Oral Sodium Fusidate (CEM-102) for the Treatment of Staphylococcal Bone or Joint Infections

NCT Number: NCT02569541

This supplement contains the following items:

1. Original/Final Protocol Version 1, 07 July 2015
2. Statistical Analysis Plan Final Version, 19 October 2017
3. Statistical Analysis Plan Amendment 1.0, 04 December 2017

CEM-102 Pharmaceuticals, Inc.

Clinical Study Protocol

Protocol Number:	CE06-302
Study Drug	CEM-102
Title:	An Open-Label, Non-Randomized, Single-Arm Multi-Center Study to Evaluate Oral Sodium Fusidate (CEM-102) for the Treatment of Staphylococcal Bone or Joint Infections in Subjects for whom Chronic Antibiotic Suppressive Therapy is Indicated
Sponsor	CEM-102 Pharmaceuticals, Inc. 6320 Quadrangle Drive, Suite 360 Chapel Hill, NC 27517 Telephone: (919) 313-6601 Fax: (919) 313-6620
Version / Date:	Version 1 / Original Protocol 07 July 2015

1 SIGNATURE PAGE

The signature of the Investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol as specified in both the clinical and administrative sections, including all statements regarding confidentiality. This study will be conducted in compliance with the protocol and all applicable regulatory requirements, in accordance with Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

Principal Investigator

_____

Printed Name

_____ _____

Signature Date

Representatives of CEM-102 Pharmaceuticals, Inc. who agree to the terms and conditions of this protocol include:

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Signature Date

2 SYNOPSIS

Name of Sponsor Company	Name of Finished Product	Name of Active Ingredient
CEM-102 Pharmaceuticals, Inc.	CEM-102 Tablets	Sodium Fusidate

Title of Study: An Open-Label, Non-Randomized, Single-Arm, Multi-Center Study to Evaluate Oral Sodium Fusidate (CEM-102) for the Treatment of Staphylococcal Bone or Joint Infections in Subjects for whom Chronic Antibiotic Suppressive Therapy is Indicated

Study No: CE06-302

Planned Number of Subjects: 30 subjects

Planned Number of Investigational Sites: Up to 20 (in the US)

Planned Study Period: 3 years

Objective:

To evaluate the safety and effectiveness of oral sodium fusidate (CEM-102) as chronic antibiotic suppressive therapy in subjects with staphylococcal bone or joint infections.

Rationale:

Subjects with bone or joint infections (with or without prosthetic material), who are unable to undergo definitive surgery (i.e. removal of infected bone, sequestrations, or foreign material) because of poor health status, age, or comorbidities, generally undergo an initial course of intravenous (IV) antibiotics followed by more limited surgery, consisting of debridement and irrigation. Often, chronic suppressive antibiotic therapy is utilized thereafter.

Some subjects experience an infection relapse, as manifested by bacteremia, purulent discharge, wound dehiscence, or pain, at some point following cessation of antibiotic therapy. Often, these subjects need to be hospitalized to receive another cycle of debridement, irrigation, and antibiotics (IV followed by oral antibiotic therapy for 3-6 months or longer). In some cases, the suppressive oral antibiotic therapy is not able to eliminate/reduce the pain and/or the wound drainage or to improve the ability to ambulate due to decreased weight bearing or lack of joint function. In addition, dosing or duration of currently available oral therapies may be limited by the emergence of treatment-limiting or treatment-related adverse events (such as renal toxicity, allergy, bone marrow suppression, paresthesias, or skin discoloration), comorbidities (such as renal insufficiency), or emergence of antimicrobial resistance. When any of these events happen, the oral antibiotic must be replaced.

Every time the infection relapses, the subject may be hospitalized to undergo another cycle of irrigation, debridement and antibiotic therapy (IV followed by oral antibiotic therapy). In some cases, amputation of the infected limb may be considered as a last resort.

There is clearly a need for additional effective oral antibiotics that can be safely administered and that will be well tolerated over extended treatment periods. Oral fusidic acid (CEM-102) has been available for use outside the US for over 4 decades and is considered safe and effective for the treatment and suppression of bone, joint, and prosthetic infections caused by staphylococcal spp.

Name of Sponsor Company	**Name of Finished Product**	**Name of Active Ingredient**
CEM-102 Pharmaceuticals, Inc.	CEM-102 Tablets	Sodium Fusidate

Methodology:

This is a prospective, open-label, non-randomized, single-arm trial to evaluate the safety and effectiveness of CEM-102 for chronic antibiotic suppressive therapy of bone or joint infections.

Subjects enrolling in this study must have a staphylococcal bone or joint infection that requires suppressive antibiotic therapy. Reasons a subject may be suitable for chronic oral antibiotic suppressive therapy include, but are not limited to, the following: 1) having an infection that cannot be managed by complete removal of the infected bone or foreign material, 2) having a refractory infection not responding to previous treatment, and 3) not being a candidate for long-term intravenous antibiotic therapy.

Subjects must have a bone or joint infection due to an inclusionary pathogen, demonstrated from a positive culture from samples obtained during surgery, biopsy, or drainage procedures within 6 weeks prior to enrollment.

Acceptable pathogens in this study include the following CEM-102-susceptible organisms: methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), and coagulase-negative staphylococci (CoNS) such as *S. epidermidis*, *S. hominis*, or *S. haemolyticus*. Specifically excluded from this list of pathogens is *S. saprophyticus*. Prior to enrollment, sensitivity of the isolate(s) to CEM-102 must be demonstrated.

Co-infection with *Corynebacterium* spp., *Propionibacterium acnes*, beta–hemolytic streptococci, and enterococci, or other bacteria susceptible to CEM-102 is permitted.

Co-infection with bacteria known or expected not to be susceptible to CEM-102 (e.g. Gram-negatives or anaerobes) is permitted, provided these bacteria can be treated with an adjunctive antibiotic to which the inclusionary staphylococcus is not susceptible, and there are no known drug-drug interactions with CEM-102.

CEM-102 must be initiated with one or more additional antibiotics (either oral or IV), referred to as companion antibiotics, for the first 1-2 weeks of the study. Companion antibiotic(s) will be selected per the Investigator's discretion on the basis of subject-specific antibiotic tolerability and pathogen susceptibilities. Because concomitant administration of rifampin results in markedly reduced levels of CEM-102 blood levels, rifampin must not be used as a concomitant antibiotic with CEM-102. After 1-2 weeks of therapy, the companion antibiotic must be discontinued. To be eligible for enrollment, the subject must be a suitable candidate for CEM-102 monotherapy after completion of 1-2 weeks of the companion antibiotic, for chronic treatment of the orthopedic infection due to the inclusionary pathogen.

This study comprises two parts: Part A (enrollment through the 6-month visit) and Part B (6-24 months post-enrollment). In Part A, all subjects will receive 6 months of CEM-102 treatment. The Investigator will evaluate each subject completing Part A for clinical response at the 6-month visit (primary endpoint). For Part B, a subject who completes Part A and, in the Investigator's opinion, requires continued suppressive therapy may continue to receive CEM-102. Alternatively, if the Investigator considers the infection resolved and that no further antibiotic therapy is required, study drug will be discontinued and the subject followed for evidence of relapse until End of Study (EOS).

During the first 6 months of treatment, study Part A, subjects will be monitored monthly (±1 week) for safety and clinical response to CEM-102. During study Part B, subjects will be monitored every 3 months (±2 weeks) until the End of Study Visit (24 months).

A subject who discontinues study drug because of treatment failure will have an EOS visit at that time. A subject who discontinues study drug due to an adverse event (AE) will be followed until the AE is resolved or stabilized. A subject who discontinues study drug due to clinical cure will be followed for relapse until EOS. If a subject withdraws from the study at any time, for any reason, an EOS visit will be performed at that time.

Duration of Subject Participation: The anticipated duration of participation for each subject will be 24 months. If the subject requires additional long-term chronic suppressive therapy with CEM-102 beyond study closure, the subject may be enrolled into an expanded access protocol to continue therapy.

Number of Subjects: 30 subjects

Name of Sponsor Company	**Name of Finished Product**	**Name of Active Ingredient**
CEM-102 Pharmaceuticals, Inc.	CEM-102 Tablets	Sodium Fusidate

Diagnosis and Criteria for Inclusion:

Screened subjects meeting all the inclusion and exclusion criteria described below may be enrolled in this protocol:

Inclusion Criteria:

1. Male or female subject ≥ 18 years of age, and adolescents between the ages of 12 and 18 years who weigh greater than 60 kg.
2. Subject must have a bone or joint infection due to an inclusionary pathogen demonstrated from a culture from samples obtained during surgery, biopsy, or drainage procedures within 6 weeks prior to enrollment.
   - Note: If subject does not have a confirmatory culture result, the Investigator must provide documentation as to why subject is suspected to have a staphylococcal infection and must discuss the subject with the medical monitor for approval of enrollment.
3. Inclusionary pathogen(s) include the following staphylococcal bacteria:
   - *S. aureus*: MSSA or MRSA
   - CoNS, such as *S. epidermidis*, *S. hominis*, or *S. haemolyticus* (*S. saprophyticus* is not an inclusionary pathogen)

   Note: Co-infection with *Corynebacterium* spp., *Propionibacterium acnes*, beta-hemolytic streptococci, and enterococci, or other bacteria susceptible to CEM-102 is permitted. Co-infection with bacteria known or expected not to be susceptible to CEM-102 (e.g. Gram-negative or anaerobic bacteria) is permitted, provided these bacteria can be treated with an adjunctive antibiotic to which the inclusionary staphylococcus is not susceptible, and there are no known drug-drug interactions with CEM-102.
4. Inclusionary pathogen, if identified, must be susceptible to CEM-102.
5. If the subject has a prosthetic joint, the implant is secured and fixed.
6. After completion of 1-2 weeks of the companion antibiotic, subject must be a suitable candidate for CEM-102 monotherapy for chronic treatment of the orthopedic infection due to the inclusionary pathogen.
7. Subject is not a candidate, as determined by the Investigator, for suitable alternative therapy. Reasons include, but are not limited to, the following:
   - Cannot undergo definitive curative surgical treatment (removal of all infected bone, joint, or foreign material) due to poor health status, age, or comorbidities
   - Not a candidate for long-term IV antibiotic therapy
8. The subject must be a suitable candidate for oral antibiotic therapy (i.e. able to swallow study medication tablets/capsules intact and have no known deficiency in gastrointestinal absorption).
9. The subject (or subject's legal guardian) must express commitment to comply with all study visits, procedures, and requirements for the duration of the study.
10. The subject (or subject's legal guardian has voluntarily signed the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved informed consent form (ICF). In cases of mental incapacity, the legal guardian is permitted to sign the ICF.
11. Female subjects of childbearing potential must use an acceptable contraception method (abstinence or double-barrier methods) for the duration of the study-drug treatment phase of the study and 30 days thereafter, and must have a negative serum or urine pregnancy test at Screening.

Exclusion Criteria:

1. Medical history of hypersensitivity or allergic reaction to sodium fusidate, fusidic acid (Fucidin® or any systemic or topical product containing fusidic acid) or its excipients.
2. Endovascular, infected intravascular foreign material, or infective endocarditis; or central nervous system infection, including meningitis

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3. Female subject who is pregnant or lactating.
4. Known severe renal impairment, as indicated by estimated creatinine clearance (CrCl) <30 mL/min (by Cockcroft-Gault calculation).
5. Immunocompromised subject or requirement for immunosuppressive therapy; Prior use of immunosuppressant agents (i.e. cyclosporine, TNFα antagonist) within 30 days of study medication administration.
6. Malignancy requiring ongoing cytotoxic chemotherapy.
7. Neutropenia (absolute neutrophil count <500/μL); Thrombocytopenia (platelet count <60,000/μL).
8. Known human immunodeficiency virus (HIV) infection and currently receiving antiretroviral therapy; Current CD4 count ≤200 cells/mm^3 (documented within 3 months prior to enrollment); If CD4 count is unknown, subject may not enroll.
9. Evidence of significant liver disease: alanine aminotransferase (ALT) >3 × upper limit of normal (ULN) or direct bilirubin >ULN; known cirrhosis with decompensation (i.e. Child-Pugh Class B or C disease).
10. Known hepatitis C virus (HCV) infection and currently receiving HCV-specific antiviral therapy. HCV infection alone, in the absence of decompensated liver disease, is not exclusionary.
11. Seizure disorder requiring current therapy with anticonvulsant.
12. Any underlying condition (e.g. addiction or clinically significant disease), that in the opinion of the Investigator, would be likely to interfere with assessment of the infection or completion of the study.
13. The use of an investigational drug within 4 weeks prior to screening.
14. Requires concomitant treatment with the following:
    - OATP1B1 and OATP1B3 substrates, in particular statins (e.g. HMG-CoA reductase inhibitors)
    - Medications metabolized by CYP2C8, such as glitazones (e.g. repaglinide)
    - CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, and nafcillin)
15. Prior treatment with a CYP3A4 inducer, such as dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, or nafcillin, within 7 days prior to enrollment.
16. Subjects requiring digoxin or warfarin therapy may only be enrolled if an achievable plan for therapeutic monitoring of the drug (digoxin) or prothrombin time has been reviewed and approved by the study medical monitor.

Dose and Mode of Administration:

Test Product: CEM-102

1500 mg (5×300 mg tablets) by mouth every 12 hours for 2 doses

600 mg (2×300 mg tablets) by mouth every 12 hours thereafter

CEM-102 must be taken within a +/- 2 hour window to the scheduled dose. On days when PK samples are obtained, CEM-102 must be taken within +/- 1 hour of the scheduled dose.

CEM-102 may be taken while fasting or with food.

CEM-102 will be supplied by CEM-102 Pharmaceuticals (a subsidiary of Cempra, Inc.).

Duration of Treatment:

This study is designed to evaluate a minimum of 6 months of treatment with CEM-102. Therapy may extend for up to 24 months. If the subject requires chronic suppressive therapy with CEM-102 beyond 24 months, the Investigator may choose to roll the subject into an expanded access protocol.

Companion Antibiotic Therapy:

CEM-102 must be initiated with one or more additional antibiotics (either oral or IV) for the first 1-2 weeks of the study. Companion antibiotic(s) will be selected per the Investigator's discretion on the basis of

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subject-specific antibiotic tolerability and pathogen susceptibilities. Examples include, but are not limited to, the following: IV cefazolin, vancomycin, daptomycin, or IV/PO linezolid (rifampin must not be used as a concomitant antibiotic with CEM-102). The companion antibiotic will not be provided by the Sponsor, but will be supplied by the investigative site as standard of care. Starting an antibiotic due to signs and symptoms of clinical failure (e.g., worsening redness, swelling, pain, purulent discharge, sinus tract formation, or bacteremia) will be classified as clinical failure.

Adjunctive Antibiotic Therapy for Co-infections:

Treatment of co-infections due to bacteria known or expected to not be susceptible to fusidic acid is permitted, provided these pathogens can be treated with an adjunctive antibiotic to which the inclusionary pathogen is not susceptible (e.g. aztreonam and metronidazole are permitted for treatment of Gram-negative and anaerobic co-infections).

Concomitant Antibiotic Therapy for Unrelated Infections:

Treatment of an unrelated infection with an antibiotic to which the inclusionary pathogen is susceptible is permitted only if the antibiotic is administered for ≤ 10 days on any single occasion, and ≤ 2 courses during any 6-month period during the study (and provided there are no known drug-drug interactions with CEM-102).

Primary Endpoint:

The primary endpoint will be the proportion of subjects in the intent to treat (ITT) analysis set who meet all the criteria for clinical success at the 6-Month Visit.

Clinical success is defined to occur when subjects meet all of the following criteria:

- Subject was not hospitalized due to worsening of the study-qualifying orthopedic infection at any point between enrollment and the 6-Month Visit
- Subject did not undergo a definitive surgical procedure (such as amputation) at any point between enrollment and the 6-Month Visit
- No additional antibiotics (after completion of companion antibiotics) are required for treatment of the orthopedic infection due to the inclusionary pathogen
- Wound is closed, or the open area decreased in size (L x W) and, if a skin graft was done, the graft remains viable without evidence of infection
- No purulent discharge from the surgical wound, or new or recurring sinus tract
- No worsening of redness, tenderness, or swelling at the primary infection site
- No bacteremia of the inclusionary pathogen at any point between enrollment and the 6-Month Visit

Clinical failure defined as follows:

- Failure to meet all criteria for clinical success
- Death (due to the primary infection)
- Discontinuation of study drug due to an AE and the requirement of additional antibiotics for treatment of the primary infection
- Use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for > 10 days on any occasion, or for > 2 courses during any 6-month period

Indeterminate:

- Subject withdraws consent
- Subject is lost to follow-up

Investigators will evaluate and provide documentation of each subject for a clinically meaningful difference in each subject's response prior to making a determination of treatment failure for the primary study endpoint.

Secondary Endpoints:

- The safety and tolerability of CEM-102 for the treatment of bone and joint infections, reported as subject incidences of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs in the safety analysis set

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- The proportion of subjects in the ITT analysis set who meet all the criteria for clinical success, as defined above, at the 9-Month, 12-Month, 15-Month, 18-Month, 21-Month, and 24-Month Visits
- Pharmacokinetics of CEM-102 used chronically in subjects with orthopedic infections

Safety Evaluations:

The 6-month history of all prior antibiotics used to treat the primary infection will be recorded in the electronic case report form (eCRF). All other medications taken during the period from 7 days prior to enrollment through the End of Study (EOS) will be recorded in the eCRF.

AEs will be collected from the date of execution of the Informed Consent through 30 days after last dose of study drug or until resolution/stabilization of all AEs. Safety assessments, including laboratory assessments (serum chemistry and pregnancy test), physical examination, and vital signs, will be obtained as indicated in the Schedule of Assessments (Table 1).

The number and percent of subjects with treatment-emergent graded laboratory abnormalities (defined based on the Division of Microbiology and Infectious Diseases (DMID criteria) and vital sign changes from Baseline will be summarized.

The incidence of treatment-related AEs from enrollment until the end of the study (6-Month Visit or EOS Visit) will be tabulated by System Organ Class, preferred term, and maximum severity (mild, moderate, or severe/life threatening).

Statistical Methods and Data Analysis:

As a non-randomized, single-arm study, there will be no formal statistical analyses. This study is not powered for inferential statistical analyses, and no formal hypothesis testing will be conducted. Safety and efficacy will be descriptive. Clinical outcome will be reported as the proportion of subjects meeting the criteria of clinical success.

All safety data will be summarized using the Safety analysis set. Adverse events (AEs) will be coded with the Medical Dictionary for Regulatory Activities (MedDRA®). The number and proportion of subjects having treatment-emergent AEs will be tabulated by MedDRA System Organ Class (SOC) and preferred term, severity, and relationship to study drug.

Because this is a non-randomized, open-label, single-arm study, interim data may be summarized and reported, as needed, prior to database lock.

Details of the analysis will be provided in a separate Statistical Analysis Plan (SAP).

Table 1 Schedule of Assessments/Procedures

Assessment/Procedure	Screening[a]	Part A			Part B	
		Enrollment (Day 1 Visit)[b,c]	Day 8 (± 3 days)	Monthly During First 6 Months (±1 week)	Every 3 Months From Month 6 until End of Study (±2weeks)	End of Study (EOS)[d]
Informed Consent Form	X					
Inclusion/Exclusion Criteria Review	X	X				
Review of Clinical/ Surgical History	X	X	X	X	X	X
Microbiological specimens for culture	X	X	X[e]	X[e]	X[e]	X[e]
Enrollment		X				
Vital Signs[f]	X	X	X	X	X	X
Limited Physical Examination[g]	X	X	X	X	X	X
Examination of Infected Area[h]	X	X	X	X	X	X
Safety Laboratory Assessments[i]	X	X	X	X	X	X
Inflammation Laboratory Assessments[j]	X	X		X	X	X
CEM-102 Administration [k]		X				
Pharmacokinetic Blood Sampling				X[o]		
Dispense Oral antibiotic to Subjects[l]		X	X	X	X	
Perform Drug Accountability			X	X	X	X
Record 6-Month History of Prior Antibiotic Used to Treat the Primary Infection Leading to Enrollment	X					
Record Concomitant Medications	X	X	X	X	X	X
Record AEs[m]	X	X	X	X	X	X
Investigator Assessment of Clinical Response[n]				X	X	X

a. Within 6 weeks prior to enrollment, subjects must have a positive culture with an inclusionary pathogen susceptible to CEM-102, demonstrated from a culture from samples obtained during surgery, biopsy, or drainage procedures. If subject does not have a confirmatory culture result, the Investigator must provide

documentation as to why subject is suspected to have a staphylococcal infection and must discuss the subject with the medical monitor for approval of enrollment.

b. Enrollment is contingent on demonstration that subject fulfills the inclusion/exclusion criteria.

c. Study Day 1 corresponds to the first day of dosing with CEM-102.

d. Subjects who discontinue CEM-102 because of an adverse event (AE) or clinical failure should have a study visit around the time of drug discontinuation and will continue to be followed, as needed, for appropriate observation of treatment-related AEs until AEs have resolved or stabilized. If a subject withdraws from the study at any time, for any reason, the EOS visit will be performed around that time. Those subjects who continue CEM-102 until the Month 24 visit will undergo the assessments/procedures for the EOS visit. At study closure, at the discretion of the Investigator, subjects may be rolled over into an expanded access protocol to receive chronic suppressive CEM-102 therapy.

e. If clinically indicated, microbiological samples (tissue surrounding the foreign material, synovial fluid, bone, etc.) obtained during the study should be submitted to the local laboratory for aerobic and anaerobic culture and susceptibility testing, including to CEM-102. All isolated bacteria are to be sub-cultured and shipped to the central microbiology laboratory for organism confirmation and confirmatory susceptibility testing.

f. Vital sign measurements include height, weight, temperature, heart rate, respiratory rate, and blood pressure. Results are to be recorded in the eCRF.

g. Limited physical examination may include HEENT, cardiovascular, pulmonary, gastrointestinal, skin, lymph nodes, musculoskeletal, and extremities, among others. Results are to be documented in source and recorded in the eCRF.

h. Examination of the infected area will include the following assessments: pain, erythema, mobility, joint stability, wound closure, wound drainage, and weight bearing [for back and lower extremity infections]. The Investigator will state whether the infected area seems to have improved, deteriorated, or remained unchanged. Results are to be documented in the source and recorded in the eCRF.

i. Safety laboratory assessments will be performed at the local laboratory and will include the following: serum chemistry (ALT, AST, alkaline phosphatase [ALP], total and direct bilirubin, blood urea nitrogen [BUN], creatinine, albumin, total protein, sodium, total carbon dioxide, glucose, potassium, chloride, calcium, phosphorus, and CPK). For female subjects of child bearing potential, a urine or serum pregnancy test will be performed at Screening and will be repeated at subsequent visits per Investigator's discretion. .

j. Laboratory measurements of markers of inflammation will be performed at the local laboratory and will include the following: hematology (complete blood count [CBC] with differential), erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]). Laboratory measurements of markers of inflammation obtained on the day of a surgery or debridement should be performed before the procedure when possible, because levels of these markers are known to increase after surgery.

k. A CEM-102 loading dose strategy is utilized, in which CEM-102 is given as 1500 mg every 12 hours for 2 doses followed by 600 mg every 12 hours thereafter.

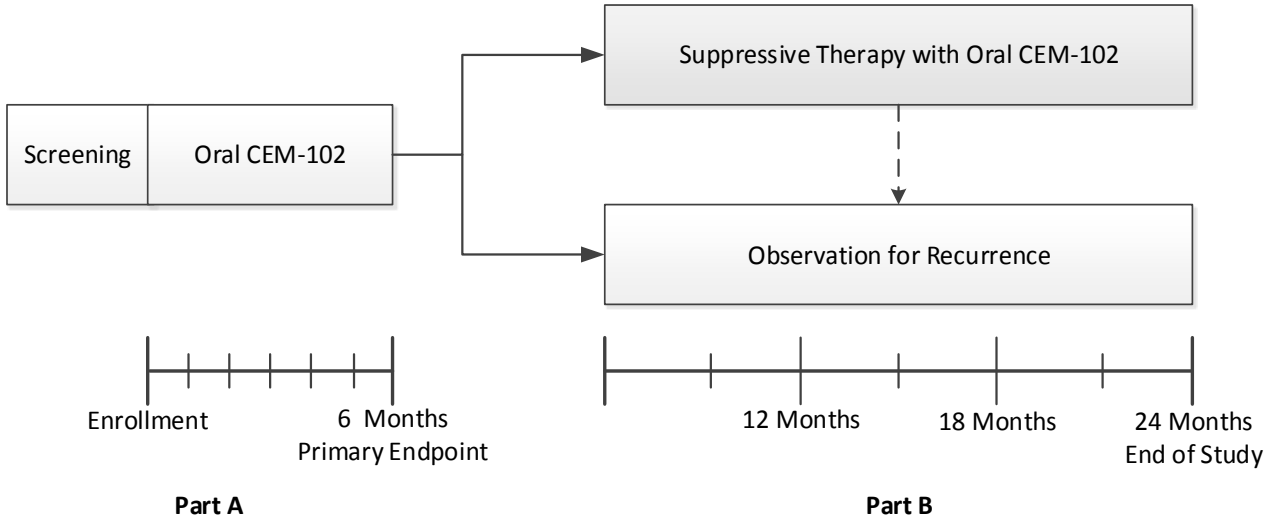
l. After 6 months of therapy, the Investigator may decide to continue chronic suppressive therapy with CEM-102 or discontinue CEM-102 due to clinical cure and no further requirement for antibiotic therapy. Subjects who stop treatment will continue to be followed on the same schedule as those who remain on therapy to monitor for infection relapse until the end of the study. Subjects who discontinue CEM-102 due to clinical failure should have an EOS visit at that time.

m. All AEs will be collected following signing of the ICF.

n. The Investigator will assess clinical response at Months 6, 9, 12, 15, 18, 21, 24 and at EOS.

o. Pharmacokinetic blood sampling will be conducted at the 3-month visit as described in Section 10.6

Figure 1 Schematic of Study Design



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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABSSSI	Acute bacterial skin and skin structure infection
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice a day
BJI	bone or joint infection
BUN	blood urea nitrogen
CBC	complete blood count
CE	clinically evaluable
CEM-102	sodium fusidate (fusidic acid)
CF	cystic fibrosis
CFR	Code of Federal Regulations
CK	Creatine kinase
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum concentration
CoNS	coagulase-negative staphylococci
CPK	creatinine phosphokinase
CrCl	creatinine clearance
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
CYP	cytochrome P450
DAR	debridement and prosthesis retention
DMID	Division of Microbiology and Infectious Diseases
ECG	electrocardiogram
eCRF	electronic case report form
EF-G	Elongation factor-G
EOS	End of Study
EOT	End of Treatment
ESR	erythrocyte sedimentation rate
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FA	Fucidic Acid
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practices
GGT	gamma-glutamyl transpeptidase

HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, throat
hERG	human ether à-go-go related gene
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
ME	medically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MHA	Mueller-Hinton Agar
MIC	Minimum Inhibitory Concentration
mITT	microbiological ITT
MRCoNS	methicillin-resistant coagulase-negative staphylococci
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NI	Non-inferiority
NOAEL	No adverse effect level
OATP1B1/ OATP1B3	hepatic drug influx transporters
PCR	polymerase chain reaction
PJI	prosthetic joint infection
PK	pharmacokinetic
PO	taken orally
PT	prothrombin time
SAE	serious AE
SAP	Statistical Analysis Plan
SI	Systeme International d'Unites
SOC	System, Organ, Class
SoC	Standard of Care
TEAE	treatment-emergent AE
TID	three times a day
TOC	test of cure
UNL	upper normal limit

5 INTRODUCTION

CEM-102 (sodium fusidate, fusidic acid) is the only member of a novel class of antibiotics, the fusidanes. It inhibits bacterial protein synthesis by interacting with elongation factor-G (EF-G). It has a unique mechanism of action, and there is little cross-resistance with other antibiotics in clinical use. Oral tablets and topical fusidic acid have been used for over 4 decades in the United Kingdom and other parts of Western Europe, as well as in many other countries, to treat infections caused by *Staphylococcus aureus*. Intravenous formulations and an oral suspension have been developed by Leo Laboratories (Ballerup, Denmark), but their clinical use has been limited. Oral CEM-102 300 mg tablets are under development in the United States (US) by CEM-102 Pharmaceuticals (a subsidiary of Cempra, Inc.) for treatment of acute bacterial skin and skin structure infection (ABSSSI).

CEM-102 has potent in vitro activity against Gram-positive aerobic organisms. Antimicrobial activity against staphylococci recovered from US subjects with blood, bone and joint, respiratory tract, and skin and skin structure infections (ABSSSI) as part of international surveillance studies conducted between 2008 and 2014 showed that CEM-102 inhibited 99.7% of *S. aureus* isolates (and 99.8% of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates) at a minimum inhibitory concentration (MIC) ≤ 1µg/mL. The majority of coagulase-negative staphylococci (CoNS) with or without oxacillin-resistance were similarly susceptible. Among other Gram-positive bacteria, CEM-102 has activity against enterococci (MIC_{90} 4 mg/L), *Corynebacterium* spp. (MICs ≤ 0.12 µg/mL), *Micrococcus luteus* (MICs ≤ 0.5 µg/mL), and *Streptococcus pyogenes* (MIC_{90} 8 µg/mL). In addition, CEM-102 is active against *Propionibacterium* spp. (MIC_{90} 1 µg/mL). CEM-102 does not have significant activity against Gram-negative aerobic and anaerobic bacteria.

Adkins and Gottlieb (Adkins 1999) reviewed published experience with fusidic acid in the treatment of bone and joint infections (BJI), citing its utility in the treatment of acute and chronic osteomyelitis, vertebral infection, septic arthritis, and prosthetic and other device related infections. The authors considered achievement of effective bone and joint fusidic acid concentrations a key factor in its historical efficacy in the treatment of these conditions. Lautenbach and colleagues measured serum and bone fusidic acid concentrations (by agar plate diffusion methods using a susceptible bacterial strain) in 36 patients with chronic osteomyelitis during the course of therapy; bone concentrations of active drug ranged from 1 to 15 µg/g, measured at approximately 9 hours after last oral dose (in most cases, 20 to 40 mg/kg/day, divided three times daily (TID) (Lautenbach 1975). Hieholzer and colleagues measured bone and soft tissue concentrations at 3 to 6 hours after last oral dose (500 mg TID dosing for at least 5 days) in a series of patients with osteomyelitis and found fusidic acid concentrations of 2 to 15 µg/g in bone and 4 to 17 µg/g in soft tissue (Hieholzer 1966, Hieholzer 1974). A second group of patients studied by the same Investigators were administered fusidic acid (500 mg TID, orally) for 5 to 13 days prior to surgery for non-infected bone disease; bone fusidic acid concentrations were, on average, up to two-fold higher than those observed in patients with osteomyelitis, and mean concentrations ranged from 46% to 94% of those observed in serum. Chater reported fusidic acid concentrations in bone and serum from 7 adult patients treated with 500 mg TID oral fusidic acid for osteomyelitis; bone concentrations were similar to those described above, and ranged from 4% to 72% of serum concentrations, with consistently higher soft tissue concentrations (ranging from 20% to >100% of serum concentrations) (Chater 1972). In summary, oral fusidic acid dosing was

found to achieve drug concentrations at the site of infection that were associated with effective treatment of osteomyelitis across a number of studies.

Subjects with bone or joint infections (with or without prosthetic material), who are unable to undergo definitive surgery (i.e. removal of infected bone, sequestrations, or foreign material) because of poor health status, age, or comorbidities, generally undergo an initial course of intravenous (IV) antibiotics followed by more limited surgery, consisting of debridement and irrigation. Often, chronic suppressive antibiotic therapy is utilized thereafter.

Some subjects experience an infection relapse, as manifested by bacteremia, purulent discharge, wound dehiscence, or pain, at some point following cessation of antibiotic therapy. Often, these subjects need to be hospitalized to receive another cycle of debridement, irrigation, and antibiotics (IV followed by oral antibiotic therapy for 3-6 months or longer). In some cases, the suppressive oral antibiotic therapy is not able to eliminate/reduce the pain and/or the wound drainage or to improve the ability to ambulate due to decreased weight bearing or lack of joint function. In addition, dosing or duration of currently available oral therapies may be limited by the emergence of treatment-limiting or treatment-related adverse events (TEAE) (such as renal toxicity, allergy, bone marrow suppression, paresthesias, or skin discoloration), comorbidities (such as renal insufficiency), or emergence of antimicrobial resistance. When any of these events happen, the oral antibiotic must be replaced.

Every time the infection relapses, the subject may be hospitalized to undergo another cycle of irrigation, debridement, and antibiotic therapy (IV followed by oral antibiotic therapy). In some cases, amputation of the infected limb may be considered as a last resort.

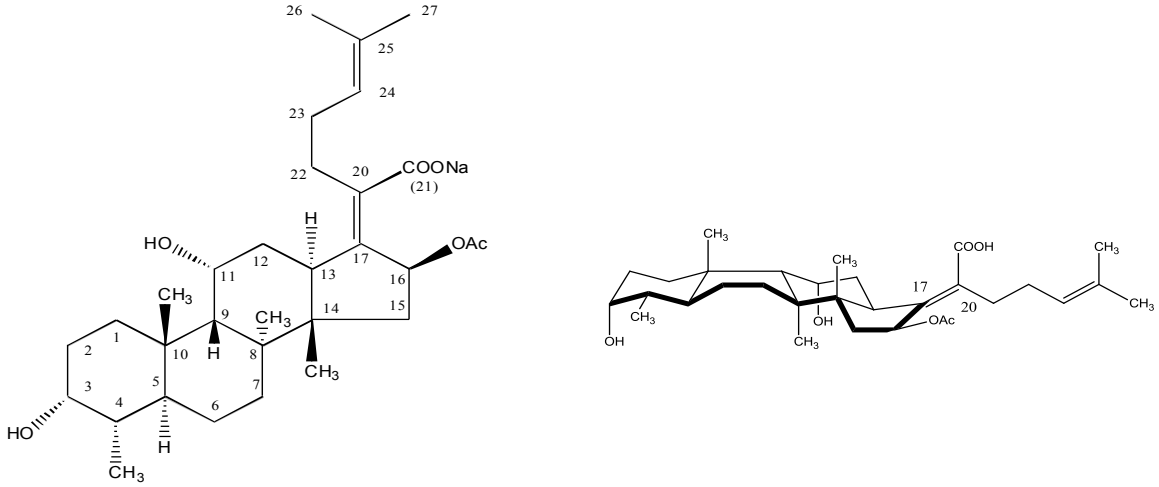
There is medical need for new oral agents with improved activity and good safety and tolerability over extended treatment periods against Gram-positive bacteria, including drug resistant pathogens. The purpose of this study is to evaluate the safety and effectiveness of CEM-102 for chronic antibiotic suppressive therapy of bone or joint infections.

In addition to adults, this study will also include adolescent subjects between the ages of 12 and 18 years who weigh greater than 60 kilograms. In a retrospective cohort study by (Olson 2014), the authors reviewed all patients in a children's Infectious Disease clinic over a 2-year period who received ≥ 14 days of oral or intravenous antimicrobial medication. Of 335 subjects enrolled, the most commonly treated principal infections were septic arthritis, acute osteomyelitis, and chronic osteomyelitis in 18%, 15% and 8% of subjects, respectively. Furthermore, in a study by Learmonth 1984, in 45 pediatric patients with osteomyelitis and septic arthritis, sodium fusidate and erythromycin for 3 weeks was found to be an effective first-line antibiotic regimen. Since pediatric patients with orthopedic infections are not uncommon, this study will attempt to obtain important safety information on CEM-102 use in this adolescent population.

5.1 Fusidic Acid (CEM-102)

Fusidic acid is chemically described as: sodium ent-16α-acetoxy-3β, 11β-dihydroxy-4β, 8β, 14α-trimethyl-18-nor-5β, 10α-cholesta-(17Z)-17(20), 24-dien-21-oate.

Figure 2 Chemical Structure of Fusidic Acid



5.1.1 Mechanism of Action and Microbiological Activity

CEM-102, the only antibiotic of the fusidane class, is active against Gram-positive bacteria through inhibition of bacterial replication, and is thus considered bacteriostatic. However, as with many bacterial protein synthesis inhibitors, CEM-102 may be bacteriostatic or bactericidal depending upon the inoculum size.

CEM-102 inhibits bacterial protein synthesis through inhibition of the Elongation Factor G (EF-G). Elongation Factor G is an essential bacterial protein that is involved in translocation on the ribosome after peptide bond formation. Due to this novel mechanism of action, little cross-resistance between fusidic acid and other antibiotics has been reported.

CEM-102 is active against staphylococci and has potent activity against staphylococci that express methicillin resistance (MRSA, including USA300 strains, MIC_{90} 0.12 µg/mL for both) and linezolid resistance (MICs <0.25 µg/mL). Coagulase negative staphylococci (CoNS) with or without oxacillin (methicillin) resistance are also highly susceptible to CEM-102. Among other Gram-positive bacteria, CEM-102 is active against Group A β-hemolytic streptococci (*S. pyogenes*) with an MIC_{90} of 8 µg/mL. At these concentrations, CEM-102 is bactericidal for *S. pyogenes*.

A total of 99.7% of methicillin-susceptible *Staphylococcus aureus* (MSSA) and 99.8% of MRSA isolates from US patients with blood, bone and joint, respiratory tract, and skin and skin structure infections, recovered during international surveillance studies conducted between 2008 and 2014, had an MIC_{90} ≤0.12 µg/mL (Table 2). In addition, the MIC_{90} was 0.25 µg/mL for CoNS with or without oxacillin resistance. The MICs against other Gram-positive bacteria were greater. CEM-102 does not have significant activity against Gram-negative aerobic and anaerobic bacteria.

Table 2 International Fusidic Acid Resistance Surveillance 2008-2011, 2014: Susceptibility of U.S. Isolates

Organism (number tested)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	% Susceptible[a]
S. aureus (15,045)	0.12	0.12	99.7
MSSA (7364)	0.12	0.12	99.6
MRSA (7681)	0.12	0.12	99.8
CoNS (1798)	0.12	0.25	92.6
MSCoNS (531)	0.12	0.12	97.6
MRCoNS (1267)	0.12	0.25	90.5
Enterococcus spp. (3876)	4	4	-
Vancomycin-resistant (≥8 mcg/mL) (1224)	4	4	-
Beta-hemolytic streptococci (2032)	8	>8	-
Group A (836)	4	8	-
Group B (906)	8	>8	-

Source: 09-CPI-04 (2008 International Surveillance for CEM-102), 09-CPI-05 (2009 International Surveillance for CEM-102), 09-CPI-03 (2010 International Surveillance for CEM-102), 11-CEM-01B (2011 International Surveillance for CEM-102), and 14-CPI-01 (2014 International Surveillance for CEM-102)

a. Determined according to published EUCAST (2015) breakpoint criteria (MIC ≤ 1 µg/mL, susceptible). For enterococci and streptococcal species, EUCAST breakpoints have not been established.

High-level resistance to fusidic acid in staphylococcal species generally occurs through mutations in *fusA,* the gene encoding EF-G (Turnidge 1999, Besier 2003). Low-level resistance is most commonly caused by acquisition through horizontal transfer of the genes *fusB* or *fusC*, which encode proteins that bind EF-G on the ribosome, enabling resumption of translation that has been stalled by the fucidic acid/EF-G interaction (O'Neill 2006, O'Neill 2007, Guo 2012). Emergence of staphylococcal resistance to fusidic acid outside of the US has probably been facilitated by the routine dosing practices (both as a topical therapy for minor skin infections (Rijinders 2012) and with oral non-loading dose strategies).

However, even after decades of fusidic acid use outside the US, including topical use, in a 2011 international surveillance, 93.4% of *S. aureus* strains circulating in Europe were susceptible to fusidic acid using the EUCAST breakpoint of 1 µg/mL. Only 1.5% of European *S. aureus* strains carried high-level resistance to fusidic acid (MIC ≥ 8 µg/mL).

Furthermore, a new loading dose regimen will achieve high blood concentrations within 24 hours and likely will reduce the emergence of resistance. This dosing regimen consists of 1500 mg Q12h for two doses, followed by 600 mg Q12h thereafter.

5.2 Nonclinical

CEM-102 showed weak inhibition of the hERG current (3.1% at 100 µM) in vitro. No significant cardiovascular effects were observed in the micropig. There were no treatment-related central nervous system effects in rats following repeat dosing of up to 250 mg/kg/day for 28 days. No treatment-related respiratory changes were observed in dogs at doses up to 250 mg/kg/day for 4 weeks.

CEM-102 is orally bioavailable in rodents and dogs, but achievable serum concentrations after oral administration are substantially lower than those expected in humans with the loading dose

regimens to be used in clinical studies. CEM-102 did not accumulate in plasma following 28 days of dosing in rats or dogs.

No studies have examined the excretion of CEM-102; however, literature reports of studies with ^{14}C-labeled fusidic acid in rats and rabbits have identified the compound as primarily excreted by the liver into bile, with very little radioactivity in the urine.

CEM-102 administration to rats and dogs for 4 weeks was generally well tolerated at doses up to 250 mg/kg/day; the major target toxicity at high doses consisted of gastrointestinal effects and adrenal gland changes in the dog. There were no serious adverse toxicities, with a no adverse effect level (NOAEL) of 100 mg/kg/day for rats and 40 mg/kg/day for dogs.

CEM-102 was not mutagenic or clastogenic in genetic toxicity assays.

No CEM-102 related effects on fertility parameters were noted in male or female rats. The NOAELs for maternal toxicity and fetal development effects were 100 and 200 mg/kg in the rat and 115 and 175 mg/kg in the rabbit, respectively. Studies on prenatal and postnatal development and maternal function have not been conducted.

5.3 Clinical

Cempra has conducted three Phase 1 studies with CEM-102 in healthy adult subjects, one Phase 2 clinical study in adults with acute bacterial skin and skin structure infections (ABSSSI), and one phase 2 trial in prosthetic joint infection (PJI). The PJI trial was terminated because of decreased fusidic acid blood concentrations secondary to concomitant rifampin administration (drug-drug interaction). A total of 234 adult subjects have received CEM-102 in Phase 1 and Phase 2 trials.

Two single-patient expanded access trials have been conducted, and one intermediate-size expanded access trial is ongoing. Study CE06-EA01 (single-patient expanded access) provided CEM-102 for a single patient with chronic MRSA bone and joint infection. Study CE06-EA02 (single-patient expanded access) provided CEM-102 for chronic methicillin-resistant *S. aureus* (MRSA) pulmonary infection in a single patient with cystic fibrosis (CF), and two subjects, both with chronic MRSA infections of a hip prosthesis, have been treated with CEM-102 in Study CE06-EA03 (intermediate-size expanded access).

5.3.1 Clinical Pharmacology and Metabolism

CEM-102 binds primarily to albumin in human plasma (96.3% to 96.8% bound); this binding is reversible.

A food effect study showed that food had no clinically significant effect on the pharmacokinetics (PK) of CEM-102. Gastrointestinal side effects, primarily nausea and vomiting, appeared to be lessened by dosing with food.

CEM-102 has a plasma half-life of approximately 12 hours, and slowly accumulates to steady state levels when administered orally as 500 mg three times daily (TID) (the recommended European dose schedule). In a Phase 1 study with CEM-102 given 500 mg TID, trough levels rose steadily from Day 1 through Day 5, attaining mean trough concentrations of 105 μg/mL prior to the final

dose on Day 5. However, by employing a loading dose strategy and twice daily (BID) administration, target therapeutic peak and trough plasma concentrations (>100 µg/mL) were achieved by 24 hours. With a loading dose of 1650 mg BID on Day 1 followed by 825 mg BID for 6.5 days, a mean trough plasma concentration of 146 µg/mL was achieved by 24 hours post-first-dose, and a mean trough plasma concentration of 204 µg/mL was reached after 7 days of dosing.

Use of a loading dose (or 'front-loading') strategy is anticipated to reduce the exposure of pathogens to sub-therapeutic drug concentrations. Pharmacokinetic studies evaluating front-loaded dosing regimens demonstrated that it was possible to rapidly achieve and sustain trough fusidic acid concentrations that are well in excess of the established breakpoint for *S. aureus* (EUCAST criteria, ≤ 1.0 µg/mL). It had been previously demonstrated that fusidic acid resistance emergence frequencies were low at high multiples of MIC (O'Neill 2006), and this observation was confirmed in hollow-fiber culture models, in which loading dose PK parameter fusidic acid exposure substantially reduced resistance emergence (Tsuji 2011).

CEM-102 is likely metabolized by multiple CYP450 isoforms, primarily CYP3A4, and in vitro does not significantly induce CYP enzymes. CEM-102 inhibits CYP2C8 activity in a dose-dependent manner, suggesting a potential for metabolism-based interactions for drugs that are metabolized by CYP2C8, such as glitazones. At high concentrations, CEM-102 is a moderate inhibitor of other CYPs.

CEM-102 inhibits a number of efflux and uptake transport proteins in vitro. These data suggest that CEM-102 has the potential to interact with a variety of drugs through transporter inhibition and offer a mechanistic explanation for the adverse interaction between statins and fusidic acid that has been previously identified, and which appears to be mediated (at least in part) by OATP1B1 and OATP1B3 inhibition.

Drug-drug interaction studies have not been completed with CEM-102. Based on Fucidin® (sodium fusidate or fusidic acid) product labeling (Fucidin®1 2013, Fucidin®2 2013, Fucidin® 2014), clinical Study CE06-200, and published reports, interactions may occur with the following: OATP1B1 and OATP1B3 substrates (in particular, statins); CYP3A4 biotransformed drugs (including target specific oral anticoagulants principally metabolized by CYP3A4 such as rivaroxaban and apixaban), cyclosporine; human immunodeficiency virus (HIV) protease inhibitors; statins; estrogens; and drugs that have a similar biliary excretion pathway); CYP3A4 inducers (such as dexamethasone, phenytoin, carbamazepine, nafcillin, rifampin, phenobarbital); and CYP3A4 inhibitors (such as azole antifungals; erythromycin, clarithromycin; and grapefruit juice).

5.3.2 Summary of Efficacy

5.3.2.1 Phase 2 ABSSSI Study

Study CE06-300 was a Phase 2 randomized, double-blind, multi-center efficacy and safety study to evaluate oral CEM-102 (a loading dose of 1500 mg BID on Day 1 followed by 600 mg BID) compared to oral linezolid 600 mg BID administered for 10 to 14 days in the treatment of patients with ABSSSI. Clinical success was defined as total resolution of local and systemic signs and

symptoms of the infection at the test of cure (TOC) visit such that no further antibiotic therapy was required. The primary efficacy endpoint was clinical success at the TOC for the Intent to Treat (ITT) and clinically evaluable (CE) populations.

Males and female subjects ≥18 years of age with a diagnosis of an ABSSSI (cellulitis, with or without focal abscess, or wound infection) suspected or confirmed to be caused by a Gram-positive pathogen (staphylococci or streptococci), in whom 10 to 14 days of oral antibacterial therapy was appropriate, were evaluated for potential enrollment. Patients were randomized using a sequence that was stratified by type of infection (cellulitis or wound infection), and then randomized in a 1:1:1 ratio to 1 of 3 treatment arms within each stratum: conventional regimen (CEM-102 600 mg BID), loading dose regimen (CEM-102 1500 mg BID on Day 1, followed by 600 mg BID), or linezolid 600 mg BID, each administered orally for 10 to 14 days.

The study was initially designed as an adaptive trial that provided for transition to a Phase 3 non-inferiority (NI) trial (n=700) with one of the two CEM-102 regimens compared to linezolid if certain predictive criteria were met. Interim analyses were performed after 90, 127, and 181 patients were enrolled and evaluated for the primary outcome of clinical response at the TOC visit as well as for safety and tolerability. At the 127 patient interim analysis, the CEM-102 non-loading dose and loading dose regimens showed comparable safety and tolerability; hence, the CEM-102 conventional dose regimen was dropped, and the remaining patients were randomized 1:1 to CEM-102 loading dose or linezolid. At the 181 patient interim analysis, the predictive probability of clinical success in the clinically evaluable population in Phase 3 was 0.89, which exceeded the threshold for transitioning to the Phase 3 stage of the trial; therefore, when these results were available, enrollment in the Phase 2 stage of the trial was terminated (total n=198).

Four patient populations were analyzed for efficacy: ITT (all randomized patients); microbiological ITT (MITT; all ITT patients with ≥1 Gram-positive pathogen isolated at baseline); clinically evaluable (CE; ITT patients who met all enrollment criteria, received a pre-defined minimum course of study drug, and had a clinical response of cure or failure at the TOC [7 to 14 days after the End of Therapy (EOT)]); and microbiologically evaluable (ME; CE patients with a Gram-positive pathogen isolated at baseline).

Clinical success was defined as total resolution of local and systemic signs and symptoms of the ABSSSI such that no further antibiotic therapy was required. The primary efficacy endpoint was clinical success at the TOC for the ITT and CE populations. A total of 198 patients were randomized (ITT population) and all received ≥1 dose of study medication; 43 patients received CEM-102 conventional dose regimen prior to discontinuation of enrollment of that treatment group, 78 received CEM-102 loading dose regimen, and 77 received linezolid. Comparison is hence made between the two treatment groups carried forward to completion of the study, the CEM-102 loading dose and the linezolid treatment groups.

These two treatment groups were comparable in demographics, baseline characteristics, and percentages of ITT population in the MITT, CE and ME populations. Comparable percentages of patients in each treatment group completed study drug therapy (CEM-102 loading dose 73 of 78 [94%]; linezolid 76 of 77 [99%]). The mean duration of study drug exposure was similar in the two treatment groups (CEM-102 11.3 days and linezolid 11.5 days).

Clinical response rates at the TOC in the ITT and the CE populations are shown in Table 3, and for the MITT and ME populations in Table 4. Results were similar at the EOT for all populations.

Table 3 Clinical Response at the TOC (Intent-to-Treat and Clinically Evaluable Populations)

	CEM-102 Conventional	CEM-102 Loading Dose	Linezolid
ITT Population	N=43	N=78	N=77
Success	32/43 (74.4%)	67/78 (85.9%)	73/77 (94.8%)
Failure	4/43 (9.3%)	5/78 (6.4%)	1/77 (1.3%)
Indeterminate	7/43 (16.3%)	6/78 (7.7%)	3/77 (3.9%)
Difference versus linezolid	-0.204	-0.089	
95% CI versus linezolid [a]	-0.36, -0.05	-0.19, 0.02	
CE Population	N=34	N=65	N=68
Success	30/34 (88.2%)	60/65 (92.3%)	67/68 (98.5%)
Failure	4/34 (11.8%)	5/65 (7.7%)	1/68 (1.5%)
Difference versus linezolid	-0.103	-0.062	
95% CI versus linezolid [a]	-0.24, 0.03	-0.15, 0.02	

Source: CE06-300 CSR

a. 95% CIs were based on normal approximation of the binomial distribution with continuity correction.

Table 4 Clinical Response at the TOC (Microbiological Intent-to-Treat and Microbiologically Evaluable Populations)

	CEM-102 Conventional	CEM-102 Loading Dose	Linezolid
MITT Population	N=33	N=59	N=58
Success	27/33 (81.8%)	52/59 (88.1%)	54/58 (93.1%)
Failure	3/33 (9.1%)	2/59 (3.4%)	1/58 (1.7%)
Indeterminate	3/33 (9.1%)	5/59 (8.5%)	3/58 (5.2%)
Difference versus linezolid	-0.113	-0.050	
95% CI versus linezolid [a]	-0.28, 0.06	-0.17, 0.07	
ME Population	N=28	N=50	N=49
Success	25/28 (89.3%)	48/50 (96.0%)	48/49 (98.0%)
Failure	3/28 (10.7%)	2/50 (4.0%)	1/49 (2.0%)
Difference versus linezolid	-0.087	-0.020	
95% CI versus linezolid [a]	-0.24, 0.06	-0.11, 0.07	

Source: CE06-300 CSR

a. 95% CIs were based on normal approximation of the binomial distribution with continuity correction.

S. aureus was the most frequently isolated baseline pathogen, documented in 72% of patients; 70% of these were MRSA. β-hemolytic streptococci were isolated at baseline in 7% of patients. Of patients with a documented MRSA ABSSSI at baseline, 91.2% of patients in the CEM-102 loading dose treatment group and 93.2% of patients in the linezolid treatment group demonstrated clinical success at the TOC.

The CEM-102 loading dose regimen demonstrated efficacy comparable to that of linezolid in the ITT, CE, MITT, and ME populations.

5.3.2.2 Phase 2 Prosthetic Joint Infection (PJI) Study

Study CE06-200 was designed to evaluate the safety and efficacy of CEM-102 in combination with oral rifampin in comparison with standard of care (SoC) IV antibiotic treatment for patients with prosthetic joint or spacer infection managed by two-stage prosthesis exchange or debridement and retention (DAR). Among the 14 randomized patients, 12 completed study drug dosing on the initial randomized treatment.

Among CEM-102/RIF treated subjects, 4 of 7 (57%) were considered treatment successes. Two of the 3 treatment failures were not due to a microbiological failure. However, the third patient had unequivocal microbiological failure. MRSA isolated at the time of explant (first-stage) surgery was rifampin susceptible, prior to study drug therapy. Rifampin-resistant MRSA was re-isolated at the second-stage surgery. Although treatment failure for MRSA PJI is well described even with standard of care therapy, we surmise that the reduced CEM-102 exposure in this patient set the stage for 'functional monotherapy' with rifampin, with emergence of resistance as might be expected in this circumstance. Thus, despite the literature describing successful therapy with the combination of fusidic acid and rifampin, we have concluded that the interaction has clinical and deleterious significance.

Among IV SoC treated subjects, 4 of 7 patients overall (57%), and 4 of 5 in whom final outcomes were known (80%), were treatment successes. One patient had clinical failure due to a drug related AE ('vancomycin fever') that necessitated a change in therapy (to daptomycin).

5.3.3 Summary of Safety

5.3.3.1 Phase 1 PK Studies

Three completed Phase 1 studies showed that CEM-102 was safe and generally well tolerated in healthy adult subjects when administered as single oral doses up to 2200 mg, or as repeated twice daily doses over 5.5 days of up to 1650 mg. CEM-102 was also safe and generally well tolerated in healthy adult subjects when administered as loading dose regimens of up to 1650 mg Q12h on Day 1 followed by up to 825 mg Q12h for 6.5 days. No clinically significant changes in physical examinations, vital signs, electrocardiograms (ECGs), or laboratory parameters were observed in any subject in these studies. Transient, low-level, non-clinically significant increases in bilirubin were noted in Phase 1 studies. These reversible increases were dose-related and are consistent with the known effects of sodium fusidate.

The threshold for gastrointestinal intolerance for multiple doses (Q12h for 5.5 consecutive days) was reached between 1100 and 1650 mg. AEs appeared to be related to dose and duration of exposure, with gastrointestinal symptoms reported more frequently after 3 to 5 days of dosing and at higher doses.

5.3.3.2 Phase 2 Studies

In the Phase 2 ABSSSI Study (CE06-300), the percentage of subjects who experienced ≥1 TEAE during the study was 46.5% in the CEM-102 conventional regimen, 61.5% in the CEM-102 loading dose regimen, and 63.6% in the linezolid treatment group. The majority of TEAEs were mild or moderate in intensity. Overall, the type, incidence, and severity of TEAEs were comparable among the 3 treatment groups. AEs experienced by ≥5.0% of patients in the CEM-102 conventional regimen, CEM-102 loading dose regimen, or the linezolid treatment group, respectively, were nausea (14.0%, 21.8%, and 26.0%), vomiting (16.3%, 12.8%, and 9.1%), diarrhea (0%, 12.8%, and 13.0%), headache (0%, 5.1%, and 11.7%), dizziness (7.0%, 3.8%, and 2.6%), and dyspepsia (0%, 7.7%, and 2.6%).

The majority of treatment-related AEs were associated with gastrointestinal disorders. Three subjects in the CEM-102 loading dose regimen experienced ≥1 serious AE (SAE) during the study (preferred terms: herpes simplex; pyelonephritis; and head injury and back pain). The SAEs were considered by the Investigator to be unlikely related or unrelated to study drug.

Four subjects (1 subject in the CEM-102 conventional regimen (preferred terms: lip swelling and rash) and 3 subjects in the CEM-102 loading dose regimen (preferred terms: nausea and chills; blister and rash maculopapular; nausea, vomiting, and anorexia)) experienced ≥1 TEAE that resulted in premature discontinuation of study drug; of these, 1 subject in the CEM-102 loading dose regimen was also prematurely discontinued from the study due to TEAEs (preferred terms: nausea, vomiting, and anorexia).

Clinical laboratory tests and vital sign measurements did not demonstrate clinically significant changes during the study. Comparison of baseline and post-treatment ECGs did not demonstrate clinically relevant changes following treatment with CEM-102 or linezolid. In conclusion, the overall safety and tolerability of the CEM-102 loading dose regimen was comparable to that of linezolid.

In the Phase 2 PJI Study (CE06-200), the most frequently reported treatment-related AEs were gastrointestinal events (nausea, emesis, vomiting, diarrhea, loose stools) and elevated laboratory parameters, such as total or direct bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and creatine kinase (CK). Elevated gamma-glutamyl transpeptidase (GGT) levels were also observed in Patient 111-01, and was attributed to rifampin. There were reports of international normalized ratio (INR) or PT elevation, skin rash, worsening of anemia, pruritus, worsening renal function and eye floaters.

There were no clinically significant changes in physical examinations or vital signs in the Phase 2 studies. Serial ECGs done in these studies demonstrated no adverse cardiac effects with administration of CEM-102.

5.3.3.3 Ex-US Post-Marketing Safety Experience:

The fusidic acid labeling in countries where the drug is approved notes the organ systems most commonly associated with AEs, and the AEs in those systems, as:

- Gastrointestinal: flatulence, vomiting, nausea, hepatic transaminase elevation, diarrhea, anorexia, abdominal pain, jaundice, dyspepsia.
- Allergic: rash, pruritus, anaphylaxis, angioneurotic edema, urticaria, edema.
- Hematologic: leukopenia, anemia, neutropenia, thrombocytopenia, pancytopenia, granulocytopenia, agranulocytosis.
- Neurologic/psychiatric: headache, blurred vision, dizziness, lethargy, psychic disturbance.

The labeling also includes precautions regarding concomitant drug administration and use in patients with impaired liver function to limit potential hepatic AEs.

Published studies and AE reports from over 4 decades of clinical use outside the US indicate that oral sodium fusidate is safe and generally well tolerated when administered as 500 mg 2 or 3 times daily for 7 to 14 days. Higher doses (3000 to 4000 mg/day) for longer periods of time have also been used safely to treat patients with more serious or chronic infections. The most commonly reported AEs (gastrointestinal disturbances) were more frequent at higher doses and were decreased when sodium fusidate was administered with food. The most common AEs in those trials were gastrointestinal, and most often, not treatment limiting.

Hyperbilirubinemia has been reported with use of sodium fusidate; however, the hyperbilirubinemia was reversible and reported to result from inhibition of hepatic transporter function rather than hepatocellular injury. Reports of serious hepatotoxicity associated with sodium fusidate are rare and have primarily been reported with use of the IV formulation.

5.4 Rationale for the Use of CEM-102 in Staphylococcal Bone or Joint Infection

The rationale for developing CEM-102 in this indication is as follows:

- CEM-102 has a unique mechanism of action and shows little cross-resistance with any other known class of antibiotic. Sodium fusidate has been used for over 4 decades in many countries for the treatment of staphylococcal infections and has been shown to be safe and effective in the treatment of bone / joint infection, including prosthetic joint infection.
- Currently, the majority of bone or joint infections occurring in the US are caused by Gram-positive pathogens. *S. aureus*, including both MSSA and MRSA, is the most common pathogen identified. CoNS, including *Staphylococcus epidermidis,* are identified nearly as often. Other Gram-positive pathogens, including enterococci, viridans streptococci, propionibacteria, occasionally cause infection. In the US, the majority of these pathogens are susceptible to CEM-102.
- CEM-102 displayed excellent microbiological activity against *S. aureus* isolates collected in the US from 2008 to 2014, including MRSA (MIC_{90} 0.12 μg/mL). Of 1798 isolates of CoNS tested, only 133 (7.4%) were resistant to CEM-102. The MIC range of CEM-102

against more than 836 isolates of Group A streptococci was mostly 4 to 8 µg/mL, concentrations substantially lower than achievable CEM-102 plasma concentrations.

- CEM-102 was safe and generally well tolerated when administered to healthy subjects in single doses of up to 2200 mg and in multiple daily doses of up to 1650 mg BID for 5.5 days. Nausea was the most common AE, occurring most frequently after 3 to 5 days of dosing with 1650 mg BID. No safety concerns were identified for any single or multiple dosing regimens.
- CEM-102 was safe and well tolerated in loading dose regimens of 1100/550 mg BID and 1650/825 mg BID for a total of 7.5 days. Loading dose regimens appeared to be better tolerated than conventional dosing regimens for similar levels of overall plasma exposure. Both loading dose regimens produced trough plasma concentrations that approached steady-state levels at 24 hours after the first dose, suggesting that an optimal PK profile for treatment of target pathogens can be provided with this dosing approach. As with in vitro studies, fully effective antimicrobial exposures achieved earlier in treatment in a clinical context are expected to substantially reduce the likelihood emergence of resistance to CEM-102.

5.5 Rationale for the Dosing Regimen

Fusidic acid has been used for several decades outside the U.S., for the treatment of Gram-positive pathogen skin and skin structure infections, administered in oral and intravenous formulations, most often dosed three times daily. In this context, the occasional emergence of fusidic acid resistance during therapy has been observed and the overall prevalence of staphylococci with fusidic acid resistance has risen gradually. The latter process has been hastened by the widespread use of topical fusidic acid formulations for superficial skin infections. Fusidic acid has also been used globally for treatment of prosthetic joint infections (PJI), most often in combination with rifampin, due to rifampin's activity in biofilm associated infections.

Cempra recognized that the use of a fusidic acid (CEM-102) loading dose (or 'front-loading') strategy would substantially reduce the exposure of pathogens to sub-therapeutic drug concentrations. Pharmacokinetic studies evaluating front-loaded dosing regimens demonstrated that it was possible to rapidly achieve and sustain trough fusidic acid concentrations that were well in excess of the established breakpoint for *S. aureus* (EUCAST criteria, ≤ 1.0 µg/mL) (Still 2011). It had been previously demonstrated that fusidic acid resistance emergence frequencies were low at high multiple of MIC (O'Neill, 2006), and this observation was confirmed in hollow-fiber culture models, in which loading dose PK parameter fusidic acid exposure substantially reduced resistance emergence (Tsuji 2011). In a phase 2/3 ABSSSI trial that compared oral fusidic acid with a loading dose to oral linezolid, the success rate for *S. aureus* infections was 96%, comparable to that of linezolid (Section 5.3.2).

Recognizing fusidic acid's utility in the treatment of bone and joint infections, Cempra conducted a randomized phase 2 trial of oral fusidic acid with a loading dose in combination with rifampin versus standard of care intravenous antibiotics for treatment of prosthetic bone and joint infections. PK data was collected from enrolled subjects, and it was determined that a significant fusidic acid-rifampin drug interaction occurs, resulting in markedly reduced fusidic acid exposure. In this context, emergence of rifampin-resistance (but not fusidic acid resistance) in a previously

susceptible MRSA strain was observed and linked as a contributing factor to a case of treatment failure, and the study was terminated.

In this study, front-loaded fusidic acid (1500 mg every 12 hours for 2 doses, followed by 600 mg every 12 hours thereafter) will be used in combination, for the first 1-2 weeks, with a companion antibiotic (not rifampin). Use of the dual strategies of rapidly reducing bacterial pathogen burden (with companion antibiotic therapy), and assuring that steady state trough fusidic acid concentrations are rapidly achieved (within 24 hours) using a loading dose, is expected to set a high barrier to the emergence of bacterial fusidic acid resistance. In addition, fusidic acid has been demonstrated to be effective against biofilm in an in vitro model with *S. aureus* both as a single agent and in combination with daptomycin, vancomycin or linezolid (Siala 2015). This observation is supported by the long history of successful use of fusidic acid monotherapy for the treatment of bone and joint infections (Adkins 1999).

6 STUDY OBJECTIVE

To evaluate the safety and effectiveness of CEM-102 as chronic antibiotic suppressive therapy in subjects with staphylococcal bone or joint infections.

6.1 Primary Endpoint

The primary endpoint will be the proportion of subjects in the ITT analysis set who meet all the criteria for clinical success at the 6-Month Visit, as described in Section 14.1.

6.2 Secondary Endpoints

The secondary endpoints are the proportion of subjects in the ITT analysis set who meet all criteria for clinical success at the 9-Month, 12-Month, 15-Month, 18-Month, 21-Month, and 24-Month Visits; the safety and tolerability of CEM-102 in the Safety Analysis Set, as described in Section 14.2, and the pharmacokinetics of CEM-102 used chronically in subjects with orthopedic infections.

6.3 Pharmacokinetic Endpoints

- Peak measured plasma concentration (C_{max})
- Area under the concentration versus time curve ($AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$)
- Time to peak concentration (tmax)
- Apparent terminal elimination half-life ($t_{½}$)
- Apparent first-order terminal elimination rate constant (K_{el})
- Apparent Volume of distribution (V_d/F)
- Apparent Clearance (CL/F)

7 OVERALL STUDY DESIGN

This is a prospective, open-label, non-randomized, single-arm trial to evaluate the safety and effectiveness of CEM-102 for chronic antibiotic suppressive therapy of bone or joint infections.

Subjects enrolling in this study must have a staphylococcal bone or joint infection that requires suppressive antibiotic therapy. Reasons a subject may be suitable for chronic oral antibiotic suppressive therapy include, but are not limited to, the following: 1) having an infection that cannot be managed by complete removal of the infected bone or foreign material, 2) having a refractory infection not responding to previous treatment, 3) not being a candidate for long-term intravenous antibiotic therapy.

Subjects must have a bone or joint infection due to an inclusionary pathogen susceptible to CEM-102, demonstrated from a positive culture from samples obtained during surgery, biopsy, or drainage procedures within 6 weeks prior to enrollment.

Acceptable inclusionary pathogens in this study include the following CEM-102-susceptible organisms: methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), and CoNS, such as *S. epidermidis*, *S. hominis*, or *S. haemolyticus*. Specifically excluded from this list of pathogens is *S. saprophyticus*. Prior to enrollment, sensitivity of the isolate(s) to CEM-102 must be demonstrated.

Co-infection with *Corynebacterium* spp., *Propionibacterium acnes*, beta-hemolytic streptococci, enterococci, or other Gram-positive bacteria susceptible to CEM-102 is permitted.

Co-infection with bacteria known or expected not to be susceptible to CEM-102 (e.g. Gram-negatives or anaerobes) is permitted, provided these bacteria can be treated with an adjunctive antibiotic to which the inclusionary staphylococcus is not susceptible, and there are no known drug-drug interactions with CEM-102.

CEM-102 must be initiated with one or more additional antibiotics (either oral or IV), referred to as companion antibiotics, for the first 1-2 weeks of the study. Companion antibiotic(s) will be selected per the Investigator's discretion on the basis of subject-specific antibiotic tolerability and pathogen susceptibilities. Because concomitant administration of rifampin results in markedly reduced levels of CEM-102 blood levels, rifampin must not be used as a concomitant antibiotic with CEM-102. After 1-2 weeks of therapy, the companion antibiotic must be discontinued. To be eligible for enrollment, the subject must be a suitable candidate for CEM-102 monotherapy after completion of 1-2 weeks of the companion antibiotic, for chronic treatment of the orthopedic infection due to the inclusionary pathogen.

This study comprises two parts: Part A (enrollment through the 6-month visit) and Part B (6 to 24 months post-enrollment). In Part A, all subjects will receive 6 months of CEM-102 treatment. The Investigator will evaluate each subject completing Part A for clinical response at the 6-month visit (primary endpoint). For Part B, a subject who completes Part A and, in the Investigator's opinion, requires continued suppressive therapy, may continue to receive CEM-102. Alternatively, if the Investigator considers the infection resolved and that no further antibiotic therapy is required, study drug will be discontinued and the subject followed for evidence of relapse until the end of study (EOS).

During the first 6 months of treatment, study Part A, subjects will be monitored monthly (±1week) for safety and clinical response to CEM-102. During study Part B, subjects will be monitored every 3 months (±2 weeks) until the End of Study Visit (24 months).

A subject who discontinues study drug because of treatment failure will have an EOS visit at that time. A subject who discontinues study drug due to an AE will be followed until the AE is resolved or stabilized. A subject who discontinues study drug due to clinical success will be followed for relapse until EOS.

If a subject withdraws from the study at any time, for any reason, an EOS visit will be performed at that time.

7.1 Duration of Subject Participation

This study is designed to evaluate a minimum of 6 months of oral CEM-102 therapy but may extend for up to 24 months.

This study comprises two parts: Part A (enrollment through the 6-month visit) and Part B (6 to 24 months post-enrollment). In Part A, all subjects will receive 6 months of CEM-102 treatment. The Investigator will evaluate each subject completing Part A for clinical response at the 6-month visit (primary endpoint). For Part B, a subject who completes Part A and, in the Investigator's opinion, requires continued suppressive therapy, may continue to receive CEM-102 for up to 24 months. Alternatively, if the Investigator considers the infection resolved and that no further antibiotic therapy is required, study drug will be discontinued and the subject will be followed for evidence of relapse until EOS. If the subject requires chronic suppressive therapy with CEM-102 beyond 24 months, the Investigator may choose to roll the subject into an expanded access protocol.

7.2 Number of Subjects

Thirty subjects will be enrolled at up to 20 investigative sites in the United States.

7.3 Duration of Study

The study duration from first subject, first visit until last subject, last visit will be determined based upon enrollment rates and will be will be approximately 3 years.

7.4 Study Drug Dosage and Administration

Subjects will receive a loading dose of 1500 mg by mouth every 12 hours for 2 doses, followed by 600 mg every 12 hours thereafter.

Study drug must be taken within a +/- 2 hour window of the scheduled dose. On days when PK samples are obtained, study drug must be taken within +/- 1 hour of the scheduled dose.

After the first two loading doses are taken 12 hours apart, the dosing schedule may be adjusted once to allow for a more convenient dosing schedule (e.g., if a dose is to be taken between 11pm and 3am, then the dosage time may be rounded down to 11pm; or if the a dose is to be taken

between 3am and 7am, then the dosage time may be rounded up to 7am). Subsequent dosing must continue on an every 12 hour dosing schedule.

CEM-102 may be taken with or without food.

7.5 Dose Modification

Dosage modifications are not required. The pharmacokinetics of CEM-102 in subjects with renal and hepatic insufficiency have not been studied. Subjects with severe renal impairment (CrCl <30 mL/min) or significant liver disease (ALT >3x ULN or direct bilirubin >ULN) are excluded at enrollment.

At the discretion of the Investigator, study drug may be withheld for several days due to intolerance or an AE, such as a laboratory abnormality. After appropriate follow-up, if clinically indicated, study drug may be restarted. If study drug needs to be permanently discontinued due to intolerance/AE, and additional antibiotics are required to treat the chronic orthopedic infection due to the inclusionary pathogen, this will be classified as a clinical failure.

8 SELECTION OF STUDY POPULATION

The following criteria for enrollment must be followed explicitly. A subject will not be enrolled unless the inclusion/exclusion criteria are met. The Investigator or other study site personnel must document in the source documents that the informed consent form (ICF) was signed and dated prior to study screening. The date on which the ICF was obtained will be recorded in the source documents and electronic case report form (eCRF). The presence of inclusion criteria and absence of exclusion criteria will be verified in the eCRF.

8.1 Inclusion Criteria

1. Male or female subject ≥ 18 years of age, and adolescents between the ages of 12 and 18 years who weigh greater than 60 kg.
2. Subject must have a bone or joint infection due to an inclusionary pathogen demonstrated from a culture from samples obtained during surgery, biopsy, or drainage procedures within 6 weeks prior to enrollment.
   - Note: If a subject does not have a confirmatory culture result, the Investigator must provide documentation as to why subject is suspected to have a staphylococcal infection and must discuss the subject with the medical monitor for approval of enrollment.
3. Inclusionary pathogen(s) include the following staphylococcal bacteria:
   - *S. aureus*: MSSA or MRSA
   - CoNS such as *S. epidermidis*, *S. hominis*, or *S. haemolyticus* (*S. saprophyticus* is not an inclusionary pathogen)

     Note: Co-infection with *Corynebacterium* spp., *Propionibacterium acnes*, beta-hemolytic streptococci, enterococci, or other bacteria susceptible to CEM-102 is permitted. Co-infection with bacteria known or expected not to be susceptible to CEM-102 (e.g. Gram-negatives or anaerobes) is permitted, provided these bacteria can be treated with an adjunctive antibiotic to which the staphylococcus is not susceptible, and there are no known drug-drug interactions with CEM-102.
4. Inclusionary pathogen, if identified, must be susceptible to CEM-102.
5. If the subject has a prosthetic joint, the implant is secured and fixed.
6. After completion of 1-2 weeks of the companion antibiotic, the subject must be a suitable candidate for CEM-102 monotherapy for chronic treatment of the orthopedic infection due to the inclusionary pathogen.
7. Subject is not a candidate, as determined by the Investigator, for suitable alternative therapy. Reasons include, but are not limited to, the following:
   - Cannot undergo definitive curative surgical treatment (removal of all infected bone, joint, or foreign material) due to poor health status, age, or comorbidities
   - Not a candidate for long-term IV antibiotic therapy

8. The subject must be a suitable candidate for oral antibiotic therapy (i.e. able to swallow study medication tablets/capsules intact and have no known deficiency in gastrointestinal absorption).
9. The subject (or subject's legal guardian) must express commitment to comply with all study visits, procedures, and requirements for the duration of the study.
10. The subject, or the subject's legal guardian, has voluntarily signed the Independent Ethics Committee or Institutional Review Board approved informed consent form (ICF). In cases of mental incapacity, the legal guardian is permitted to sign the ICF.
11. Female subjects of childbearing potential must use an acceptable contraception method (abstinence or double barrier methods) for the duration of the study-drug treatment phase of the study and 30 days thereafter, and must have a negative serum or urine pregnancy test at Screening.

8.2 Exclusion Criteria

Subjects may be screened on the basis of suspected or confirmed infection but will not be eligible for enrollment if any of the following exclusion criteria are met:

1. Medical history of hypersensitivity or allergic reaction to sodium fusidate, fusidic acid (Fucidin® or any systemic or topical product containing fusidic acid) or its excipients.
2. Endovascular, infected intravascular foreign material, or infective endocarditis; or central nervous system infection, including meningitis.
3. Female subject who is pregnant or lactating.
4. Known severe renal impairment, as indicated by estimated creatinine clearance (CrCl) <30 mL/min (by Cockcroft-Gault calculation).
5. Immunocompromised subject or requirement for immunosuppressive therapy; Prior use of immunosuppressant agents (i.e. cyclosporine, TNFα antagonist) within 30 days of study medication administration.
6. Malignancy requiring ongoing cytotoxic chemotherapy.
7. Neutropenia (absolute neutrophil count <500/μL); Thrombocytopenia (platelet count <60,000/μL).
8. Known human immunodeficiency virus (HIV) infection and currently receiving antiretroviral therapy; Current CD4 count ≤ 200 cells/mm3 (documented within 3 month prior to enrollment); If CD4 count is unknown, subject may not enroll.
9. Significant liver dysfunction, defined as follows: alanine aminotransferase (ALT) >3x upper limit of normal (ULN) or direct bilirubin >ULN; Known cirrhosis with decompensation (i.e. Child-Pugh Class B or C disease).
10. Known hepatitis C virus (HCV) infection and currently receiving HCV-specific antiviral therapy. HCV infection alone, in the absence of decompensated liver disease, is not exclusionary.
11. Seizure disorder requiring current therapy with anticonvulsant.

12. Any underlying condition (e.g. addiction or clinically significant disease), that in the opinion of the Investigator, would be likely to interfere with assessment of the infection or completion of the study.
13. The use of an investigational drug within 4 weeks prior to Screening.
14. Requires concomitant treatment with the following::
    - OATP1B1 and OATP1B3 substrates, such as statins (HMG-CoA reductase inhibitors)
    - Metabolized by CYP2C8, such as glitazones (such as repaglinide)
    - CYP3A4 inducers (such as dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, and nafcillin)
15. Prior treatment with a CYP3A4 inducer, such as dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, or nafcillin, within 7 days prior to enrollment.
16. Subjects requiring digoxin or warfarin therapy may only be enrolled if an achievable plan for therapeutic monitoring of the drug (digoxin) or prothrombin time has been reviewed and approved by the study medical monitor.

8.3 Recording of Prior Antibiotics and Concomitant Treatment

Reasonable efforts will be made to record in the electronic case report form (eCRF) the 6-month history of prior antibiotics used to treat the primary infection leading to enrollment. The medication name, route of administration, dose, frequency, indication, and duration of the treatment/procedure (start and stop dates) will be recorded. Furthermore, reasonable efforts will be made to determine all relevant treatment (concomitant medications, including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacological treatments) received by the subject within 7 days before administration of study drug and will be recorded in the eCRF. The medication name, route of administration, dose, frequency, indication, and duration of the treatment/procedure (start and stop dates) will be recorded. Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

8.4 Permitted Medications and Treatment

Medications to treat any AE the subject experiences during the study are permitted. Routine wound care, including debridement of devitalized tissue, is permitted. Definitive surgical procedures to treat worsening of the primary infection, such as amputation or removal of infected prosthetic material, will be classified as clinical failure.

8.5 Companion Antibiotics to Treat the Primary Infection

CEM-102 must be initiated with one or more additional antibiotics (either oral or IV) for the first 1-2 weeks of the study. Companion antibiotic(s) will be selected per the Investigator's discretion on the basis of subject-specific antibiotic tolerability and pathogen susceptibilities. Examples include, but are not limited to, IV cefazolin, vancomycin, daptomycin, and IV/PO linezolid. Rifampin must not be used as a companion antibiotic with CEM-102. After 1-2 weeks of companion antibiotic therapy, the companion antibiotic must be discontinued.

Starting an antibiotic due to signs and symptoms of clinical failure (e.g. worsening redness, swelling, pain, purulent discharge, sinus tract formation, or bacteremia) will be classified as clinical failure.

8.6 Adjunctive Antibiotic Therapy for Co-infections

Treatment of co-infection(s) due to bacteria known or expected to not be susceptible to fusidic acid is permitted, provided these pathogens can be treated with an adjunctive antibiotic to which the inclusionary pathogen is not susceptible (e.g. aztreonam and metronidazole are permitted for treatment of Gram-negative and anaerobic co-infections).

8.7 Concomitant Antibiotic Therapy for Unrelated Infections

Treatment of an unrelated infection with an antibiotic to which the inclusionary pathogen is susceptible is permitted only if the antibiotic is administered for ≤ 10 days on any single occasion, and ≤ 2 courses during any 6-month period during the study (and provided there are no known drug-drug interactions with CEM-102).

Use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for > 10 days on any occasion, or for > 2 courses during any 6-month period, will be classified as clinical failure.

8.8 Prohibited Medications

Co-administration of CEM-102 with HMG-CoA reductase inhibitors (statins), as well as rifampin, is prohibited. Potential clinical drug-drug interactions with oral sodium fusidate are described in Section 7.4.1 of the CEM-102 Investigator's Brochure and in the Fucidin® product labeling or published reports.

9 STUDY DRUG

This is an open-label study that requires no blinding of CEM-102. Companion antibiotic therapy will not be provided by the Sponsor.

9.1 CEM-102 Tablets

CEM-102 300 mg tablets contain 300 mg of fusidate sodium as the active pharmaceutical ingredient and commonly used excipients.

9.2 Study Drug Labeling and Packaging

CEM-102 300 mg tablets will be provided by CEM-102 Pharmaceuticals and will be labeled and supplied according to applicable regulatory requirements. CEM-102 300 mg dual-coated tablets will be supplied in 120 cc PET bottles of 130 tablets in an open-label fashion.

9.3 Study Drug Storage Conditions

The Investigator or an approved representative (e.g., pharmacist) will ensure that all study drugs are stored in a locked secured area (with limited access available to appropriate study personnel), only under recommended storage conditions and in accordance with applicable regulatory requirements. Standard of care medications will be stored in accordance with their label, as directed by the Investigator and/or associated care team members.

The Investigator or approved designee (e.g. Pharmacist), will be responsible for recording daily, the temperature of all study drugs on the log provided or an approved existing log. Additionally, it is the responsibility of the Investigator to ensure that all temperature deviations and excursions from those noted in the protocol are reported to the Sponsor QA group who will assess the approval for continued use of the products.

CEM-102 will be stored at controlled room temperature 59°F to 77°F (15°C - 25°C) and protected from light. Keep bottles tightly closed to protect from moisture.

In the event of an excursion, please send an email to Anita Healey at **ahealey@cempra.com** explaining the excursion and attach temperature logs for the duration of the excursion(s).

9.4 Receipt of Supplies

Upon receipt of the investigational drug, the pharmacist or designated study site personnel will visually inspect the shipment and verify the drug information, quantity, and condition of the kits received. The Investigational Drug Transmittal and Receipt Form will be completed and signed by the pharmacist.

9.5 Study Drug Accountability

9.5.1 Overall

It is the responsibility of the Investigator to ensure that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and available to Regulatory Agencies for inspection at any time.

9.5.2 Instructions for Subject

The site personnel will review the dosing instructions with the subject on the first oral dosing day and each subsequent study visit. The subject will bring the bottles to each study visit through end of study drug treatment, when the bottle will be collected by site personnel. The subject must return any study drug not taken to site personnel.

9.5.3 Study Drug Handling and Return

Upon the completion or termination of the study, and upon written authorization from Sponsor or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that Sponsor or its representative has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the Sponsor monitor (or designee).

10 STUDY ASSESSENTS AND PROCEDURES

The schedule of assessments and procedures is summarized in Table 1. Subjects will provide written informed consent before any study-related procedures are performed.

10.1 Screening

Screening procedures may be initiated after signing of the IRB-approved ICF. The following information will be collected, and the following evaluations/procedures will be performed:

1. Review all Inclusion/Exclusion criteria.
2. Record demographics (date of birth, sex, race, and ethnicity) and significant clinical/surgical history.
3. Obtain microbiological specimens for culture (or document a culture positive for inclusionary pathogen obtained within 6 weeks prior to enrollment).
    - Subjects must have a positive culture with an inclusionary pathogen susceptible to CEM-102, demonstrated from a culture from samples obtained during surgery, biopsy, or drainage procedures within 6 weeks prior to enrollment. If subject does not have a confirmatory culture result, the Investigator must provide documentation as to why the subject is suspected to have a staphylococcal infection.
4. Measure vital signs (height, weight, blood pressure, heart rate, respiratory rate, and temperature [highest recorded temperature in the previous 24 hours]).
5. Perform limited physical examination.
6. Examine the infected area, including assessing pain, redness, mobility, joint stability, wound closure, wound drainage, and weight bearing (for back and lower extremity infections). If clinically relevant, measure length (L) and width (W) of the wound, using longest length in the head to toe orientation and widest perpendicular [90° angle] width.
7. Collect blood samples for clinical safety laboratory determinations and lab measurements of markers of inflammation.
8. For female subjects of childbearing potential, collect urine or blood for pregnancy test (either test is acceptable).
9. Calculate the subject's estimated CrCl using the serum creatinine value (in conventional units) and the Cockcroft-Gault formula below (actual body weight should be used in this formula):

$$\text{Males: CrCl} = \frac{(140\text{-age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: CrCl} = \frac{(140\text{-age in years}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

If the serum creatinine value is reported in Systeme International d'Unites (SI) (i.e. µmol/L), convert to conventional units (mg/mL) using the following formula:

$$\text{Conventional units (mg/mL)} = \frac{\text{SI units (µmol/L)}}{88.4}$$

10. Record 6-month history of all antibiotics administered to the subject to treatment current infection leading to enrollment.
11. Record concomitant medications including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacological treatments received by the subject within 7 days of the Screening visit.
12. Review of available radiographic data (imaging is not specifically requested in the protocol, but is expected to be performed in accordance with standard of care procedure). Results should be recorded in the eCRF.
13. Review and record all AEs and SAEs

10.2 Treatment Period

10.2.1 Enrollment (Study Day 1)

Enrollment can proceed after the subject meets all eligibility requirements. Study Day 1 corresponds to the first day of dosing with CEM-102. The following are performed on Study Day 1:

1. Review clinical/surgical history.
2. If clinically indicated, obtain microbiological specimens for culture.
3. Measure vital signs (height, weight, blood pressure, heart rate, respiratory rate, and temperature [highest documented temperature in the previous 24 hours]).
4. Perform a limited physical examination.
5. Examination the infected area and assess pain, redness, mobility, joint stability, wound closure, wound drainage, and weight bearing (for back and lower extremity infections). If clinically relevant, measure length (L) and width (W) of the wound, using longest length in the head to toe orientation and widest perpendicular [90° angle] width. The Investigator will assess whether the infected area seems to have improved, deteriorated, or remained unchanged from previous assessment.
6. Collect blood samples for clinical safety laboratory determinations and lab measurements of markers of inflammation.

7. Administer a loading dose of CEM-102 (1500 mg) and instruct the subject when to take second loading dose 12 hours later.
8. Dispense CEM-102 tablets to the subject.
9. Review and record all AEs and SAEs.
10. Record concomitant medications, including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacological treatments received by the subject.

10.2.2 Day 8 (±3 days)

The following are performed on Study Day 8:

1. Review clinical/surgical history.
2. If clinically indicated, obtain microbiological specimens for culture.
3. Measure vital signs (height, weight, blood pressure, heart rate, respiratory rate, and temperature [highest documented temperature in the previous 24 hours]).
4. Perform limited physical examination.
5. Examine the infected area and assess pain, redness, mobility, joint stability, wound closure, wound drainage, and weight bearing (for back and lower extremity infections). If clinically relevant, measure length (L) and width (W) of the wound, using longest length in the head to toe orientation and widest perpendicular [90° angle] width. The Investigator will assess whether the infected area seems to have improved, deteriorated, or remained unchanged.
6. Collect blood samples for clinical safety laboratory determinations.
7. Review and record all AEs and SAEs.
8. Dispense CEM-102 tablets to the subject.
9. Perform drug accountability assessment.
10. Record concomitant medications, including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacological treatments received by the subject.

10.2.3 Monthly During First 6 Months (±1 Week)

The following are performed monthly during the first 6 months:

1. Review clinical/surgical history.
2. If clinically indicated, obtain microbiological specimens for culture.
3. Measure vital signs (height, weight, blood pressure, heart rate, respiratory rate, and temperature [highest documented temperature in the previous 24 hours]).
4. Perform limited physical examination.
5. Examine the infected area and assess pain, redness, mobility, joint stability, wound closure, wound drainage, and weight bearing (for back and lower extremity infections). If clinically

relevant, measure length (L) and width (W) of the wound, using longest length in the head to toe orientation and widest perpendicular [90° angle] width. The Investigator will assess whether the infected area seems to have improved, deteriorated, or remained unchanged.

6. Collect blood samples for clinical safety laboratory determinations and lab measurements of markers of inflammation.
7. Dispense CEM-102 tablets to the subject and perform a drug accountability assessment.
8. Review and record all AEs and SAEs.
9. Record concomitant medications including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacological treatments received by the subject.
10. At 3-month visit, obtain blood for PK sampling, described in Section 10.6. If PK sampling cannot be done at 3-month visit, it may be completed at either the prior or subsequent monthly visit if needed.
11. At 6-month visit, perform an Investigator assessment of clinical response

10.2.4 Every 3 Months (+/- 2 weeks) from Month 6 until End of Study (24 Months)

Subjects who continue on chronic suppressive antibiotic therapy with CEM-102 will be followed quarterly for response to therapy until EOS. If the infection is deemed to have resolved and antibiotic therapy is no longer required, the subject will be followed quarterly for clinical relapse until EOS. The following are performed every 3 months until EOS:

1. Review clinical/surgical history.
2. If clinically indicated, obtain microbiological specimens for culture.
3. Measure vital signs (height, weight, blood pressure, heart rate, respiratory rate, and temperature [highest documented temperature in the previous 24 hours]).
4. Perform a limited physical examination.
5. Examine the infected area and assess pain, redness, mobility, joint stability, wound closure, wound drainage, and weight bearing (for back and lower extremity infections). If clinically relevant, measure length (L) and width (W) of the wound, using longest length in the head to toe orientation and widest perpendicular [90° angle] width. The Investigator will assess whether the infected area seems to have improved, deteriorated, or remained unchanged.
6. Collect blood samples for clinical safety laboratory determinations and lab measurements of markers of inflammation.
7. Dispense CEM-102 tablets to the subject and perform a drug accountability assessment (in subjects receiving chronic suppressive antibiotic therapy with CEM-102).
8. Review and record all AEs and SAEs.
9. Record concomitant medications including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacological treatments received by the subject.

10. Perform an Investigator assessment of clinical response.

10.3 End of Study (EOS)

A subject who discontinues study drug because of treatment failure will have an EOS visit at that time. A subject who discontinues study drug due to clinical cure will be followed for relapse until EOS. If a subject withdraws from the study, an EOS visit will be performed at that time.

1. Review clinical/surgical history.
2. Obtain microbiological specimens for culture.
3. Measure vital signs (height, weight, blood pressure, heart rate, respiratory rate and temperature [highest documented temperature in the previous 24 hours]).
4. Perform a limited physical examination.
5. Examine the infected area and assess pain, redness, mobility, joint stability, wound closure, wound drainage, and weight bearing (for back and lower extremity infections). If clinically relevant, measure length (L) and width (W) of the wound, using longest length in the head to toe orientation and widest perpendicular [90° angle] width.
6. Collect blood samples for clinical safety laboratory determinations and lab measurements of markers of inflammation.
7. Perform drug accountability assessment.
8. Review and record all AEs and SAEs.
9. Record concomitant medications including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacological treatments received by the subject.
10. Perform an Investigator assessment of clinical response.
11. If the subject requires additional long-term chronic suppressive therapy with CEM-102 beyond study closure, the subject may be enrolled into an expanded access protocol to continue therapy.

10.4 Local Laboratory Assessments

The clinical safety laboratory tests outlined below will be performed locally according to the schedule of assessments (Table 1):

- Serum Chemistry: creatinine, BUN (urea), aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), total and direct bilirubin, albumin, total protein, sodium, total carbon dioxide, glucose, potassium, chloride, calcium, phosphorus, and creatinine phosphokinase (CPK).
- Markers of inflammation: complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).
- Serum or urine pregnancy test for female subjects of childbearing potential.

10.5 Microbiology Assessments

All enrolled subjects must have a positive culture with an inclusionary pathogen, demonstrated from a culture from samples obtained during surgery, biopsy, or drainage procedures, within 6 weeks prior to enrollment. If a subject does not have a confirmatory culture result, the Investigator must provide documentation as to why the subject is suspected to have a staphylococcal infection and must discuss the subject with the medical monitor for approval of enrollment. If clinically indicated, microbiological samples obtained during the study should also be submitted to the local laboratory for aerobic and anaerobic culture.

Collection, transport, and processing of samples (including blood, tissue, synovial fluid, bone, etc.) should follow the local laboratory standard operating procedures and protocols. Each local laboratory will perform an initial isolate identification and susceptibility testing of Gram-positive pathogens. All isolated bacteria are to be sub-cultured and shipped to the Central Microbiology Laboratory for organism confirmation and additional susceptibility testing.

10.5.1 Susceptibility Testing of Bacterial Pathogens (Local Laboratory)

Initial susceptibility testing to CEM-102 will be done by disk diffusion at the local laboratory following procedures detailed in the Laboratory Manual. The Central Microbiology Laboratory will provide CEM-102 (10 µg) disks to be used to assess the susceptibility of Gram-positive species identified as pathogens. Clinical and Laboratory Standards Institute (CLSI) M02-A12 (2015) and M100-S25 (2015) methods should be followed while performing the disk diffusion tests, including appropriate concurrent quality control testing (Table 5).

Table 5 Disk Zone Diameter Quality Control Limits

Organism	Media	Fusidic Acid QC Range[a] (mm)
S. aureus ATCC 25923	Mueller Hinton agar (MHA)	24-32
S. pneumoniae ATCC 49619	MHA + 5% sheep blood	9-16

a. Quality Control Limits per the CLSI M02-A12 (2015) and CLSI M100-S25 (2015) guidelines

The EUCAST recommended interpretive criteria for fusidic acid when testing *Staphylococcus* spp. are: (MIC [susceptible (S)/resistant (R)], ≤1/>1 µg/mL; zone diameter [S/R], ≥24/<24 mm for a 10 µg disk). However, these breakpoints were established taking into account the plasma levels obtained with the European dosing regimen. Given the high plasma trough levels (>100 µg/mL) achieved within 24 hours using the fusidic acid loading dose regimen, and the results of a disk versus broth correlation analysis where applying breakpoints of <1 µg/ml (>22 mm) for S and >4 µg/ml (<19 mm) for R provided 99.9% absolute intermethod categorical agreement (Jones 2010), The following provisional breakpoints for interpretation of zone diameters will be applied to isolates (Table 6).

Table 6 Provisional CEM-102 Disk Zone Breakpoints

Zone Diameter Breakpoints (mm) for Staphylococcal spp.[a]		
Susceptible (S)	**Intermediate (I)**	**Resistant (R)**
≥22	20-21	≤19

a. Interpretation of disk zone diameters of non-staphylococcal Gram-positive spp. should be discussed with the Sponsor's Medical Monitor/Microbiologist.

10.5.2 Local Laboratory Storage of All Isolates

All Baseline and any subsequent isolates will be stored frozen at ≤ -70°C (-20°C is acceptable for a period of no more than 35 days if a -70°C freezer is not available) in pathogen-appropriate media. The Central Laboratory will provide storage media in cryovials for isolate retention. Procedures related to freezing and storage of isolates are described in the Laboratory Manual.

After submission of an isolate to the Central Laboratory, frozen backup isolates should be maintained at the local laboratory until the end of the study.

10.5.3 Shipping of Bacterial Strains to the Central Laboratory

Isolates will be shipped to the Central Microbiology Laboratory for identity confirmation and antibiotic susceptibility testing. The Central Laboratory will provide a Laboratory Manual detailing handling and shipping instructions, isolate submission forms, shipping containers, and pre-printed air bills for sending strains to the Central Laboratory. When a shipment of isolates is to be initiated, the isolates should be sub-cultured from the frozen storage cryovials, grown overnight on routine laboratory media and inspected for purity after 24 hours incubation.

Organism names (as reported by the local laboratory) and the accession numbers of any isolates sent to the Central Microbiology Laboratory will be recorded in the eCRF. If organism identifications from the local and Central Laboratories are discrepant, or if the Central Laboratory is unable to recover any isolates from the material received, the local laboratory will be requested to ship another sub-cultured specimen.

10.5.4 Central Microbiology Laboratory Procedures

Isolates will be identified to genus and species. Additional testing to characterize isolates, including genetic typing and identification of virulence factors, may be performed. The Central Microbiology Laboratory will conduct susceptibility testing, by Kirby Bauer disk diffusion assay and by broth dilution or agar dilution MIC assays to CEM-102 and other antibiotics.

10.6 Pharmacokinetic Assessments

Blood samples for PK analysis will be obtained from all consenting subjects at the 3-month Visit. PK analysis will be described in a separate Pharmacokinetics Analysis Plan.

PK Sampling: collected as close as possible to the following times:

At the 3-Month Visit: Blood samples (5 in total) will be obtained at trough (30 minutes before study drug dosing), 1, 2, 4, and 6 hours after study drug dosing.

If PK sampling cannot be done at 3-month visit, it may be completed at either the prior or subsequent monthly visit, if needed.

An instruction manual that details the sampling, handling, and shipping procedures for PK samples will be provided to each participating site.

11 STUDY DRUG DISCONTINUATION AND SUBJECT WITHDRAWAL

A clear distinction will be made between subjects who discontinue study drug dosing and those who withdraw or are withdrawn from the study. Subjects who are lost to follow-up, are unwilling to comply with protocol procedures, or who withdraw consent and/or refuse any further contact with respect to the study will be withdrawn from the study. Subjects who discontinue study drug due to clinical failure will also be withdrawn from the study. Subjects discontinued from study drug dosing and/or withdrawn for the study will not be replaced, regardless of the reason.

11.1 Screening Failures

Subjects who sign and date the ICF but who fail to meet inclusion and exclusion criteria and do not receive any doses of CEM-102 are defined as primary screen failures. A screening log, which documents the subject initials and reason for all screen failures, is to be maintained by the Investigator. A copy of the log should be retained in the Investigator's study files. Screen failures will be entered into the eCRF.

11.2 Discontinuation from Study Drug

A subject may have study drug discontinued for any of the following reasons:

- Safety, including AEs or development of clinically significant laboratory abnormalities. The subject must be followed clinically until the event is resolved or deemed stable.
- Investigator discretion
- Determination of clinical cure and no need for further antibiotic therapy to treat the primary infection (subject will continue to be followed for clinical relapse until EOS).
- Pregnancy
- Sponsor request

11.3 Withdrawal from Study

A subject may be withdrawn from the study for any of the following reasons:

- Subject wishes to withdraw consent for reasons other than an adverse experience
- Subject is lost to follow-up
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol
- Clinical failure
- Investigator discretion
- Sponsor request

If a subject withdraws from the study at any time, for any reason, an EOS visit will be performed around that time.

11.4 Study Site Discontinuation

Reasons for discontinuation of the study at an investigational site may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Subject enrollment is unsatisfactory
- Investigator request to withdraw from participation
- Sponsor's decision
- Serious and/or persistent non-compliance by the Investigator with the protocol, the clinical research agreement, and/or applicable regulatory guidelines in conducting the study
- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) decision to terminate or suspend approval for the investigation or the Investigator
- Investigator fraud (altered data, omitted data, or manufactured data)

12 SAFETY ASSESSMENTS

Safety assessments will include attention to relevant changes in physical examinations, vital signs, and safety laboratory tests that are identified as occurring after the ICF is signed.

12.1 Adverse Events

An "adverse event" is any untoward medical occurrence associated with the use of a study drug in humans, whether or not considered drug related. An AE can be a clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with CEM-102, regardless of causal relationship. A "pre-existing" condition is one that is present prior to study drug administration and is reported as part of the subject's medical history. A pre-existing condition should be reported as an AE only if the frequency, intensity, or character of the pre-existing condition worsens during the course of the study.

Laboratory abnormalities are not considered AEs unless they are associated with clinical signs or symptoms or require medical intervention. However, a clinically significant laboratory abnormality (e.g. detected on clinical chemistry, coagulation, or hematology) that is independent from the underlying medical condition and that requires medical or surgical intervention or leads to study drug interruption or discontinuation will usually be considered an AE.
A constellation of signs and symptoms associated with an underlying etiology should be reported as the unifying event (for example, cough, fever, rhinorrhea, and malaise due to a cold should be reported as 'viral syndrome').

In general, lack of efficacy/clinical failure is captured as an efficacy measure and will not be considered an AE. However, clinical failure that results in hospitalization or death is reported as AEs/SAEs.

12.1.1 Recording of Adverse Events

Adverse events will be collected following signing of the ICF through discharge from the study. In addition, the Investigator should seek to elicit any clinical or objective reactions by specific questioning (e.g. "How have you been feeling?) and, as appropriate, by examination. Information on all AEs should be recorded on the eCRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. The component parts of the diagnosis may be listed for verification. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality.

To avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology on the eCRF and on the medical record rather than in the subject's own words. Each AE will also be described in terms of duration (start and stop date), severity, association with the study drug, action(s) taken, and outcome.

12.1.2 Severity of Adverse Events

Adverse event severity will be graded in accordance with the criteria of the Adult Toxicity Table (Modified) from the NIH/National Institute of Allergy and Infectious Diseases/Division of Microbiology and Infectious Diseases (DMID), November 2007 Adult Toxicity assessment table (Appendix A).

Mild: Transient or mild discomfort; no medical intervention/therapy required.

Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.

Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity assessment changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

12.1.3 Relationship Assessment

For each AE, the Investigator must make an assessment of the relationship of the event to the study drug as:

- Unrelated (there is not a reasonable possibility that the drug caused the event)
- Related (there is a reasonable possibility that the drug caused the event. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the study drug and the AE)

12.1.4 Action Taken

For each AE, the action(s) taken will be recorded (more than 1 may be recorded) as follows:

- No action taken
- Non-pharmacologic treatment
- Pharmacologic treatment
- Study drug discontinued
- Withdrawn from study
- New or prolonged hospitalization

12.1.5 Outcome

For each AE, the outcome will be recorded as either:

- Recovered
- Ongoing
- Death
- Unknown

12.2 Serious Adverse Events

An SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death

  "Death" is an outcome and is NOT the AE. In the event of death, the cause of death should be recorded as the AE. The only exception is "sudden death" when the cause is unknown.

- Life-threatening experience

  An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, it places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more serious form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization. A "planned" hospitalization for study procedures or preexisting conditions is NOT an SAE.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly/birth defect.

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

12.2.1 Other Reportable Events

Reports of overdose (with or without an AE), inadvertent or accidental exposure, and pregnancy should be forwarded in the same time frame as an SAE.

Overdose occurs when a patient is administered or has taken a dose greater than the intended or scheduled dose specified by the protocol.

All pregnancies occurring during the study must be followed for information regarding the course of pregnancy, delivery, and condition of the newborn. Follow-up should be provided by the Investigator to the Medical Monitor in a timely manner.

12.2.2 Reporting SAEs and Other Reportable Events

All SAEs that result in death or are life threatening, regardless of causal relationship, must be reported to the Medical Monitor (or designee) within 24 hours of the site's knowledge of the event. A copy of the initial SAE report must be received within 1 business day.

All other SAEs and other reportable events will be forwarded to the Medical Monitor within 1 business day.

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: subject identification, reporting source, causality, and an event outcome. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. CEM-102 Pharmaceuticals or its designee may contact the investigational site to solicit additional information or to follow up on the event.

As with all AEs (Section 12.1.3) , the report must also include an assessment of whether there is a reasonable possibility that the study drug caused the event (i.e. whether the event is related or unrelated to study drug). "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE.

If there is any doubt whether the information constitutes an SAE, the information will be treated as an SAE for the purposes of this protocol.

SAEs will be followed until resolution or return to Baseline (when worsening of a pre-existing condition is reported).)Subjects who sign and date the informed consent form but who fail to meet the inclusion and exclusion criteria are defined as screen failures. A screening log, which documents the subject initials and reason(s) for screen failure, is to be maintained by the Investigator for all screen failures. A copy of the log should be retained in the Investigator's study files.

13 DATA MANAGEMENT

Study data will be entered into eCRFs at the study sites (Section 15.7). Prior to database lock, programmed computer edit checks will be run against the database to check for discrepancies and reasonableness of the data. All issues resulting from the computer-generated checks will be resolved. The database will be locked after all subjects have completed the EOS visit.

14 STATISTICAL METHODS AND DATA ANALYSIS

As a non-randomized, single-arm study, there will be no formal statistical analyses. This study is not powered for inferential statistical analyses, and no formal hypothesis testing will be conducted. Safety and efficacy will be descriptive. Clinical outcome will be reported as the proportion of subjects meeting criteria of clinical success.

All safety data will be summarized using the Safety analysis set. Adverse events will be coded with the Medical Dictionary for Regulatory Activities (MedDRA®). The number and proportion of subjects having treatment-emergent AEs will be tabulated by MedDRA System Organ Class (SOC) and preferred term, severity, and relationship to study drug.

Since this is a non-randomized, open-label, single-arm study, interim data may be summarized and reported, as needed, prior to database lock.

Details of the analysis will be provided in a separate Statistical Analysis Plan (SAP).

14.1 Efficacy Analyses

The primary endpoint will be the proportion of subjects in the ITT analysis set who meet all the criteria for clinical success at the 6-Month Visit.

Clinical success is defined for subjects who meet all of the following criteria:

- Subject was not hospitalized due to worsening of the study-qualifying orthopedic infection at any point between enrollment and the 6-Month Visit
- Subject did not undergo a definitive surgical procedure (such as amputation) at any point between enrollment and the 6-Month Visit
- No additional antibiotics (after completion of the companion antibiotics) are required for treatment of the orthopedic infection due to the inclusionary pathogen
- Wound is closed, or the open area decreased in size (L x W) and, if a skin graft was done, the graft remains viable without evidence of infection
- No purulent discharge from the surgical wound, or new or recurring sinus tract
- No worsening of redness, tenderness, or swelling at the primary infection site
- No bacteremia of the inclusionary pathogen at any point between enrollment and the 6-Month Visit

Clinical failure is defined as follows:

- Not meeting all criteria for clinical success
- Death (due to the primary infection)
- Discontinuation of study drug due to an AE and the requirement of additional antibiotics for treatment of the primary infection

- Use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for > 10 days on any occasion, or for > 2 courses during any 6-month period

Indeterminate:

- Subject withdraws consent
- Subject is lost to follow-up

Investigators will evaluate and provide documentation of each subject for a clinically meaningful difference in each subject's response prior to making a determination of treatment failure for the primary study endpoint.

The secondary efficacy endpoints are as follows:

- Proportion of subjects in the ITT analysis set who meet all criteria for clinical success, as defined above, at the 9-Month, 12-Month, 15-Month, 18-Month, 21-Month, and 24-Month Visits

- Pharmacokinetics of CEM-102 used chronically in subjects with orthopedic infections

14.2 Safety Analyses

Safety and tolerability of CEM-102 for the treatment of bone and joint infections, reported as subject incidences of TEAEs, SAEs, deaths, and discontinuations due to AEs in the safety analysis set.

14.3 Pharmacokinetic Analysis

Analysis of the PK data will be described in detail in the PK analysis plan.

15 ADMINISTRATIVE ASPECTS

15.1 Compliance with Regulatory Requirements

This protocol will be conducted in compliance with the protocol and all regulatory requirements, in accordance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

15.2 Institutional Review Board or Independent Ethics Committee Approval

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB/IEC for approval. IRB/IEC approval of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

The Principal Investigator is responsible for keeping the IRB/IEC advised of the progress of the study and of any changes made to the protocol as deemed appropriate (at least once per year).. The Principal Investigator is also responsible for notifying the IRB/IEC of all unanticipated risks involving human subjects that occur during the study.

15.3 Informed Consent

It is the policy of CEM-102 Pharmaceuticals that written informed consent is obtained from subjects. The informed consent document must be signed and dated prior to any study-related procedures are performed at Screening/Baseline. The original signed ICF for each participating subject shall be filed with records kept by the Investigators(s). A copy of the informed consent document must be provided to the subject. Where applicable, it will be provided in a certified translation of the local language.

15.4 Confidentiality

Personal study subject data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of CEM-102 Pharmaceuticals and the clinical research organization (CRO), the IRB/IEC approving this research, and the US Food and Drug Administration (FDA), as well as any other applicable regulatory authorities, will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the subject identities will remain confidential.

15.5 Compensation, Insurance and Indemnity

Information regarding compensation, insurance, and indemnity is addressed in the Clinical Trial Research Agreement.

15.6 Protocol Amendment

If a protocol has been filed with regulatory agencies or submitted to an IRB/IEC and requires changes, a protocol amendment must be written. Any changes to the protocol will be made by the Sponsor. All amendments will be sent to the study sites, which are then responsible for submitting the amendment to their IRB/IECs for approval.

15.7 Electronic Case Report Forms (eCRF)

An eCRF will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be electronically signed by the Principal Investigator or a Sub-investigator (listed on the Form FDA 1572). It is the responsibility of the Principal Investigator to ensure the eCRFs are completed in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change, and person making change). At the completion of the study, CEM-102 Pharmaceuticals will be provided with the per-subject eCRF in an individual subject profile on disk or other electronic medium.

15.8 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondence, computer printouts, laboratory data, and drug accountability records. All source documents produced in this study will be maintained by the Investigator(s) and made available for inspection by CEM-102 Pharmaceuticals representatives, the FDA, or other regulatory authorities.

15.9 Study Monitoring Requirements

Site visits will be conducted by an authorized CEM-102 Pharmaceuticals representative (the monitor) to inspect study data, subject medical records, and eCRFs in accordance with ICH guidelines, GCPs, and the respective US or national regulations and guidelines, as applicable. It will be the monitor's responsibility to inspect the eCRF at regular intervals throughout the study and to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRFs.

The Investigator will permit representatives of CEM-102 Pharmaceuticals, the US FDA, and/or respective health authorities to inspect facilities and records relevant to this study.

15.10 Study File Management

It is the responsibility of the Investigator(s) to ensure that the study file at the site is maintained. The study file will contain, but not be limited to, the following:

- Investigator's Brochure (including updated or revised versions)
- Final study protocol
- Protocol amendments (if applicable)

- Fully executed Clinical Trial Agreement
- Investigator Manual (if applicable)
- ICF (blank)
- Revised ICFs and/or all addenda (blank)
- Copy of signed form(s) US FDA Form 1572
- DHHS number for IRB or other documentation of IRB/IEC compliance with FDA
- Curricula Vitae (CV) of Investigators and Sub-investigators
- Financial disclosure information provided to the Sponsors
- A list of the IRB/IEC members and their qualifications as well as a description of the IRB processes.
- If the Investigator is a member of the IRB/IEC, documentation stating he/she did not vote on the study
- Documentation of IRB/IEC approval of protocol, consent form, any protocol amendments, and any consent form revisions
- Annual IRB/IEC updates and approvals
- All correspondence between the Investigator, IRB/IEC, and CEM-102 Pharmaceuticals (or designee)
- Copies of all Investigational New Drug (IND) Safety Reports submitted to the FDA or other regulatory agencies and IRB/IEC correspondence documenting their submission (if applicable)
- Laboratory certifications/normal laboratory value ranges
- Screening log
- Clinical Research Associate (CRA) monitoring log
- Drug accountability records and invoices for receipt/return of study drug
- Protocol Signature Page
- Laboratory Director's CV and medical/professional license, if available

15.11 Study Completion

CEM-102 Pharmaceuticals requires that the following data and materials be on file at the study site before a study can be considered completed or terminated:

- Laboratory findings, clinical data, and all special test results from Screening through the end of the study follow-up period
- eCRFs properly completed by appropriate study personnel and electronically signed and dated by the Investigator

- Complete Drug Accountability records (drug inventory log and an inventory of returned or destroyed clinical material)
- Copies of protocol amendments and IRB/IEC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (an IRB/IEC summary letter is acceptable)

15.12 Audits

During the course of the study, or after completion of the study, each study site may be subject to an audit by a CEM-102 Pharmaceuticals Quality Assurance Auditor (or an auditor appointed by CEM-102 Pharmaceuticals or its authorized representative) and/or an inspector from the FDA and/or other regulatory authority. Every attempt will be made to notify the Investigator in writing in advance of the audit.

15.13 Retention of Records

CEM-102 Pharmaceuticals follows US regulations and ICH guidelines in its retention policy.

US IND regulations (21 CFR 312.62) require that records and documents pertaining to the conduct of this study and the distribution of investigational drugs, including eCRFs, consent forms, laboratory test results and medication inventory records, be kept on file by the Principal Investigator for 2 years after a marketing application is approved for the drug for the indication for which it is being studied. If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the FDA has been notified. ICH guidelines indicate that documents should be retained until at least 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. If there is a country or institutional policy that specific records and documents be retained for a longer period than described above, the applicable sites must comply with those policies in addition to US and ICH policies. No study records should be destroyed without prior authorization from CEM-102 Pharmaceuticals.

15.14 Disclosure of Data

The Investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of Investigators, their addresses, qualifications, and extent of involvement. It is understood that the Investigator is required to provide CEM-102 Pharmaceuticals with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by the US FDA and other regulatory authorities, by CEM-102 Pharmaceuticals, and by the IRB as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during the course of this study is confidential, and disclosure to third parties other than those noted above is prohibited.

15.15 Financial Disclosure

The US FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require Sponsors to obtain certain financial information from Investigators participating in covered clinical studies; each Principal Investigator and Sub-investigator is required to provide the required financial information before participating in the study and to promptly update CEM-102 Pharmaceuticals with any relevant changes to this information throughout the course of the clinical study and for up to 1 year after its completion. This rule applies to all Investigators and Sub-investigators participating in covered clinical studies to be submitted to the FDA in support of an application for marketing approval.

15.16 Publication Policy

The publication policy is outlined in the Clinical Trial Agreement.

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Appendix A Toxicity Table

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE (MODIFIED)

NOVEMBER 2007 - DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
Rx = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables, use the scale below to estimate grade of severity:

GRADE 1	**Mild**: Transient or mild discomfort; no medical intervention/therapy required
GRADE 2	**Moderate**: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	**Life-threatening**: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event.

LABORATORY RANGES

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5-10.5 gm/dL	8.0-9.4 gm/dL	6.5-7.9 gm/dL	<6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000 mm^3
% Polymorphonuclear Leucocytes + Band Cells	>80%	90–95%	>95%	---------
Activated Partial Thromboplastin (APTT)	1.01-1.66×ULN	1.67-2.33×ULN	2.34--3×ULN	>3×ULN
CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	<116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	>165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0-3.4 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L or intensive replacement therapy or hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6-6.0 mEq/L	6.1-6.5 mEq/L	6.6-7.0 mEq/L	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4-7.8 mg/dL	7.7-7.0 mg/dL	6.9-6.1 mg/dL	<6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

Hypercalcemia (corrected for albumin)	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4-1.2 mEq/L	1.1-0.9 mEq/L	0.8-0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL or replacement Rx required	1.0-1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1-<1.25xULN	1.25-<1.5xULN	1.5–1.75xULN	>1.75xULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1-<1.5xULN	1.5-<2.0xULN	2.0–3.0xULN	>3.0xULN
BUN	1.25-2. 5xULN	2.6-5xULN	5.1-10xULN	>10xULN
Hyperuricemia (uric acid)	7.5–10.0 mg/dL	10.1–12.0 mg/dL	12.1–15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1-1.5xULN	1.6-3.0xULN	3.1-6xULN	>6xULN or dialysis required
ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1-<2.0xULN	2.0–<3. 0xULN	3.0–8. 0xULN	>8xULN
ALT (SGPT)	1.1-<2.0xULN	2.0–<3.0xULN	3.0–8. 0xULN	>8xULN
Alkaline Phosphatase	1.1-<2.0xULN	2.0–<3.0xULN	3.0–8. 0xULN	>8xULN
URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg – 1gm loss/day	2-3+ or 1-2 gm loss/day	4+ or 2-3.5gm loss/day	nephrotic syndrome or >3.5 gm loss/day
Hematuria	microscopic only <10 RBC/hpf	gross, no clots >10 RBC/hpf	gross, with or without clots, OR RBC casts	obstructive or required transfusion
CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent symptomatic Rx required	unstable dysrhythmia; hospitalization and treatment required

Hypertension	transient increase >20 mm/Hg; no treatment	recurrent, chronic increase >20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20beats/min or decreased by <10mm/Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20mm/Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60 mm/Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused
RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70%-80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50%-70% (of peak flow)	no normalization with bronchodilator; FEV_1 25%-50% of peak flow; or retractions present	cyanosis: FEV_1 <25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	Dyspnea requiring oxygen therapy
GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required
Vomiting	1 episode in 24hours	2-5 episodes in 24hours	>6 episodes in 24hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon

Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last <1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2 L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids
NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	Incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness, no objective symptoms/signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	Paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g. vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (moderate decreased sensation, e.g. vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (i.e. upper and lower extremities)	sensory loss involves limbs and trunk; paralysis or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling – and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis
SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15mm	15-30 mm	>30mm	
Erythema	<15mm	15-30 mm	>30mm	
Edema	<15mm	15-30 mm	>30mm	
Rash at Injection Site	<15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	
SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	Anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy

Fever: oral	37.7-38.5°C or 100.0-101.5 °F	38.6-39.5 °C or 101.6-102.9 °F	39.6-40.5 °C or 103-105 °F	>40 °C or >105 °F
Fatigue	normal activity reduced <48 hours	normal activity decreased 25-50% >48 hours	normal activity decreased >50% can't work	unable to care for self

CEM-102 Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

Study Title:	An Open-Label, Non-Randomized, Single-Arm Multi-Center Study to Evaluate Oral Sodium Fusidate (CEM-102) for the Treatment of Staphylococcal Bone or Joint Infections in Subjects for whom Chronic Antibiotic Suppressive Therapy is Indicated
Phase:	2/3
Protocol No.:	CE06-302
Protocol Date	Original Protocol: 07 July 2015
Analysis Plan Version and Date	Final Version, 19 October 2017
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Prepared For:	CEM-102 Pharmaceuticals, Inc 6320 Quadrangle Drive, Suite 360 Chapel Hill, NC 27517

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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TABLE OF CONTENTS

1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of efficacy and safety data from Protocol CE06-302. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection, and to the Pharmacokinetics (PK) Report for the analysis of plasma concentrations of CEM-102.

1.1. STUDY OVERVIEW

Protocol CE06-302 is a phase 2/3, prospective, open-label, non-randomized, single-arm trial to evaluate the safety and effectiveness of CEM-102 for chronic antibiotic suppressive therapy of bone or joint infections. Subjects enrolling in this study must have a suspected or confirmed staphylococcal bone or joint infection due to an inclusionary pathogen susceptible to CEM-102 that requires suppressive antibiotic therapy. The infection should be demonstrated from a positive culture from samples obtained during surgery, biopsy, or drainage procedures within 6 weeks prior to enrollment. If the subject does not have a positive culture, the Investigator must provide documentation as to why the subject is suspected to have a staphylococcal infection and discuss with the medical monitor for approval of enrollment.

This study comprises two parts: Part A (enrollment through the 6-month visit) and Part B (6 to 24 months post-enrollment). In Part A, all subjects will receive 6 months of CEM-102 treatment. The Investigator will evaluate each subject completing Part A for clinical response at the 6-month visit (primary endpoint). For Part B, a subject who completes Part A and, in the Investigator's opinion, requires continued suppressive therapy, may continue to receive CEM-102. Alternatively, if the Investigator considers the infection resolved and that no further antibiotic therapy is required, study drug will be discontinued and the subject followed for evidence of relapse until the end of study (EOS; 24 months).

During the first 6 months of treatment, study Part A, subjects will be monitored monthly (±1 week) for safety and clinical response to CEM-102. During study Part B, subjects will be monitored every 3 months (±2 weeks) until the EOS Visit (24 months).

1.2. SCHEDULE OF ASSESSMENTS/PROCEDURES

Assessment/Procedure	Screening[a]	Part A			Part B	End of Study (EOS)[d]
		Enrollment (Day 1 Visit)[b,c]	Day 8 (± 3 days)	Monthly During First 6 Months (±1 week)	Every 3 Months From Month 6 until End of Study (±2weeks)	
Informed Consent Form	X					
Inclusion/Exclusion Criteria Review	X	X				
Review of Clinical/ Surgical History	X	X	X	X	X	X
Microbiological specimens for culture	X	X	X[e]	X[e]	X[e]	X[e]
Enrollment	X	X				
Vital Signs[f]	X	X	X	X	X	X
Limited Physical Examination[g]	X	X	X	X	X	X
Examination of Infected Area[h]	X	X	X	X	X	X
Safety Laboratory Assessments[i]	X	X	X	X	X	X
Inflammation Laboratory Assessments[j]	X	X		X	X	X
CEM-102 Administration[k]		X				
Pharmacokinetic Blood Sampling				X[o]		
Dispense Oral antibiotic to Subjects[l]		X	X	X	X	
Perform Drug Accountability			X	X	X	X
Record 6-Month History of Prior Antibiotic Used to Treat the Primary Infection Leading to Enrollment	X					
Record Concomitant Medications	X	X	X	X	X	X
Record AEs[m]	X	X	X	X	X	X

Investigator Assessment of Clinical Response[n]				X	X	X

a. Within 6 weeks prior to enrollment, subjects must have a positive culture with an inclusionary pathogen susceptible to CEM-102, demonstrated from a culture from samples obtained during surgery, biopsy, or drainage procedures. If subject does not have a confirmatory culture result, the Investigator must provide documentation as to why subject is suspected to have a staphylococcal infection and must discuss the subject with the medical monitor for approval of enrollment.
b. Enrollment is contingent on demonstration that subject fulfills the inclusion/exclusion criteria.
c. Study Day 1 corresponds to the first day of dosing with CEM-102.
d. Subjects who discontinue CEM-102 because of an adverse event (AE) or clinical failure should have a study visit around the time of drug discontinuation and will continue to be followed, as needed, for appropriate observation of treatment-related AEs until AEs have resolved or stabilized. If a subject withdraws from the study at any time, for any reason, the EOS visit will be performed around that time. Those subjects who continue CEM-102 until the Month 24 visit will undergo the assessments/procedures for the EOS visit. At study closure, at the discretion of the Investigator, subjects may be rolled over into an expanded access protocol to receive chronic suppressive CEM-102 therapy.
e. If clinically indicated, microbiological samples (tissue surrounding the foreign material, synovial fluid, bone, etc.) obtained during the study should be submitted to the local laboratory for aerobic and anaerobic culture and susceptibility testing, including to CEM-102. All isolated bacteria are to be sub-cultured and shipped to the central microbiology laboratory for organism confirmation and confirmatory susceptibility testing.
f. Vital sign measurements include height, weight, temperature, heart rate, respiratory rate, and blood pressure. Results are to be recorded in the eCRF.
g. Limited physical examination may include HEENT, cardiovascular, pulmonary, gastrointestinal, skin, lymph nodes, musculoskeletal, and extremities, among others. Results are to be documented in source and recorded in the eCRF.
h. Examination of the infected area will include the following assessments: pain, erythema, mobility, joint stability, wound closure, wound drainage, and weight bearing [for back and lower extremity infections]. The Investigator will state whether the infected area seems to have improved, deteriorated, or remained unchanged. Results are to be documented in the source and recorded in the eCRF.
i. Safety laboratory assessments will be performed at the local laboratory and will include the following: serum chemistry (ALT, AST, alkaline phosphatase [ALP], total and direct bilirubin, blood urea nitrogen [BUN], creatinine, albumin, total protein, sodium, total carbon dioxide, glucose, potassium, chloride, calcium, phosphorus, and CPK). For female subjects of child bearing potential, a urine or serum pregnancy test will be performed at Screening and will be repeated at subsequent visits per Investigator's discretion .
j. Laboratory measurements of markers of inflammation will be performed at the local laboratory and will include the following: hematology (complete blood count [CBC] with differential), erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]). Laboratory measurements of markers of inflammation obtained on the day of a surgery or debridement should be performed before the procedure when possible, because levels of these markers are known to increase after surgery.
k. A CEM-102 loading dose strategy is utilized, in which CEM-102 is given as 1500 mg every 12 hours for 2 doses followed by 600 mg every 12 hours thereafter.
l. After 6 months of therapy, the Investigator may decide to continue chronic suppressive therapy with CEM-102 or discontinue CEM-102 due to clinical cure and no further requirement for antibiotic therapy. Subjects who stop treatment will continue to be followed on the same schedule as those who remain on therapy to monitor for infection relapse until the end of the study. Subjects who discontinue CEM-102 due to clinical failure should have an EOS visit at that time.
m. All AEs will be collected following signing of the ICF.
n. The Investigator will assess clinical response at Months 6, 9, 12, 15, 18, 21, 24 and at EOS.
o. Pharmacokinetic blood sampling will be conducted at the 3-month visit as described in Section 10.6

1.3. LIST OF ABBREVIATIONS

AE	adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CEM-102	sodium fusidate (fusidic acid)
CPK	creatinine phosphokinase
CRP	C-reactive protein
HEENT	head, eyes, ears, nose, throat
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
SAE	serious AE
TEAE	treatment-emergent AE
WBC	white blood cell

2. OBJECTIVE

The study objective is to evaluate the safety and effectiveness of CEM-102 as chronic antibiotic suppressive therapy in subjects with staphylococcal bone or joint infections.

3. ENDPOINTS

Primary Endpoint

The primary endpoint will be the proportion of subjects in the safety population who meet all the criteria for clinical success at the 6-Month Visit.

Secondary Endpoints

Efficacy

- The proportion of subjects in the safety population who meet all criteria for clinical success at the 9-Month, 12-Month, 15-Month, 18-Month, 21-Month, and 24-Month Visits

Safety and Tolerability

- The proportion of subjects in the safety population who experience a treatment-emergent adverse event (TEAE), a serious adverse event (SAE), an SAE that results in death, or a TEAE that results in discontinuation from study or study drug

Additional Endpoints

Efficacy

- Change in composite symptom and function score at each Visit
- Change in wound status at each Visit
- Change in ESR as a surrogate marker of infection status over time

Safety and Tolerability

- Changes from baseline in selected chemistry and hematology laboratory assessments by visit
- The proportion of subjects who experience laboratory toxicity grade shifts from baseline
- The proportion of subjects who experience treatment-emergent graded laboratory abnormalities

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. SAMPLE SIZE AND POWER

As a non-randomized, single-arm study, there will be no formal statistical analyses. This study is not powered for inferential statistical analyses. Thirty subjects will be enrolled at up to 20 investigative sites in the United States.

4.2. RANDOMIZATION AND MASKING

Since this is a non-randomized open-label study, randomization and masking are not applicable.

4.3. HANDLING OF DATA

4.3.1. Strata and Covariates

There are no planned adjustments for covariates.

4.3.2. Examination of Subject Subsets

There are no planned subsets.

4.3.3. Multiple Testing and Comparisons

Adjustments for multiple comparisons are not applicable.

4.3.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects. See section 4.3.6 for details of imputing missing dates. Unless otherwise specified, other missing data will not be imputed.

Should an adverse event have a missing relationship to study medication, it will be classified as having the strongest relationship to study medication.

4.3.5. Derived and Transformed Data

For purposes of analysis, subjects who are deemed a clinical failure (see section 4.3.8) due to use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for >10 days on any occasion, or for >2 courses during any 6-month period, will be programmatically assigned an indeterminate response.

Signs and symptoms data from the primary infection exam will be combined to derive a composite symptom and function score (see section 4.3.8).

4.3.6. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary in order to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation of incomplete start/stop dates for adverse events and prior/concomitant medications, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1 (defined in section 4.3.8).

All events with an incomplete end date are assumed to have ended on or before the day the form was completed. For scheduled visit data, missing dates will be imputed based on the nominal visit day relative to Day 1. For other data, if the month/year is the same as the Day 1 month/year then the date will be set to

the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. A list of incomplete and imputed dates will be prepared by the project statistician or statistical programmer(s) and will be submitted for review by the clinical project manager and sponsor.

4.3.7. By-Study Visit Displays

Visits will be presented according to the nominal visit (efficacy analyses) or analysis visit (safety analyses) as obtained from the eCRF. For vendor data, the collection date will be used to assign the visit.

For safety analyses, all data, including scheduled and unscheduled visits, will be windowed to an analysis visit as follows:

Analysis Visit	**Study Day**
Baseline	Last non-missing value obtained prior to or on the day of initiation of study treatment (CEM-102)
Day 8	5-11
Month 1	23-37
Month 2	54-68
Month 3	84-98
Month 4	115-129
Month 5	145-159
Month 6	176-190
Month 9	260-288
Month 12	352-380
Month 15	443-471
Month 18	535-563
Month 21	626-654
Month 24	718-746

For each safety outcome, analyses will utilize assessments occurring during the analysis visit windows in the table above. Thus, if a subject has a scheduled Month 1 visit that occurs outside of the study day 23-37 window, the assessment will not be summarized with the Month 1 assessments but will instead be considered an unscheduled visit. If both a scheduled and an unscheduled visit occur within an analysis visit window, the value taken from the scheduled visit will be used. If multiple scheduled visits occur within an analysis visit window, or if multiple unscheduled visits occur and no scheduled visit occurs, then the last value will be used.

For summaries of laboratory values and of treatment-emergent laboratory abnormalities, worst overall post-baseline values will also be summarized. This will include data from all assessments.

With the exception of worst overall post-baseline summaries, post-baseline visits that do not occur within any analysis visit window will be excluded from the summary presentations, but included in the listings.

4.3.8. Definitions and Terminology

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to or on the day of initiation of study treatment (CEM-102). Because time of initiation of treatment is not captured, events defined by the protocol as occurring before treatment initiation will be considered baseline-eligible. All pathogens recovered from cultures performed prior to first dose will be considered baseline pathogens. Baseline values may come from scheduled or unscheduled visits.

Study Day
The date vital signs were collected at the nominal Day 1 visit (a surrogate for the date of first dose of study drug) will be considered as study day 1, and the day before vital signs were collected at the nominal Day 1 visit will be study day -1.

If an event date is on or after the Day 1 date, then Study Day is calculated as:

- Study Day = event date – date of Day 1+1

If an event date is prior to the date of Day 1, then Study Day is calculated as:

- Study Day = event date – date of Day 1

Days on Study
Days on Study is the number of days from Day 1 to the visit date of the end of study or early termination visit.

Pathogens
Pathogen determination is based on the genus and species identification from the central laboratory. If the local laboratory grows an acceptable pathogen but the central laboratory is not able to grow the isolate, if isolates are lost during transportation or storage, or there are major discrepancies between the local and central laboratory in the identification of species, the central laboratory will request that the local laboratory resend the isolate. The central laboratory identification of genus and species is used for analysis except in those cases where there is no central laboratory determination of genus and species. In this case, the local laboratory determination is used for pathogen identification.

The following organisms recovered from baseline specimens obtained during surgery, biopsy or drainage procedures (e.g. tissue biopsy, bone biopsy, joint aspirate, etc.) or from blood are considered inclusionary pathogens: *Staphylococcus aureus* (including both methicillin-susceptible *S. aureus* [MSSA] and methicillin-resistant *S. aureus* [MRSA]), and coagulase-negative staphylococci (CoNS) such as *Staphylococcus epidermidis*, *Staphylococcus hominis*, or *Staphylococcus haemolyticus*. Other pathogens include: *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Corynebacterium striatum*, and *Propionibacterium acnes*. All isolates, including other bacteria not listed here, will be reviewed by the Sponsor on a case-by-case basis to confirm BJI pathogen status. Fungal isolates (*Candida albicans*) will not be considered pathogens.

S. aureus will be considered methicillin-resistant (MRSA) based on oxacillin susceptibility results (MIC ≥4 μg/ml; resistant) from the central laboratory. If isolate test results are not available from the central

laboratory, MRSA/MSSA designation will be as reported in the eCRF (as part of the organism name). MRSA and MSSA will be considered distinct pathogens.

Investigator Assessment of Clinical Response:
Clinical success is defined to occur when subjects meet all of the following criteria:

- Subject was not hospitalized due to worsening of the study-qualifying orthopedic infection at any point between enrollment and the 6-Month Visit
- Subject did not undergo a definitive surgical procedure (such as amputation) at any point between enrollment and the 6-Month Visit
- No additional antibiotics (after completion of companion antibiotics) are required for treatment of the orthopedic infection due to the inclusionary pathogen
- Wound is closed, or the open area decreased in size (L x W) and, if a skin graft was done, the graft remains viable without evidence of infection
- No purulent discharge from the surgical wound, or new or recurring sinus tract
- No worsening of redness, tenderness, or swelling at the primary infection site
- No bacteremia of the inclusionary pathogen at any point between enrollment and the 6-Month Visit

Clinical failure is defined to occur when subjects meet any of the following criteria:

- Failure to meet all criteria for clinical success
- Death (due to the primary infection)
- Discontinuation of study drug due to an AE and the requirement of additional antibiotics for treatment of the primary infection

An indeterminate response is defined to occur when subjects meet any of the following criteria:

- Subject withdraws consent
- Subject is lost to follow-up

For purposes of analysis, subjects who are deemed a clinical failure due to use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for >10 days on any occasion, or for >2 courses during any 6-month period, will be programmatically assigned an indeterminate response.

Primary Infection Exam (Signs and Symptoms): Baseline Evaluation
The baseline evaluation for outcome assessments is based on the Screening and Study Day 1 data according to the table below:

Screening Visit Evaluation	Study Day 1 Visit Evaluation	Baseline Evaluation
Present	New	Present
	No change	Present
	Improved	Present
	Worsening	Present
	Not Assessed	Present
	Resolved	Absent
Absent	New	Present
	No change	Absent
	Improved	N/A
	Worsening	N/A
	Not Assessed	Absent
	Resolved	N/A
Not Assessed	New	Present
	No change	N/A
	Improved	N/A
	Worsening	N/A
	Not Assessed	Not Assessed
	Resolved	Absent

Primary Infection Exam (Signs and Symptoms): Change from Previous Visit
Change from previous visit for a given endpoint is defined as a qualitative comparison between the evaluation during the previous visit to the evaluation at the current visit. The possible responses are:

New - The sign/symptom was not present during the previous visit and is present at the current visit
No change - The severity of the sign/symptom has not changed from the previous visit
Improved - There is improvement from the previous visit, but the sign/symptom has not been resolved
Worsening - The sign/symptom has gotten worse from the previous visit
Not assessed - The sign/symptom was not assessed during the current visit
Resolved - The sign/symptom has been resolved as of the current visit

Primary Infection Exam (Signs and Symptoms): Composite Symptom and Function Score
Data from the following signs and symptoms will be combined to derive a composite score: Swelling/Edema, Warmth, Redness, Pain at Rest, Pain with Movement, Decreased Mobility, and Limited Weight Bearing. The score will be calculated according to the following algorithm:

- Each symptom with a baseline evaluation of "Present" will be assigned a value of 7. Each symptom with a baseline evaluation of "Absent" or "Not Assessed" will be assigned a value of 0.

- At each month, the individual sign and symptom scores will be calculated. These will be calculated by taking the baseline score and adjusting it in a cumulative manner up to the month being reported. The score will be adjusted according to change from previous visit result as follows:
    - New – increase by 7.0
    - No Change – no change
    - Improved – decrease by 0.5
    - Worsening – increase by 0.5
    - Not Assessed – no change
    - Resolved – decrease to 0
- At any given timepoint, the composite score is calculated by summing the scores of each sign or symptom.

Treatment-emergent Adverse Event
Any adverse event reported on the eCRF that occurs on or after the receipt of study drug (Day 1) through 28 days after the last dose of study drug is considered treatment-emergent. Events with a missing start date or that occur on the date of dosing and have a missing start time will be considered treatment-emergent.

Treatment-emergent Laboratory Abnormality
A treatment-emergent laboratory abnormality is defined as an increase of at least one toxicity grade from the baseline assessment at any post baseline visit up to and including 28 days after the last dose date of study drug administration. If the relevant baseline assessment is missing, then any graded abnormality (i.e., at least Grade 1) is considered to be treatment-emergent.

Laboratory abnormalities will be graded according to the Division of Microbiology and Infection Diseases (DMID) 1-4 scale. Values not considered Grade 1 or higher will be classified as "Normal". Grading guidelines are listed in Appendix I.

Antibiotic and Non-antibiotic Medications
Antibiotic and non-antibiotic medications are recorded on separate forms of the eCRF. Reasons for antibiotic medications are recorded on the eCRF as therapy for the primary infection before enrollment, companion antibiotic therapy after enrollment, adjunctive antibiotic therapy for co-infections, or therapy for unrelated infections.

Prior and Concomitant Medications
A prior medication is defined as any medication taken prior to the date of first dose of study drug (Study Day 1). A concomitant medication (including companion and adjunctive antibiotic therapy) is defined as any medication that has a stop date that is on or after the date of first dose of study drug, or is ongoing. A medication can be considered both prior and concomitant.

4.4. TIMING OF ANALYSES

An interim analysis will be conducted once the last subject completes the 6-month visit or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and locked. A final analysis will be conducted once the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and locked.

5. ANALYSIS POPULATIONS

5.1. INTENT TO TREAT (ITT) POPULATION

The ITT population will include all subjects who were enrolled in the study. To be enrolled, subjects must provide informed consent and meet all eligibility criteria. Analysis of subject disposition, demographic and baseline disease characteristics, and all efficacy analyses will be conducted using the ITT population. With the exception of the inclusion/exclusion criteria and informed consent listing, all listings will be produced on the ITT population.

5.2. SAFETY POPULATION

The safety population will include all subjects who were enrolled and received at least one dose of CEM-102. Analysis of concomitant medications received and all safety analyses will be conducted using the safety population.

5.3. SCREENED POPULATION

The screened population will include all subjects who signed the informed consent form (ICF). Screen failures are subjects who signed the ICF and were not enrolled in the study. The inclusion/exclusion criteria and date of informed consent listing will be produced on the screened population.

6. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by subject number, and then by date within each subject number.

The statistical analyses will be conducted with the SAS® software package version 9.2 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

6.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS, DURATION OF TREATMENT

6.1.1. Subject Disposition and Duration of Treatment

Subject disposition will be presented, including summaries of eligibility, number of subjects who complete the study, number of subjects who prematurely discontinued from study, reasons for study discontinuation, number of subjects who discontinued study drug, reasons for study drug discontinuation, number of days on study, number of days on study drug, and number of subjects who completed each visit.

Study drug dispensation and accountability will be presented in a listing.

6.1.2. Demographics and Baseline Characteristics

Demographic data and baseline characteristics including age, sex, race, ethnicity, height, weight, BMI, infection type, site of infection, and risk factors for bone or joint infection will be summarized using descriptive statistics for the safety population.

6.1.3. Baseline Pathogens

The pathogenic organisms identified from baseline (screening or historical) cultures of the primary infection site or blood cultures will be summarized. MRSA and MSSA are considered distinct pathogens. The number and percentage of subjects with each pathogen will be presented by genus and species for the safety analysis population. The same pathogen identified from both the culture of a BJI specimen and/or blood culture will be counted only once in the summary.

A listing will be provided that includes all culture results and will indicate the specimen collection date, study day, type of specimen, Gram stain results, organism name (local and central laboratory identification), and a flag for whether or not each isolate is considered a baseline or post-baseline pathogen. A by-subject listing of isolate MICs, and disk diffusion zone diameters, and susceptibilities (if applicable) will also be provided. Isolates are considered susceptible (S), intermediate (I), or resistant (R) to CEM-102 according to Table 1.

Table 1 Provisional Interpretative Criteria for Fusidic Acid (CEM-102)

	Broth Microdilution MIC (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	Susceptible	**Intermediate**	**Resistant**	**Susceptible**	**Intermediate**	**Resistant**
Staphylococcus species	≤ 1	2	≥ 4	≥ 22	20-21	≤ 19
β-hemolytic streptococci[a]	≤ 1	2-8	≥ 16	≥ 16	11-15	≤ 10

a. Includes: *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae*

6.1.4. Concomitant Medications

Prior and concomitant medications will be coded using the World Heath Organization (WHO) Drug dictionary (September 2015). Antibiotic and non-antibiotic concomitant medications will be summarized by frequency of classification and generic name. Antibiotic concomitant medications will be summarized separately for primary infections before enrollment, companion antibiotics, co-infections, and unrelated or other antibiotics. Prior and concomitant medications will be presented in a data listing.

6.2. EFFICACY

The counts and percentages of subjects who have clinical success, clinical failure, and an indeterminate clinical response, and reasons for clinical failure and indeterminate response will be summarized at the 6-Month, 9-Month, 12-Month, 15-Month, 18-Month, 21-Month, and 24-Month Visits. Exact, binomial 95% confidence intervals will be provided for the percentage of subjects who have clinical success at each visit.

The composite symptom and function score and change from baseline score will be summarized by visit. Only subjects who are on study drug at a given visit will be included in the summary for that visit. As an exploratory analysis to examine the relationship between the composite symptom and function score and the proportion of subjects who meet all the criteria for clinical success, a logistic regression model of the probability of clinical success with a fixed effect for composite symptom and function score will be performed. For this analysis, an indeterminate response will be considered a failure.

Wound status will be characterized by three signs/symptoms from the primary infection exam: Sinus tract formation, open wound, and drainage. A subject will be considered to have a sign/symptom at a given visit if it is newly present or not resolved. The counts and percentages of subjects who have each sign/symptom will be presented separately. Additionally, the counts and percentages of subjects who have none of the three signs/symptoms and one or more of the signs/symptoms will be presented.

Changes in primary infection site signs and symptoms and inflammation lab results will each be presented in a listing.

A spaghetti plot of individual subject erythrocyte sedimentation rate values by study day will be generated for timepoints where the subject is either on study drug or off study drug and being followed for relapse.

The number of subjects with a pathogen showing decreasing susceptibility will be assessed manually by the Sponsor using the by-subject isolate susceptibility listing. Decreasing susceptibility of a pathogen is defined as a 4-fold or greater increase in CEM-102 MIC from baseline to any subsequent study time point.

6.3. SAFETY

6.3.1. Adverse Events

Adverse events will be coded for preferred term and system organ classification by the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

If a subject experiences multiple events that map to a single preferred term, the greatest severity and/or strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. Should an event have a missing relationship, it will be classified as having the strongest relationship to study medication.

A high level summary table of the number and percentage of subjects who experience any AE, any TEAE, any TEAE with severe intensity, any TEAE related to study drug, any TEAE leading to study discontinuation, any TEAE leading to study drug discontinuation, any treatment-emergent serious adverse event (SAE), any treatment-emergent SAE related to study drug, any treatment-emergent SAE leading to study discontinuation, and any treatment-emergent SAE leading to study drug discontinuation will be provided.

Summaries of treatment-emergent AEs will include any AEs starting on or after the initiation of study treatment through 28 days after the last dose of study drug. The occurrence of TEAEs will be summarized using preferred terms and system organ classifications. Separate summaries of TEAEs overall and by greatest severity, TEAEs related to study drug (overall and by greatest severity), TEAEs leading to discontinuation of study or study drug, treatment-emergent SAEs and treatment-emergent SAEs leading to

death will be presented.

All adverse event data listings will include the individual subjects showing both verbatim and preferred terms and system organ classification. All adverse events that occurred prior to the initiation of the study treatment will be excluded from the tables. All adverse events will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 4.3.6 to determine treatment-emergent status.

6.3.2. Clinical Laboratory Assessments

Descriptive summaries of selected clinical laboratory results as well as change from baseline values will be presented by analysis visit and worst overall post-baseline value. Selected laboratory parameters to be summarized include: ALT, AST, ALP, total bilirubin, creatine kinase, creatinine, WBC count, hematocrit, and platelets. Frequency and percentage of subjects experiencing treatment-emergent laboratory abnormalities (by Grade) will be summarized by analysis visit and worst overall post-baseline value. If criteria in both directions are shown for a single parameter, then abnormalities in each direction will be summarized separately. Laboratory toxicity grade shifts from baseline will also be summarized by analysis visit and worst overall post-baseline value.

All clinical laboratory test results will be provided in a listing. The listing will include the laboratory test value, change from baseline, and toxicity grade.

6.3.3. Other Safety Analyses

Vital sign results and all physical examination data will each be provided in a listing.

6.4. PHARMACOKINETICS ANALYSES

CEM-102 plasma concentrations will be presented in a listing. Analysis of plasma concentration data will be presented in a separate PK Report.

7. PROTOCOL DEVIATIONS

Protocol deviations identified by clinical monitoring will be provided in a data listing.

8. CHANGES IN THE PLANNED ANALYSES

For purposes of analysis, subjects who are deemed a clinical failure due to use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for >10 days on any occasion, or for >2 courses during any 6-month period, will be programmatically assigned an indeterminate response.

No other deviations in the conduct of the study or the planned analysis are anticipated. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

9. REFERENCES

None.

10. REVISION HISTORY

Date	Revision	Rationale

11. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).

- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all enrolled subjects.

- Group headers: In the summary tables, the group headers will identify the dose cohort and the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.

- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.

- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.

    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations

    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.

- Sorting: Listings will be sorted by subject number, dose cohort, and date, if applicable. Listings with multiple observations per subject will be sorted by subject number, dose cohort, treatment and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.

- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:

    - Raw measurements will be reported to the number of significant digits as captured on the eCRFs.

    - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.

- Means will be reported to the same number of significant digits as the parameter.
- Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HHMM).

12. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

Demography and Baseline Characteristics

14.1.1	Subject Disposition and Treatment Duration, ITT Population
14.1.2	Demographics and Baseline Characteristics, ITT Population
14.1.3	Pathogens Identified at Baseline, ITT Population
14.1.4	Concomitant Medications by Generic Name and Drug Classification, Safety Population

Efficacy

14.2.1	Investigator Assessment of Response and Reasons for Failure or Indeterminate Response by Visit, ITT Population
14.2.2	Composite Symptom and Function Score by Visit, ITT Population
14.2.3	Wound Status by Visit, ITT Population

Safety

14.3.1.1	Overall Adverse Events, Safety Population
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term, Overall and by Greatest Severity, Safety Population
14.3.1.3	Treatment-Emergent Adverse Events Related to Study Drug by System Organ Classification and Preferred Term, Overall and by Greatest Severity, Safety Population
14.3.2.1	Treatment-Emergent Adverse Events Leading to Discontinuation of Study by System Organ Classification and Preferred Term, Safety Population
14.3.2.2	Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Classification and Preferred Term, Safety Population
14.3.2.3	Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term, Safety Population
14.3.2.4	Treatment-Emergent Adverse Events Leading to Death by System Organ Classification and Preferred Term, Safety Population
14.3.4.1.1	Selected Chemistry Laboratory Values by Parameter and Visit, Safety Population
14.3.4.1.2	Selected Hematology Laboratory Values by Parameter and Visit, Safety Population
14.3.4.2	Laboratory Toxicity Grade Shifts from Baseline, Safety Population
14.3.4.3	Treatment-Emergent Graded Laboratory Abnormalities, Safety Population

Figures

14.2.1	Individual Erythrocyte Sedimentation Rate Values by Study Month, Safety Population

Data Listings

16.1.6	Study Drug Dispensation and Accountability, ITT Population
16.2.1.1	Subject Disposition, ITT Population
16.2.1.2	Inclusion/Exclusion Criteria and Date of Informed Consent, Screened Population
16.2.2.1	Protocol Deviations/Violations, ITT Population
16.2.4.1	Demographics, Baseline Characteristics, and Infection Type, ITT Population
16.2.4.2	Primary Infection History, ITT Population
16.2.4.3	Medical History and Risk Factors for BJI, ITT Population

16.2.5.1.1 Prior and Concomitant Antibiotics, ITT Population
16.2.5.1.2 Prior and Concomitant Medications, ITT Population
16.2.5.2 CEM-102 Plasma Concentrations, ITT Population
16.2.6.1 Investigator Assessment of Response and Reasons for Failure or Indeterminate Response at each Visit, ITT Population
16.2.6.2 Primary Infection Examination (Signs and Symptoms) at each Visit, ITT Population
16.2.6.3 Inflammation Laboratory Test Results, ITT Population
16.2.6.4 Microbiological Culture Results, ITT Population
16.2.6.5 Antibiotic Susceptibility Results, ITT Population
16.2.7.1 Adverse Events, ITT Population
16.2.8.1.1 Chemistry Laboratory Tests, ITT Population
16.2.8.1.2 Hematology Laboratory Tests, ITT Population
16.2.8.2 Surgical Interventions, ITT Population
16.2.8.3 BJI Imaging, ITT Population
16.2.8.4 Vital Signs, Height, and Weight, ITT Population
16.2.8.5 Abnormal Physical Examination Findings, ITT Population

13. APPENDIX I – TOXICITY GRADING

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE (MODIFIED)

NOVEMBER 2007 - DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
Rx = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE
For abnormalities NOT found elsewhere in the Toxicity Tables, use the scale below to estimate grade of severity:

GRADE 1 (Mild): Transient or mild discomfort; no medical intervention/therapy required

GRADE 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.

GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs
ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event.

LABORATORY RANGES

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4 gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	---------
CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia

Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/L	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required
ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

CEM-102 Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

Study Title:	An Open-Label, Non-Randomized, Single-Arm Multi-Center Study to Evaluate Oral Sodium Fusidate (CEM-102) for the Treatment of Staphylococcal Bone or Joint Infections in Subjects for whom Chronic Antibiotic Suppressive Therapy is Indicated
Phase:	2/3
Protocol No.:	CE06-302
Protocol Date	Original Protocol: 07 July 2015
Analysis Plan Version and Date	Final Version, 19 October 2017 Amendment 1, 04 December 2017
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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of efficacy and safety data from Protocol CE06-302. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection, and to the Pharmacokinetics (PK) Report for the analysis of plasma concentrations of CEM-102.

1.1. STUDY OVERVIEW

Protocol CE06-302 is a phase 2/3, prospective, open-label, non-randomized, single-arm trial to evaluate the safety and effectiveness of CEM-102 for chronic antibiotic suppressive therapy of bone or joint infections. Subjects enrolling in this study must have a suspected or confirmed staphylococcal bone or joint infection due to an inclusionary pathogen susceptible to CEM-102 that requires suppressive antibiotic therapy. The infection should be demonstrated from a positive culture from samples obtained during surgery, biopsy, or drainage procedures within 6 weeks prior to enrollment. If the subject does not have a positive culture, the Investigator must provide documentation as to why the subject is suspected to have a staphylococcal infection and discuss with the medical monitor for approval of enrollment.

This study comprises two parts: Part A (enrollment through the 6-month visit) and Part B (6 to 24 months post-enrollment). In Part A, all subjects will receive 6 months of CEM-102 treatment. The Investigator will evaluate each subject completing Part A for clinical response at the 6-month visit (primary endpoint). For Part B, a subject who completes Part A and, in the Investigator's opinion, requires continued suppressive therapy, may continue to receive CEM-102. Alternatively, if the Investigator considers the infection resolved and that no further antibiotic therapy is required, study drug will be discontinued and the subject followed for evidence of relapse until the end of study (EOS; 24 months).

During the first 6 months of treatment, study Part A, subjects will be monitored monthly (±1 week) for safety and clinical response to CEM-102. During study Part B, subjects will be monitored every 3 months (±2 weeks) until the EOS Visit (24 months).

1.2. SCHEDULE OF ASSESSMENTS/PROCEDURES

Assessment/Procedure	Screening[a]	Part A			Part B	End of Study (EOS)[d]
		Enrollment (Day 1 Visit)[b,c]	Day 8 (± 3 days)	Monthly During First 6 Months (±1 week)	Every 3 Months From Month 6 until End of Study (±2weeks)	
Informed Consent Form	X					
Inclusion/Exclusion Criteria Review	X	X				
Review of Clinical/ Surgical History	X	X	X	X	X	X
Microbiological specimens for culture	X	X	X[e]	X[e]	X[e]	X[e]
Enrollment	X	X				
Vital Signs[f]	X	X	X	X	X	X
Limited Physical Examination[g]	X	X	X	X	X	X
Examination of Infected Area[h]	X	X	X	X	X	X
Safety Laboratory Assessments[i]	X	X	X	X	X	X
Inflammation Laboratory Assessments[j]	X	X		X	X	X
CEM-102 Administration[k]		X				
Pharmacokinetic Blood Sampling				X[o]		
Dispense Oral antibiotic to Subjects[l]		X	X	X	X	
Perform Drug Accountability			X	X	X	X
Record 6-Month History of Prior Antibiotic Used to Treat the Primary Infection Leading to Enrollment	X					
Record Concomitant Medications	X	X	X	X	X	X
Record AEs[m]	X	X	X	X	X	X
Investigator Assessment of Clinical Response[n]				X	X	X

a. Within 6 weeks prior to enrollment, subjects must have a positive culture with an inclusionary pathogen susceptible to CEM-102, demonstrated from a culture from samples obtained during surgery, biopsy, or drainage procedures. If subject does not have a confirmatory culture result, the Investigator must provide documentation as to why subject is suspected to have a staphylococcal infection and must discuss the subject with the medical monitor for approval of enrollment.
b. Enrollment is contingent on demonstration that subject fulfills the inclusion/exclusion criteria.
c. Study Day 1 corresponds to the first day of dosing with CEM-102.
d. Subjects who discontinue CEM-102 because of an adverse event (AE) or clinical failure should have a study visit around the time of drug discontinuation and will continue to be followed, as needed, for appropriate observation of treatment-related AEs until AEs have resolved or stabilized. If a subject withdraws from the study at any time, for any reason, the EOS visit will be performed around that time. Those subjects who continue CEM-102 until the Month 24 visit will undergo the assessments/procedures for the EOS visit. At study closure, at the discretion of the Investigator, subjects may be rolled over into an expanded access protocol to receive chronic suppressive CEM-102 therapy.
e. If clinically indicated, microbiological samples (tissue surrounding the foreign material, synovial fluid, bone, etc.) obtained during the study should be submitted to the local laboratory for aerobic and anaerobic culture and susceptibility testing, including to CEM-102. All isolated bacteria are to be sub-cultured and shipped to the central microbiology laboratory for organism confirmation and confirmatory susceptibility testing.
f. Vital sign measurements include height, weight, temperature, heart rate, respiratory rate, and blood pressure. Results are to be recorded in the eCRF.
g. Limited physical examination may include HEENT, cardiovascular, pulmonary, gastrointestinal, skin, lymph nodes, musculoskeletal, and extremities, among others. Results are to be documented in source and recorded in the eCRF.
h. Examination of the infected area will include the following assessments: pain, erythema, mobility, joint stability, wound closure, wound drainage, and weight bearing [for back and lower extremity infections]. The Investigator will state whether the infected area seems to have improved, deteriorated, or remained unchanged. Results are to be documented in the source and recorded in the eCRF.
i. Safety laboratory assessments will be performed at the local laboratory and will include the following: serum chemistry (ALT, AST, alkaline phosphatase [ALP], total and direct bilirubin, blood urea nitrogen [BUN], creatinine, albumin, total protein, sodium, total carbon dioxide, glucose, potassium, chloride, calcium, phosphorus, and CPK). For female subjects of child bearing potential, a urine or serum pregnancy test will be performed at Screening and will be repeated at subsequent visits per Investigator's discretion .
j. Laboratory measurements of markers of inflammation will be performed at the local laboratory and will include the following: hematology (complete blood count [CBC] with differential), erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]). Laboratory measurements of markers of inflammation obtained on the day of a surgery or debridement should be performed before the procedure when possible, because levels of these markers are known to increase after surgery.
k. A CEM-102 loading dose strategy is utilized, in which CEM-102 is given as 1500 mg every 12 hours for 2 doses followed by 600 mg every 12 hours thereafter.
l. After 6 months of therapy, the Investigator may decide to continue chronic suppressive therapy with CEM-102 or discontinue CEM-102 due to clinical cure and no further requirement for antibiotic therapy. Subjects who stop treatment will continue to be followed on the same schedule as those who remain on therapy to monitor for infection relapse until the end of the study. Subjects who discontinue CEM-102 due to clinical failure should have an EOS visit at that time.
m. All AEs will be collected following signing of the ICF.
n. The Investigator will assess clinical response at Months 6, 9, 12, 15, 18, 21, 24 and at EOS.
o. Pharmacokinetic blood sampling will be conducted at the 3-month visit as described in Section 10.6

1.3. LIST OF ABBREVIATIONS

AE	adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CEM-102	sodium fusidate (fusidic acid)
CPK	creatinine phosphokinase
CRP	C-reactive protein
HEENT	head, eyes, ears, nose, throat
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
SAE	serious AE
TEAE	treatment-emergent AE
WBC	white blood cell

2. OBJECTIVE

The study objective is to evaluate the safety and effectiveness of CEM-102 as chronic antibiotic suppressive therapy in subjects with staphylococcal bone or joint infections.

3. ENDPOINTS

Primary Endpoint

The primary endpoint will be the proportion of subjects in the safety population who meet all the criteria for clinical success at the 6-Month Visit.

Secondary Endpoints

Efficacy

- The proportion of subjects in the safety population who meet all criteria for clinical success at the 9-Month, 12-Month, 15-Month, 18-Month, 21-Month, and 24-Month Visits

Safety and Tolerability

- The proportion of subjects in the safety population who experience a treatment-emergent adverse event (TEAE), a serious adverse event (SAE), an SAE that results in death, or a TEAE that results in discontinuation from study or study drug

Additional Endpoints

Efficacy

- Change in composite symptom and function score at each Visit
- Change in wound status at each Visit
- Change in ESR as a surrogate marker of infection status over time

Safety and Tolerability

- Changes from baseline in selected chemistry and hematology laboratory assessments by visit
- The proportion of subjects who experience laboratory toxicity grade shifts from baseline
- The proportion of subjects who experience treatment-emergent graded laboratory abnormalities

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. SAMPLE SIZE AND POWER

As a non-randomized, single-arm study, there will be no formal statistical analyses. This study is not powered for inferential statistical analyses. Thirty subjects will be enrolled at up to 20 investigative sites in the United States.

4.2. RANDOMIZATION AND MASKING

Since this is a non-randomized open-label study, randomization and masking are not applicable.

4.3. HANDLING OF DATA

4.3.1. Strata and Covariates

There are no planned adjustments for covariates.

4.3.2. Examination of Subject Subsets

There are no planned subsets.

4.3.3. Multiple Testing and Comparisons

Adjustments for multiple comparisons are not applicable.

4.3.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects. See section 4.3.6 for details of imputing missing dates. Unless otherwise specified, other missing data will not be imputed.

Should an adverse event have a missing relationship to study medication, it will be classified as having the strongest relationship to study medication.

4.3.5. Derived and Transformed Data

For purposes of analysis, subjects who are deemed a clinical failure (see section 4.3.8) due to use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for >10 days on any occasion, or for >2 courses during any 6-month period, will be programmatically assigned an indeterminate response.

Signs and symptoms data from the primary infection exam will be combined to derive a composite symptom and function score (see section 4.3.8).

4.3.6. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary in order to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation of incomplete start/stop dates for adverse events and prior/concomitant medications, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1 (defined in section 4.3.8).

All events with an incomplete end date are assumed to have ended on or before the day the form was completed. For scheduled visit data, missing dates will be imputed based on the nominal visit day relative to Day 1. For other data, if the month/year is the same as the Day 1 month/year then the date will be set to

the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. A list of incomplete and imputed dates will be prepared by the project statistician or statistical programmer(s) and will be submitted for review by the clinical project manager and sponsor.

4.3.7. By-Study Visit Displays

Visits will be presented according to the nominal visit (efficacy analyses) or analysis visit (safety analyses) as obtained from the eCRF. For vendor data, the collection date will be used to assign the visit.

For safety analyses, all data, including scheduled and unscheduled visits, will be windowed to an analysis visit as follows:

Analysis Visit	**Study Day**
Baseline	Last non-missing value obtained prior to or on the day of initiation of study treatment (CEM-102)
Day 8	5-11
Month 1	23-37
Month 2	54-68
Month 3	84-98
Month 4	115-129
Month 5	145-159
Month 6	176-190
Month 9	260-288
Month 12	352-380
Month 15	443-471
Month 18	535-563
Month 21	626-654
Month 24	718-746

For each safety outcome, analyses will utilize assessments occurring during the analysis visit windows in the table above. Thus, if a subject has a scheduled Month 1 visit that occurs outside of the study day 23-37 window, the assessment will not be summarized with the Month 1 assessments but will instead be considered an unscheduled visit. If both a scheduled and an unscheduled visit occur within an analysis visit window, the value taken from the scheduled visit will be used. If multiple scheduled visits occur within an analysis visit window, or if multiple unscheduled visits occur and no scheduled visit occurs, then the last value will be used.

For summaries of laboratory values and of treatment-emergent laboratory abnormalities, worst overall post-baseline values will also be summarized. This will include data from all assessments.

With the exception of worst overall post-baseline summaries, post-baseline visits that do not occur within any analysis visit window will be excluded from the summary presentations, but included in the listings.

4.3.8. Definitions and Terminology

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to or on the day of initiation of study treatment (CEM-102). Because time of initiation of treatment is not captured, events defined by the protocol as occurring before treatment initiation will be considered baseline-eligible. All pathogens recovered from cultures performed prior to first dose will be considered baseline pathogens. Baseline values may come from scheduled or unscheduled visits.

Study Day
The date vital signs were collected at the nominal Day 1 visit (a surrogate for the date of first dose of study drug) will be considered as study day 1, and the day before vital signs were collected at the nominal Day 1 visit will be study day -1.

If an event date is on or after the Day 1 date, then Study Day is calculated as:

- Study Day = event date – date of Day 1+1

If an event date is prior to the date of Day 1, then Study Day is calculated as:

- Study Day = event date – date of Day 1

Days on Study
Days on Study is the number of days from Day 1 to the visit date of the end of study or early termination visit.

Pathogens
Pathogen determination is based on the genus and species identification from the central laboratory. If the local laboratory grows an acceptable pathogen but the central laboratory is not able to grow the isolate, if isolates are lost during transportation or storage, or there are major discrepancies between the local and central laboratory in the identification of species, the central laboratory will request that the local laboratory resend the isolate. The central laboratory identification of genus and species is used for analysis except in those cases where there is no central laboratory determination of genus and species. In this case, the local laboratory determination is used for pathogen identification.

The following organisms recovered from baseline specimens obtained during surgery, biopsy or drainage procedures (e.g. tissue biopsy, bone biopsy, joint aspirate, etc.) or from blood are considered inclusionary pathogens: *Staphylococcus aureus* (including both methicillin-susceptible *S. aureus* [MSSA] and methicillin-resistant *S. aureus* [MRSA]), and coagulase-negative staphylococci (CoNS) such as *Staphylococcus epidermidis*, *Staphylococcus hominis*, or *Staphylococcus haemolyticus*. Other pathogens include: *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Corynebacterium striatum*, and *Propionibacterium acnes*. All isolates, including other bacteria not listed here, will be reviewed by the Sponsor on a case-by-case basis to confirm BJI pathogen status. Fungal isolates (*Candida albicans*) will not be considered pathogens.

S. aureus will be considered methicillin-resistant (MRSA) based on oxacillin susceptibility results (MIC ≥4 µg/ml; resistant) from the central laboratory. If isolate test results are not available from the central

laboratory, MRSA/MSSA designation will be as reported in the eCRF (as part of the organism name). MRSA and MSSA will be considered distinct pathogens.

Investigator Assessment of Clinical Response:
Clinical success is defined to occur when subjects meet all of the following criteria:

- Subject was not hospitalized due to worsening of the study-qualifying orthopedic infection at any point between enrollment and the 6-Month Visit
- Subject did not undergo a definitive surgical procedure (such as amputation) at any point between enrollment and the 6-Month Visit
- No additional antibiotics (after completion of companion antibiotics) are required for treatment of the orthopedic infection due to the inclusionary pathogen
- Wound is closed, or the open area decreased in size (L x W) and, if a skin graft was done, the graft remains viable without evidence of infection
- No purulent discharge from the surgical wound, or new or recurring sinus tract
- No worsening of redness, tenderness, or swelling at the primary infection site
- No bacteremia of the inclusionary pathogen at any point between enrollment and the 6-Month Visit

Clinical failure is defined to occur when subjects meet any of the following criteria:

- Failure to meet all criteria for clinical success
- Death (due to the primary infection)
- Discontinuation of study drug due to an AE and the requirement of additional antibiotics for treatment of the primary infection

An indeterminate response is defined to occur when subjects meet any of the following criteria:

- Subject withdraws consent
- Subject is lost to follow-up

For purposes of analysis, subjects who are deemed a clinical failure due to use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for >10 days on any occasion, or for >2 courses during any 6-month period, will be programmatically assigned an indeterminate response.

Primary Infection Exam (Signs and Symptoms): Baseline Evaluation
The baseline evaluation for outcome assessments is based on the Screening and Study Day 1 data according to the table below:

Screening Visit Evaluation	Study Day 1 Visit Evaluation	Baseline Evaluation
Present	New	Present
	No change	Present
	Improved	Present
	Worsening	Present
	Not Assessed	Present
	Resolved	Absent
Absent	New	Present
	No change	Absent
	Improved	N/A
	Worsening	N/A
	Not Assessed	Absent
	Resolved	N/A
Not Assessed	New	Present
	No change	N/A
	Improved	N/A
	Worsening	N/A
	Not Assessed	Not Assessed
	Resolved	Absent

Primary Infection Exam (Signs and Symptoms): Change from Previous Visit
Change from previous visit for a given endpoint is defined as a qualitative comparison between the evaluation during the previous visit to the evaluation at the current visit. The possible responses are:

New - The sign/symptom was not present during the previous visit and is present at the current visit
No change - The severity of the sign/symptom has not changed from the previous visit
Improved - There is improvement from the previous visit, but the sign/symptom has not been resolved
Worsening - The sign/symptom has gotten worse from the previous visit
Not assessed - The sign/symptom was not assessed during the current visit
Resolved - The sign/symptom has been resolved as of the current visit

Primary Infection Exam (Signs and Symptoms): Composite Symptom and Function Score
Data from the following signs and symptoms will be combined to derive a composite score: Swelling/Edema, Warmth, Redness, Pain at Rest, Pain with Movement, Decreased Mobility, and Limited Weight Bearing. The score will be calculated according to the following algorithm:

- Each symptom with a baseline evaluation of "Present" will be assigned a value of 7. Each symptom with a baseline evaluation of "Absent" or "Not Assessed" will be assigned a value of 0.

- At each month, the individual sign and symptom scores will be calculated. These will be calculated by taking the baseline score and adjusting it in a cumulative manner up to the month being reported. The score will be adjusted according to change from previous visit result as follows:
    - New – increase by 7.0
    - No Change – no change
    - Improved – decrease by 0.5
    - Worsening – increase by 0.5
    - Not Assessed – no change
    - Resolved – decrease to 0
- At any given timepoint, the composite score is calculated by summing the scores of each sign or symptom.

Treatment-emergent Adverse Event
Any adverse event reported on the eCRF that occurs on or after the receipt of study drug (Day 1) through 28 days after the last dose of study drug is considered treatment-emergent. Events with a missing start date or that occur on the date of dosing and have a missing start time will be considered treatment-emergent.

Treatment-emergent Laboratory Abnormality
A treatment-emergent laboratory abnormality is defined as an increase of at least one toxicity grade from the baseline assessment at any post baseline visit up to and including 28 days after the last dose date of study drug administration. If the relevant baseline assessment is missing, then any graded abnormality (i.e., at least Grade 1) is considered to be treatment-emergent.

Laboratory abnormalities will be graded according to the Division of Microbiology and Infection Diseases (DMID) 1-4 scale. Values not considered Grade 1 or higher will be classified as "Normal". Grading guidelines are listed in Appendix I.

Antibiotic and Non-antibiotic Medications
Antibiotic and non-antibiotic medications are recorded on separate forms of the eCRF. Reasons for antibiotic medications are recorded on the eCRF as therapy for the primary infection before enrollment, companion antibiotic therapy after enrollment, adjunctive antibiotic therapy for co-infections, or therapy for unrelated infections.

Prior and Concomitant Medications
A prior medication is defined as any medication taken prior to the date of first dose of study drug (Study Day 1). A concomitant medication (including companion and adjunctive antibiotic therapy) is defined as any medication that has a stop date that is on or after the date of first dose of study drug, or is ongoing. A medication can be considered both prior and concomitant.

4.4. TIMING OF ANALYSES

An interim analysis will be conducted once the last subject completes the 6-month visit or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and locked. A final analysis will be conducted once the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and locked.

5. ANALYSIS POPULATIONS

5.1. INTENT TO TREAT (ITT) POPULATION

The ITT population will include all subjects who were enrolled in the study. To be enrolled, subjects must provide informed consent and meet all eligibility criteria. Analysis of subject disposition, demographic and baseline disease characteristics, and all efficacy analyses will be conducted using the ITT population. With the exception of the inclusion/exclusion criteria and informed consent listing, all listings will be produced on the ITT population.

5.2. SAFETY POPULATION

The safety population will include all subjects who were enrolled and received at least one dose of CEM-102. Analysis of concomitant medications received and all safety analyses will be conducted using the safety population.

5.3. SCREENED POPULATION

The screened population will include all subjects who signed the informed consent form (ICF). Screen failures are subjects who signed the ICF and were not enrolled in the study. The inclusion/exclusion criteria and date of informed consent listing will be produced on the screened population.

6. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by subject number, and then by date within each subject number.

The statistical analyses will be conducted with the SAS® software package version 9.2 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

6.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS, DURATION OF TREATMENT

6.1.1. Subject Disposition and Duration of Treatment

Subject disposition will be presented, including summaries of eligibility, number of subjects who complete the study, number of subjects who prematurely discontinued from study, reasons for study discontinuation, number of subjects who discontinued study drug, reasons for study drug discontinuation, number of days on study, number of days on study drug, and number of subjects who completed each visit.

Study drug dispensation and accountability will be presented in a listing.

6.1.2. Demographics and Baseline Characteristics

Demographic data and baseline characteristics including age, sex, race, ethnicity, height, weight, BMI, infection type, site of infection, and risk factors for bone or joint infection will be summarized using descriptive statistics for the safety population.

6.1.3. Baseline Pathogens

The pathogenic organisms identified from baseline (screening or historical) cultures of the primary infection site or blood cultures will be summarized. MRSA and MSSA are considered distinct pathogens. The number and percentage of subjects with each pathogen will be presented by genus and species for the safety analysis population. The same pathogen identified from both the culture of a BJI specimen and/or blood culture will be counted only once in the summary.

A listing will be provided that includes all culture results and will indicate the specimen collection date, study day, type of specimen, Gram stain results, organism name (local and central laboratory identification), and a flag for whether or not each isolate is considered a baseline or post-baseline pathogen. A by-subject listing of isolate MICs, and disk diffusion zone diameters, and susceptibilities (if applicable) will also be provided. Isolates are considered susceptible (S), intermediate (I), or resistant (R) to CEM-102 according to Table 1.

Table 1 Provisional Interpretative Criteria for Fusidic Acid (CEM-102)

	Broth Microdilution MIC (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	Susceptible	**Intermediate**	**Resistant**	**Susceptible**	**Intermediate**	**Resistant**
Staphylococcus species	≤ 1	2	≥ 4	≥ 22	20-21	≤ 19
β-hemolytic streptococci[a]	≤ 1	2-8	≥ 16	≥ 16	11-15	≤ 10

a. Includes: *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae*

6.1.4. Concomitant Medications

Prior and concomitant medications will be coded using the World Heath Organization (WHO) Drug dictionary (September 2015). Antibiotic and non-antibiotic concomitant medications will be summarized by frequency of classification and generic name. Antibiotic concomitant medications will be summarized separately for primary infections before enrollment, companion antibiotics, co-infections, and unrelated or other antibiotics. Prior and concomitant medications will be presented in a data listing.

6.2. EFFICACY

The counts and percentages of subjects who have clinical success, clinical failure, and an indeterminate clinical response, and reasons for clinical failure and indeterminate response will be summarized at the 6-Month, 9-Month, 12-Month, 15-Month, 18-Month, 21-Month, and 24-Month Visits. Exact, binomial 95% confidence intervals will be provided for the percentage of subjects who have clinical success at each visit. Early termination results will be carried forward to all subsequent visits for subjects who did not complete

each visit such that the denominator will be equal to the number of subjects in the ITT population.

The composite symptom and function score and change from baseline score will be summarized by visit. Only subjects who are on study drug at a given visit will be included in the summary for that visit. As an exploratory analysis to examine the relationship between the composite symptom and function score and the proportion of subjects who meet all the criteria for clinical success, a logistic regression model of the probability of clinical success with a fixed effect for composite symptom and function score will be performed. For this analysis, an indeterminate response will be considered a failure.

Wound status will be characterized by three signs/symptoms from the primary infection exam: Sinus tract formation, open wound, and drainage. A subject will be considered to have a sign/symptom at a given visit if it is newly present or not resolved. The counts and percentages of subjects who have each sign/symptom will be presented separately. Additionally, the counts and percentages of subjects who have none of the three signs/symptoms and one or more of the signs/symptoms will be presented.

Changes in primary infection site signs and symptoms and inflammation lab results will each be presented in a listing.

A spaghetti plot of individual subject erythrocyte sedimentation rate values by study day will be generated for timepoints where the subject is either on study drug or off study drug and being followed for relapse.

The number of subjects with a pathogen showing decreasing susceptibility will be assessed manually by the Sponsor using the by-subject isolate susceptibility listing. Decreasing susceptibility of a pathogen is defined as a 4-fold or greater increase in CEM-102 MIC from baseline to any subsequent study time point.

6.3. SAFETY

6.3.1. Adverse Events

Adverse events will be coded for preferred term and system organ classification by the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

If a subject experiences multiple events that map to a single preferred term, the greatest severity and/or strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. Should an event have a missing relationship, it will be classified as having the strongest relationship to study medication.

A high level summary table of the number and percentage of subjects who experience any AE, any TEAE, any TEAE with severe intensity, any TEAE related to study drug, any TEAE leading to study discontinuation, any TEAE leading to study drug discontinuation, any treatment-emergent serious adverse event (SAE), any treatment-emergent SAE related to study drug, any treatment-emergent SAE leading to study discontinuation, and any treatment-emergent SAE leading to study drug discontinuation will be provided.

Summaries of treatment-emergent AEs will include any AEs starting on or after the initiation of study treatment through 28 days after the last dose of study drug. The occurrence of TEAEs will be summarized using preferred terms and system organ classifications. Separate summaries of TEAEs overall and by

greatest severity, TEAEs related to study drug (overall and by greatest severity), TEAEs leading to discontinuation of study or study drug, treatment-emergent SAEs and treatment-emergent SAEs leading to death will be presented.

All adverse event data listings will include the individual subjects showing both verbatim and preferred terms and system organ classification. All adverse events that occurred prior to the initiation of the study treatment will be excluded from the tables. All adverse events will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 4.3.6 to determine treatment-emergent status.

6.3.2. Clinical Laboratory Assessments

Descriptive summaries of selected clinical laboratory results as well as change from baseline values will be presented by analysis visit and worst overall post-baseline value. Selected laboratory parameters to be summarized include: ALT, AST, ALP, total bilirubin, creatine kinase, creatinine, WBC count, hematocrit, and platelets. Frequency and percentage of subjects experiencing treatment-emergent laboratory abnormalities (by Grade) will be summarized by analysis visit and worst overall post-baseline value. If criteria in both directions are shown for a single parameter, then abnormalities in each direction will be summarized separately. Laboratory toxicity grade shifts from baseline will also be summarized by analysis visit and worst overall post-baseline value.

All clinical laboratory test results will be provided in a listing. The listing will include the laboratory test value, change from baseline, and toxicity grade.

6.3.3. Other Safety Analyses

Vital sign results and all physical examination data will each be provided in a listing.

6.4. PHARMACOKINETICS ANALYSES

CEM-102 plasma concentrations will be presented in a listing. Analysis of plasma concentration data will be presented in a separate PK Report.

7. PROTOCOL DEVIATIONS

Protocol deviations identified by clinical monitoring will be provided in a data listing.

8. CHANGES IN THE PLANNED ANALYSES

For purposes of analysis, subjects who are deemed a clinical failure due to use of a concomitant antibiotic to which the inclusionary pathogen is susceptible for >10 days on any occasion, or for >2 courses during any 6-month period, will be programmatically assigned an indeterminate response.

No other deviations in the conduct of the study or the planned analysis are anticipated. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

9. REFERENCES

None.

10. REVISION HISTORY

Date	Revision	Rationale
04 DEC 2017	Updated text in section 6.2 so that early termination results are carried forward to all subsequent visits for the analysis of Investigator Assessment of Response (Table 14.2.1). The denominator is set to the number of subjects in the ITT population.	Including early termination results will allow for the analysis of cumulative failure.

11. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).

- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all enrolled subjects.

- Group headers: In the summary tables, the group headers will identify the dose cohort and the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.

- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.

- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.

    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations

    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.

- Sorting: Listings will be sorted by subject number, dose cohort, and date, if applicable. Listings with multiple observations per subject will be sorted by subject number, dose cohort, treatment and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.

- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:

    - Raw measurements will be reported to the number of significant digits as captured on the eCRFs.

    - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.

- ♦ Means will be reported to the same number of significant digits as the parameter.
- ♦ Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - ♦ Time will be presented according to the 24-hour clock (HHMM).

12. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

Demography and Baseline Characteristics

14.1.1	Subject Disposition and Treatment Duration, ITT Population
14.1.2	Demographics and Baseline Characteristics, ITT Population
14.1.3	Pathogens Identified at Baseline, ITT Population
14.1.4	Concomitant Medications by Generic Name and Drug Classification, Safety Population

Efficacy

14.2.1	Investigator Assessment of Response and Reasons for Failure or Indeterminate Response by Visit, ITT Population
14.2.2	Composite Symptom and Function Score by Visit, ITT Population
14.2.3	Wound Status by Visit, ITT Population

Safety

14.3.1.1	Overall Adverse Events, Safety Population
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term, Overall and by Greatest Severity, Safety Population
14.3.1.3	Treatment-Emergent Adverse Events Related to Study Drug by System Organ Classification and Preferred Term, Overall and by Greatest Severity, Safety Population
14.3.2.1	Treatment-Emergent Adverse Events Leading to Discontinuation of Study by System Organ Classification and Preferred Term, Safety Population
14.3.2.2	Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Classification and Preferred Term, Safety Population
14.3.2.3	Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term, Safety Population
14.3.2.4	Treatment-Emergent Adverse Events Leading to Death by System Organ Classification and Preferred Term, Safety Population
14.3.4.1.1	Selected Chemistry Laboratory Values by Parameter and Visit, Safety Population
14.3.4.1.2	Selected Hematology Laboratory Values by Parameter and Visit, Safety Population
14.3.4.2	Laboratory Toxicity Grade Shifts from Baseline, Safety Population
14.3.4.3	Treatment-Emergent Graded Laboratory Abnormalities, Safety Population

Figures

14.2.1	Individual Erythrocyte Sedimentation Rate Values by Study Month, Safety Population

Data Listings

16.1.6	Study Drug Dispensation and Accountability, ITT Population
16.2.1.1	Subject Disposition, ITT Population
16.2.1.2	Inclusion/Exclusion Criteria and Date of Informed Consent, Screened Population
16.2.2.1	Protocol Deviations/Violations, ITT Population
16.2.4.1	Demographics, Baseline Characteristics, and Infection Type, ITT Population
16.2.4.2	Primary Infection History, ITT Population
16.2.4.3	Medical History and Risk Factors for BJI, ITT Population

16.2.5.1.1 Prior and Concomitant Antibiotics, ITT Population
16.2.5.1.2 Prior and Concomitant Medications, ITT Population
16.2.5.2 CEM-102 Plasma Concentrations, ITT Population
16.2.6.1 Investigator Assessment of Response and Reasons for Failure or Indeterminate Response at each Visit, ITT Population
16.2.6.2 Primary Infection Examination (Signs and Symptoms) at each Visit, ITT Population
16.2.6.3 Inflammation Laboratory Test Results, ITT Population
16.2.6.4 Microbiological Culture Results, ITT Population
16.2.6.5 Antibiotic Susceptibility Results, ITT Population
16.2.7.1 Adverse Events, ITT Population
16.2.8.1.1 Chemistry Laboratory Tests, ITT Population
16.2.8.1.2 Hematology Laboratory Tests, ITT Population
16.2.8.2 Surgical Interventions, ITT Population
16.2.8.3 BJI Imaging, ITT Population
16.2.8.4 Vital Signs, Height, and Weight, ITT Population
16.2.8.5 Abnormal Physical Examination Findings, ITT Population

13. APPENDIX I – TOXICITY GRADING

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE (MODIFIED)

NOVEMBER 2007 - DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
Rx = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE
For abnormalities NOT found elsewhere in the Toxicity Tables, use the scale below to estimate grade of severity:

GRADE 1 (Mild): Transient or mild discomfort; no medical intervention/therapy required

GRADE 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.

GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs
ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event.

LABORATORY RANGES

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4 gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	---------
CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia

Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/L	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required
ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN