway's lesions 4. Immunologic phenomena, such as glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor 5. Microbiologic evidence: positive blood cultures for *S. aureus* but with no major clinical criterion met or serologic evidence of active infection **Left-sided endocarditis**: involvement of mitral and/or aortic valve **Right-sided endocarditis**: involvement of pulmonic and/or tricuspid value **Left- and right-sided endocarditis**: involvement of mitral and/or aortic valve **AND** pulmonic and/or tricuspid value

Complicated *S. aureus* BSI	• Patient did not have endocarditis based on the Modified Duke Criteria; and • *S. aureus* was isolated from blood culture; and • Patient had one or more of the following: o Blood culture positive for *S. aureus* on more than one day o Signs or symptoms of catheter-related infection with clots in the vein at the catheter site seen on ultrasound o Signs or symptoms of metastatic foci of infection (e.g., deep tissue abscess, septic pulmonary emboli) or hematogenous seeding (e.g., septic arthritis) confirmed by physical examination, imaging, or culture o *S. aureus* isolated from sterile body site other than blood o Persistent fever (oral temperature equivalent ≥ 38.0°C [≥ 100.4°F]) at 72 hours or more after the initial blood culture o Skin examination findings suggesting the presence of acute systemic infection (e.g., presence of ecchymosis, infarcts, petechiae, pustules, or vasculitis) o Met criteria for severe sepsis or septic shock during the time of diagnosis/presumptive diagnosis of bacteremia ▪ Severe sepsis defined as a documented or presumed infection associated with either organ dysfunction, hypoperfusion, or hypotension (systolic blood pressure < 90 mm Hg or a decrease of > 4 mm Hg from baseline systolic measure in the absence of other causes of hypotension) AND the presence of SIRS (defined in Section 10.1) ▪ Septic shock defined as persistent hypotension and perfusion abnormalities despite adequate fluid resuscitation or organ function not capable of maintaining homeostasis o Significantly immunocompromised: ▪ AIDS (HIV positive with an AIDS-defining condition or a CD4 count < 200 cells/mm³) ▪ Severe leukopenia defined as ANC <500 cells/mL for ≥ 3 days in the 7 days prior to the qualifying blood culture ▪ Post organ-transplantation including autologous bone marrow transplantation ▪ On treatment for active graft vs. host disease ▪ On immunosuppressive therapy (e.g., ≥ 15 mg of prednisone or equivalent for more than 5 days, biologics such as infliximab, monoclonal antibodies such as daclizumab, methotrexate, cyclophosphamide, or similar agents) ▪ On chemotherapy treatment
Uncomplicated *S. aureus* BSI[a]	• Patient did not have endocarditis based on the Modified Duke Criteria; and • *S. aureus* was isolated from blood culture; and • Patient did not meet criteria for complicated *S. aureus* BSI

a Patients with known or suspected uncomplicated *S. aureus* BSI are not eligible for the study. The definition is included here in the event that patients are determined to have this diagnosis post-randomization.

23.2. Appendix 2: Apache II score

Certain components of the Apache II score will be determined locally (including oxygenation, Glasgow Coma Scale, and chronic health points) and other components will be obtained from central laboratory data.

Apache II Score Form

		HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	PHYSIOLOGIC VARIABLE	+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature rectal (°C)[a]	>=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 A-aDO_2 or PaO_2(mmHg) a)FiO_2>0.5:record A-aDO_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 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	130-139		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) 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) (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

a The method of temperature collection will be recorded in the eCRF and will be converted in programming to rectal temperature equivalent for Apache II score calculation.

Table continued on next page

Apache II Score Form

Glasgow Coma Scale (Circle appropriate response)		**B** Age Points	**C** Chronic Health Points	**Apache-II Score** (sum of A+B+C)
Eyes open 4 - spontaneously 3 - to verbal 2 - to painful stimuli 1 - no response Motor response 6 - to verbal command 5 - localizes to pain 4 - withdraws to pain 3 - decorticate 2 - decerebrate 1 - no response	verbal - nonintubated 5 - oriented and conversant 4 - disoriented and talks 3 - inappropriate words 2 - incomprehensible sounds 1 - no response verbal - intubated 5 - seems able to talk 3 - questionable ability to talk 1 - generally unresponsive	Age Points <44 0 45-54 2 55-64 3 65-74 5 >75 6 **Age points =**	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. Liver - Cirrhosis with PHT or encephalopathy Cardiovascular - Class IV angina or at rest or with minimal self-care activities Pulmonary - Chronic hypoxemia or hypercapnia or polycythaemia of PHT > 40 mmHg Kidney - Chronic peritoneal or haemodialysis Immune - Immune compromised host **Chronic Health Points =**	**A** APS points (from prior page) + **B** Age points + **C** Chronic Health Points _____ = Total Apache-II

Source: Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system" *Critical Care Medicine*. 1985;13(10);818–29.

23.3. Appendix 3: Microbiological Sample Collection and Processing

Patients who meet all screening criteria and have blood culture positive for *S. aureus* determined by rapid diagnostic or conventional method or Gram stain showing Gram-positive cocci in clusters plus positive tube coagulase test from blood culture specimens collected within 72 hours prior to randomization are eligible for the study.

Two aerobic blood cultures preferably from 2 different sites will be collected at screening at least 30 minutes apart and as close to the start of study drug dosing as possible, and at least one aerobic blood culture will be collected daily during the study until negative for 2 consecutive days and at Days 7 and 14 after CF-301/placebo administration. Additional blood cultures will be performed as clinically indicated. Cultures should be taken from a peripheral venipuncture site when possible using proper skin decontamination.

Blood samples must be transported to the local microbiology laboratory as soon as possible and incubated within less than 24 hours of collection. Each set (taken from different peripheral venipunctures) should be processed separately.

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 labs are encouraged to utilize the direct tube coagulase test when available. Patients may be enrolled if their Gram stain shows Gram-positive cocci in clusters and the direct tube coagulase test is positive after 4 hours of incubation.

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, as listed in the table below.

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

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

Blood must be directly inoculated on non-selective agar medium (e.g. tryptic soy agar + 5% sheep blood) to confirm organism identification and purity. Organisms must be isolated in pure culture and identified according to the local laboratory's standard operating procedures. Only *S. aureus* strains will be sent to the designated central microbiology laboratory for confirmation of identification and standardized susceptibility testing.

Results of Gram stain, organism identification, and rapid diagnostic testing will be recorded on the CRF.

Susceptibility Testing

Susceptibility testing of *S. aureus* should 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 should test susceptibilities to daptomycin, vancomycin, and oxacillin or cefoxitin (CLSI recommended surrogate for oxacillin to detect MRSA).

Results of susceptibility testing will be recorded on the CRF.

Archiving and Shipment of Isolates

All *S. aureus* strains will be stored frozen at -70°C in duplicate (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 central microbiology laboratory manual. Backup isolates will remain in storage at the site until notification from ContraFect. The sites local microbiology laboratory must maintain a shipment tracking log for each subject. This log should contain the subject number, specimen collection date/time, local lab accession number, genus/species and date of shipment.

23.4. Appendix 4: Central Laboratory Testing

The following laboratory tests will be performed by central laboratories. Only those laboratory tests required for eligibility screening will be performed by the local safety laboratory as described in Section 12.13.

Hematology	**Serum Chemistry**	**Coagulation Profile**	**Urinalysis**	**Immunologic Tests**	**Pregnancy**	**Exploratory Testing**	**Pharmaco-kinetics**
Hematocrit	Albumin	Prothrombin time (PT)/international normalized ratio (INR)	Color and appearance	CF-301-specific anti- drug antibody (ADA)	Serum pregnancy test	Future research[c]	PK samples for Subsets 1, 2, and 3[d]
Hemoglobin	Alkaline phosphatase	aPTT (activated partial thromboplastin time)	pH and Specific Gravity	CF-301-specific IgE			
Mean corpuscular hemoglobin (MCH)	Alanine aminotransferase (ALT)		Bilirubin	Serum tryptase (in event of anaphylaxis; (Section 11.2.3.1)[b]			
Mean corpuscular hemoglobin concentration (MCHC)	Aspartate aminotransferase (AST)		Glucose				
Mean corpuscular volume (MCV)	Bicarbonate		Ketones				
Platelet count	Bilirubin – total, direct, indirect		Leukocytes[a]				
Red blood cell (RBC) distribution width	Blood urea nitrogen (BUN)		Nitrite				
RBC count	Calcium		Protein				
White blood cell (WBC) count	Chloride		Urobilinogen				
WBC differential (% and absolute)	Creatinine						
Basophils	Gamma-glutamyl transferase (GGT)						
Eosinophils	Glucose						
Lymphocytes	Lactate dehydrogenase						
Monocytes	Phosphorus						
Neutrophils	Potassium						
Immature neutrophils	Sodium						
	Total protein						

a. 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, lukocyte esterase, nitrite.
b. If the serum tryptase sample is positive or equivocal, the sample may also be tested for β-tryptase.
c. Optional future research (e.g., cytokine and chemokine assays and/or biomarker evaluation). Note: future use samples will NOT be collected from patients in Israel.
d. PK Subset 1 will not be conducted in Israel.