STATISTICAL ANALYSIS PLAN

Protocol Title:	**Phase 1b/2a, Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Escalation Study of the Safety, Tolerability, and Efficacy of Intravenous AP-SA02 as an Adjunct to Best Available Antibiotic Therapy Compared to Best Available Antibiotic Therapy Alone for the Treatment of Adults With Bacteremia Due to *Staphylococcus aureus***
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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-phage antibodies
ADaM	Analysis Data Model
AE	Adverse event
AKI	acute kidney injury
ATC	Anatomical therapeutic chemical
BAT	Best available therapy
CDISC	Clinical Data Interchange Standards Consortium
CEAC	Clinical Efficacy Adjudication Committee
CI	Confidence interval
CRP	C-reactive protein
CVPU	Confusion, Voice, Pain, Unresponsive
eCRF	Electronic case report form
CSR	Clinical Study Report
DRC	Data Review Committee
EOS	End of Study
EOT	End of Treatment
ESKD	End-stage kidney disease
ICU	Intensive care unit
ITT	Intent-to-Treat
IV	Intravenous
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Microbiological Intent-to-Treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NCI CTCAE	National Cancer Institute Common Terminology Criteria
NEWS2	National Early Warning Score 2
PFU	Plaque-forming units
PK	Pharmacokinetics
RIFLE	Risk-Injury-Failure-Loss-End-stage renal disease
PT	Preferred term
Q6h	Every 6 hour
SA	*Staphylococcus aureus*
SAB	*Staphylococcus aureus* bacteremia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System organ class
SpO_2	Oxygen saturation
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures and Listings
TOC	Test of Cure
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number AP-SA02-101. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Phase 1b

The objective of Phase 1b is to evaluate the safety and tolerability of multiple ascending intravenous (IV) doses of AP-SA02 or placebo as an adjunct to best available therapy (BAT) compared to BAT alone in subjects with *Staphylococcus aureus* (SA) bacteremia (SAB).

2.1.2 Phase 2a

The objective of Phase 2a is to evaluate the efficacy, safety, and tolerability of multiple doses of AP-SA02 or placebo as an adjunct to BAT compared to BAT alone in subjects with complicated SAB.

2.2 Study Design

2.2.1 Overview

This is a first-in-human, prospective, Phase 1b/2a, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study to assess the safety, tolerability, and efficacy of multiple IV doses of AP-SA02 as an adjunctive therapy to BAT and compared to BAT alone for the treatment of SAB. This multiple dose escalation design will assess the safety and tolerability, as well as the efficacy, of various dosing cohorts with phage pharmacokinetics (PK) to identify a dose and duration of dosing that offers the best therapeutic potential benefit.

In Phase 1b, a standard MAD design for safety and tolerability will begin by randomizing subjects in Phase 1b Cohort 1 to receive either approximately 2×10^9 plaque-forming units (PFU) or placebo in addition to BAT. A Data Review Committee (DRC) will convene to review the data from Phase 1b Cohorts and during Phase 2a, as needed. The DRC will review emerging safety data throughout the study to determine if it is safe and appropriate to continue the study with the currently planned dose levels for the subsequent cohorts, or if further refinement of the proposed dose levels or dosing duration is warranted. The planned dose levels and dosing duration after Phase 1b Cohort 1 may be modified and/or additional cohorts may be added based on emerging information from the current study as well as other ongoing studies. The highest total daily dose will not exceed 8×10^{11} PFU and no more than 40 additional subjects will be added without a protocol amendment. The DRC will also determine how to advance the cohorts (serially or simultaneously). The DRC can receive unblinded data, if requested and deemed necessary to adequately complete their review. Further details regarding the role, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

The planned enrollment in each of the Phase 1b cohorts is 4 subjects per cohort (AP-SA02 to placebo 3:1); however, this may be modified after DRC review. Subjects in Phase 1b Cohort 1 will receive IV bolus infusion doses of blinded study drug every 6 hours for 5 study days (a total of 20 doses) in an inpatient location in addition to BAT. Following 5 days of dosing with study drug, additional study visits will be conducted at the End of Treatment (EOT) for study drug (Day 5), at the Test of Cure (TOC) for

study drug (Day 12), TOC for BAT (7 days [±1 day] after the end of BAT), and at End of Study (EOS) (28 days after the end of BAT). Subsequent cohorts (e.g., planned Phase 1b Cohort 2 or additional cohorts [up to 3]) will proceed similarly; however, the duration of dosing may be modified after the DRC review of the preceding cohort.

Study procedures will follow the Schedule of Procedures (Appendix A).

In Phase 2a, approximately 42 subjects will receive IV bolus infusion doses of blinded study drug every 6 hours, for no more than 14 days as determined by analysis during or after Phase 1b, in addition to BAT. Following 5 days of dosing with study drug, additional study visits will be conducted at EOT for study drug (Day 5), TOC for study drug (Day 12), TOC for BAT (7 days [±1 day] after the end of BAT), and EOS (28 days after the end of BAT). If the study drug EOT is extended after the DRC review, the study drug TOC visit will occur 7 days after the last day of dosing and the study drug EOS visit will occur 28 days after the end of BAT.

The following dose cohorts are planned:

Phase 1b

- Cohort 1 (AP-SA02 to placebo 3:1):
    - Planned approximately 2×10^9 PFU (1×10^9 PFU/phage) administered via IV bolus infusion every 6 hours for a period of 5 days;
- Cohort 2 (AP-SA02 to placebo 3:1):
    - Planned approximately 2×10^{10} PFU (1×10^{10} PFU/phage) administered via IV bolus infusion every 6 hours for a period of 5 days; and

    Note: The dose, frequency, and duration may be modified after DRC review. Maximum dosing duration will be no more than 14 days.

    Additional cohort(s) (up to 3) as determined after DRC review.

Phase 2a

- Phase 2a (AP-SA02 to placebo 2:1):
    - Dose and duration are to be determined based on safety and tolerability from or after Phase 1b, administered via IV bolus infusion.

Note: The dose, frequency, and duration may be modified after DRC review. Maximum dosing duration will be no more than 14 days.

A DRC will be convened to review all blinded safety data through TOC for study drug (Day 12) to recommend dose escalation. Safety stopping rules, including the number of dose-limiting toxicities, are prespecified in Section 4.3 of protocol. The DRC can receive unblinded data, if requested and deemed necessary to adequately complete their review. Upon completion of Phase 1b Cohort 2, Phase 2a may be initiated and may be an expansion of one of the previous cohorts.

In Phase 2a, subjects will be randomized in a 2:1 ratio to receive AP-SA02 or placebo. Randomization will be stratified by methicillin susceptibility/resistance. Subjects will be on BAT for a minimum of 28 days to 56 days (complicated SAB) and followed through 28 days after the end of BAT, for a total of 56 to 84 days in the study. The BAT must be planned for a minimum of 28 days and a maximum of 56 days, inclusive of the days on BAT started prior to study enrollment/randomization. The EOT for BAT will be defined based on the prespecified duration of therapy at the time of enrollment. The prespecified duration

of BAT at Screening may be increased within 7 days after randomization with duration of BAT no more than 56 days in the event that new/additional clinical information warrants a longer duration of therapy; this must be documented in the subject's source chart and electronic case report form (eCRF). All changes made to the subject's BAT and the reason for such changes must be documented on the appropriate eCRF.

2.2.2 Randomization and Blinding

Subjects in Phase 1b will be randomized in a 3:1 ratio in a blinded manner to receive AP-SA02 or placebo. For Phase 2a, subjects will be randomized in a 2:1 ratio in a blinded manner to receive AP-SA02 or placebo.

Subjects will be randomized using a centralized randomization system, according to a computer-generated randomization list, and stratified by methicillin susceptibility/resistance for Phase 2a only. Dosing should occur as soon as possible after randomization. Treatment group assignment will be blinded to the subjects, site study team, Sponsor study team, Contract Research Organization study team, and Investigators.

2.2.3 Study Drug

AP-SA02 is a proprietary multi-phage therapeutic candidate. [redacted]

Placebo will be a sterile dilution buffer used for active AP-SA02 [redacted].

AP-SA02 or placebo will be administered via IV bolus infusion every 6 hours for 5 consecutive days in an inpatient location. In addition, all subjects will receive at least 14 days (uncomplicated SAB) or 28 days (complicated SAB) and up to 56 days of BAT. BAT will be administered at the discretion of the Investigator.

2.2.4 Sample Size Determination

The study will enroll approximately 50 eligible subjects. Enrollment may be expanded up to a total of approximately 100 subjects to ensure that at least 8 treated and 4 placebo Phase 2a subjects are MRSA subjects and to account for additional subjects and cohorts that may be enrolled based on DRC review and Sponsor input based on emerging data. To ensure that at least 8 treated and 4 placebo Phase 2a subjects are MRSA subjects, no more than approximately 70 non-MRSA subjects will be enrolled without a protocol amendment.

The Phase 1b MAD safety cohorts will follow a standard 3 + 1 design for 2 cohorts (n = 4 for each cohort for a total of 8 subjects). However, additional cohorts (up to 3) may be added or existing cohorts expanded per recommendation of the DRC or Sponsor decision. The total sample size in Phase 1b may be increased up to a total of 20 subjects without a protocol amendment in consultation with the DRC.

Phase 2a will have an initial sample size of approximately n = 42 with a study drug to placebo allocation of 2:1 in order to enroll at least 38 subjects meeting the Microbiological Intent-to-Treat (MITT) Population criteria with the assumption that approximately 90% of randomized subjects will satisfy the MITT Population criteria. This will provide at least 80% power to detect a difference of 50% in the proportion of subjects in each treatment arm, with a 30% placebo portion meeting all conditions for Clinical Improvement or response at TOC for study drug (Day 12) in the MITT Population with a type 1 error rate of 0.05 (1-sided) using Fisher's exact test. Additional subjects may be included in Phase 2a after a protocol amendment.

2.3 Study Endpoints

2.3.1 Phase 1b Multiple Ascending Dose Safety

The primary endpoint is safety. Safety will be evaluated by presenting summaries of the following:

- Treatment-emergent adverse events (TEAEs), which are defined as adverse events (AEs) occurring after the first dose of study drug through TOC for study drug (Day 12) or through EOS for serious AEs (SAEs);
- Vital signs; and
- Clinical laboratory evaluations.

The endpoints listed for Phase 2a may be assessed as secondary endpoints in the safety cohorts; however, these cohorts are exploratory and not powered for any efficacy variable.

2.3.2 Phase 2a Endpoints

The Phase 2a endpoints are the following:

- Time to reach a National Early Warning Score 2 (NEWS2) score ≤2 maintained for at least 24 hours or hospital discharge (whichever comes first) for subjects on active drug versus placebo
- Clinical Improvement or response at TOC for study drug (Day 12)
- Proportion of subjects reaching a NEWS2 score ≤2 maintained for at least 24 hours or hospital discharge (whichever comes first) for subjects on active drug versus placebo at TOC for study drug (Day 12)
- Microbiological outcome at EOT for study drug (Day 5)
- Clinical Improvement or response at TOC for BAT (7 days [±1 day] after the end of BAT)
- Clinical Improvement or response at EOS (28 days after the end of BAT)
- Time to death
- NEWS2 score while hospitalized by study day
- Late composite efficacy, as defined by the following:
    - Survival at EOS (Days 39 to 81); and
    - No evidence of microbiological failure, as defined by either of the following:
        - Blood cultures that remain positive for SA ≥7 days from randomization; or
        - Isolation of SA from the blood or another sterile site (e.g., joint fluid, tissue) >14 days from randomization.
- Microbiological failure or relapse by any of the following:
    - Blood cultures that remain positive for SA ≥7 days from randomization;
    - Isolation of SA from the blood or another sterile site (e.g., joint fluid, tissue) >14 days from randomization; or
    - Blood culture positive for SA >72 hours after the first blood cultures showing clearance of SAB (defined as 2 consecutive days with negative SA blood cultures).

- Time to initial resolution of SAB
- Time to hospital discharge (and time to hospital discharge readiness)
- Need for and duration of intensive care unit (ICU) stay
- Need for and duration of endotracheal mechanical ventilation
- Need for and duration of noninvasive pressure ventilation (e.g., Continuous Positive Airway Pressure, Bilevel Positive Airway Pressure)
- PK of AP-SA02 with IV administration
- Relationship between AP-SA02 exposures and safety and efficacy endpoints
- Immunogenicity of AP-SA02 at EOS
- Time to resolution of any signs and/or symptoms of bacteremia present at Screening
- Time to resolution of any signs/symptoms related to focal site of SA infection (e.g., joint pain; redness; swelling; weight-bearing, back pain; weight-bearing, skin redness; drainage) from randomization on Day 1
- TEAEs, which are defined as AEs occurring after the first dose of study drug through TOC for study drug (Day 12) or through EOS for SAEs
- Proportion of subjects with acute kidney injury (AKI), defined as stage 1 or higher using modified Risk-Injury-Failure-Loss-End-stage renal disease (RIFLE) criteria at any time within the first 7 days or new need for renal replacement therapy between Day 1 and EOS
- Vital signs
- Clinical laboratory evaluations
- Change in C-reactive protein (CRP) from baseline to EOS
- Change in interleukin-10 from baseline through TOC for study drug (Day 12)
- Change in SA isolate sensitivity to AP-SA02 between initiation of study drug and the last isolation of SA from a sterile site (blood, joint fluid, tissue)
- Change in SA isolate susceptibilities to anti-staphylococcal antibiotics from baseline
- Change in SA isolate susceptibility to BAT from baseline; and
- Clinical and microbiological outcomes by foci of infection.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Definition of Baseline

Baseline is defined as the last non-missing value prior to the first dose of study drug. If a subject was randomized but not treated, the baseline value is last non-missing value on or prior to randomization date. Baseline SAB is defined as SA isolated from positive blood culture within 72 hours prior to first dose of study treatment. Blood culture results are obtained from local microbiology laboratories.

Any eligibility protocol deviation from the 72-hour blood culture timepoint (relative to randomization) will be discussed and approved for individual subject inclusion in the per protocol MITT population before database lock.

3.1.3 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

All data will be listed by subject based on randomized subjects.

3.1.4 Hypothesis Testing

No formal testing will be done.

3.1.5 Handling of Dropouts and Missing Data

In cases of incomplete dates for AEs and concomitant medications, the missing component(s) will be assumed as the most conservative value possible. No imputation of start/end dates or times will be performed.

- If a medication date is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a concomitant medication.
- If the partial AE onset date information does not indicate that the event started prior to or after the treatment, the event will be classified as treatment emergent.

3.2 Analysis Populations

3.2.1 Intent-to-Treat Population (Efficacy Population 1)

The Intent-to-Treat (ITT) Population is defined as all randomized subjects in Phase 1b and Phase 2a who receive at least 1 dose of study drug . This will not include individuals that screen failed or were randomized but did not receive phage or placebo - at least one dose of phage or placebo must have been received.

3.2.2 Per Protocol Microbiological Intent-to-Treat (MITT) Population (Efficacy Population 2)

The Per Protocol MITT Population is defined as all subjects in the ITT population and enrolled in Phase 2a with baseline SAB and who receive at least 4 initial doses of study drug (placebo or phage). All protocol deviations for inclusion and exclusion will be determined prior to database lock and documented in the TMF.

3.2.3 Phage Persistence and Clearance Population (Efficacy Population 3)

All subjects in Phase 1b and Phase 2a who have at least 1 PK sample drawn and received at least 4 initial doses of study drug will be divided into one of the following:

- Phage Persistence Population: defined as viable phage recovered at 3 hours post first administration of study drug
- Phage Clearance Population: defined as viable phage no longer recovered at 3 hours post first administration of study drug

Phage Persistence and Phage Clearance Population will be reported by the Sponsor separately. Subject lists for Phage Persistence Population and Phage Clearance Population will be provided by Sponsor for analysis.

3.2.4 Phage-Sensitive Intent-to-Treat Population (Efficacy Population 4)

The Phage-Sensitive ITT Population is defined as all randomized subjects in Phase 1b and Phase 2a who received at least 4 initial doses of study drug, and whose SA isolate is sensitive to at least 1 of the phage components that comprise the study drug.

Phage-Sensitive ITT Population will be reported by the Sponsor separately.

3.2.5 Safety Population

The Safety Population is defined as all randomized subjects in Phase 1b and Phase 2a who receive at least 1 dose of study drug (ITT population).

3.2.6 Pharmacokinetics Population

The PK Population is defined as all subjects in Phase 1b and Phase 2a with at least 1 PK sample drawn and analyzed.

The PK analysis will be described by a separate PK Analysis Plan and the PK Population will not be included in this SAP analyses.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

The following subject disposition categories will be summarized via counts and percentages by Phase and treatment for all randomized subjects:

- Subjects who were randomized
- Subjects who were treated with study drug
- Subjects who completed study treatment
- Subjects with early termination of study drug (count and percentage will be calculated based on subjects who were treated with study drug)
    - Primary reason
- Subjects who completed study
- Subjects who discontinued the study
    - Primary reason

All randomized subject disposition data will be presented in a data listing.

3.3.2 Protocol Deviations

Counts and percentages of subjects with CSR reportable protocol deviations by deviation category will be summarized by Phase and treatment based on the randomized Population. The definition of CSR reportable protocol deviations is referring to protocol deviation plan.

The protocol deviations will be presented in a data listing based on randomized subjects.

3.3.3 Analysis Populations

Counts and percentages of subjects in ITT and Safety populations will be summarized by Phase and treatment based on subjects who were treated with study drug.

Counts and percentages of subjects in Per Protocol MITT population will be summarized by Phase and treatment based on subjects who received at least 4 doses of study drug.

Counts and percentages of subjects in Phage Persistence and Phage Clearance populations will be summarized by Phase and treatment based on subjects who are in Phase 1b Cohort 2 and Phase 2a and received at least 4 doses of study drug.

Counts and percentages of subjects in Phage-sensitive ITT population will be summarized by Phase and treatment based on subjects who received at least 4 doses of study drug and for whom the central laboratory received a blood SA isolate for phage sensitivity testing. Subjects with a blood SA isolate will include all subjects who have blood culture isolates based on blood culture samples from central laboratory (at screening, Day 1 to Day 7, TOC for study drug, TOC for BAT, EOS, or other unscheduled visits).

Reasons for exclusion from Per Protocol MITT and PK Populations will also be summarized.

The analysis population will be presented in a data listing based on randomized subjects.

3.3.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by Phase and treatment based on the randomized subjects.

The following demographic and baseline characteristics will be summarized:

- Age (Years)
- Age categories (<65 Years, ≥65 Years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2)
- Modified Duke criteria (Major: Positive blood cultures for IE, Evidence of endocardial involvement; Minor: Predisposition, Fever, Vascular phenomena, Immunologic phenomena, Microbiologic evidence)
- Blood cultures positive for SA on Day -1 prior to study drug administration based on blood cultures tested by local microbiology laboratories
- Persistent SAB on 2 blood cultures obtained over 72 hours prior to study drug administration based on blood cultures tested by local microbiology laboratories
- Type of baseline SA from blood culture isolates based on blood cultures tested by local microbiology laboratories
    - MRSA
    - Methicillin-susceptible SA (MSSA)

  - Unknown
- Randomized based on rapid testing (Yes, No)
- Signs/symptoms for focal site of SA infection (Pain at site of infection, Joint pain, Redness, etc.)
- Foci of SA infection at Screening (Head, Neck, Spine, Chest, etc.)
- Source control (Abscess drainage, Catheter or intravascular device removal, Washout of infected joint, Other)
- Adequacy of source control achieved by physician (Yes, No)
- Signs and symptoms of SAB at Screening (per protocol section 7.3 of protocol)
  - Documented temperature ≥38.0°C (100.4°F) or ≤36.0°C (96.8°F) measured orally, ≥38.5°C (101.3°F) or ≤36.5°C (97.7°F) measured tympanically, or ≥39°C (102.2°F) or ≤37°C (98.6°F) measured rectally
  - Heart rate >90 beats per minute
  - Respiratory rate >20 breaths per minute
  - White blood cell count ≥12.0 × 10^9 cells/L or ≤0.4 × 10^9 cells/L, or ≥10% immature neutrophils
  - Systolic blood pressure <90 mmHg; and/or
  - Pain associated with focal site of infection
- Time from first hospital admission to first dose of study drug received
- Time from first hospital admission to first BAT received (the time from first hospital admission to first BAT will not be calculable for those who received first BAT in the Emergency Department prior to hospital admission).

3.3.5 Medical History

Medical history will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Counts and percentages of subjects with medical history by SOC and PT will be summarized by Phase and treatment based on the Safety Population.

All medical history data will be listed based on randomized subjects.

3.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and PT using the World Health Organization (WHO) Drug Dictionary.

For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug, and concomitant medications if they were taken at any time after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing, or started after the first dose of study drug).

Counts and percentages of subjects taking prior and concomitant medications by ATC class and PT will be summarized separately based on the Safety Population.

In addition, the BAT will be summarized with counts and percentages of subjects by ATC class and PT based on the Safety Population.

All prior and concomitant medications will be listed based on randomized subjects. A separate listing for BAT will be provided based on randomized subjects.

3.3.7 Study Drug Exposure

Days of exposure to study drug (days) will be calculated as:

- (Date/time of last dose of study drug – date/time of first dose of study drug)/3600/24

Within each dose, there are [redacted] phage types. For each phage type, compliance rate will be calculated as:

- Compliance (%) = (total number of PFUs administered / total number of PFUs planned)*100
- Total number of PFUs administered = total number of phages administered * planned PFUs
- Total number of PFUs planned = planned PFUs * 20
- Total number of phages administered = total number of doses administered * 1, since each dose has 1 phage for each phage type.

Total compliance considering [redacted] phage types in each dose is calculated as:

- Total compliance (%) = (total number of PFUs administered from [redacted] phage types / total number of PFUs planned from [redacted] phage types) * 100
- Total number of PFUs administered from [redacted] phage types = total number of phages administered from [redacted] phage types * planned PFUs
- Total number of PFUs planned from [redacted] phage types = planned PFUs * 20 * [redacted]
- Total number of phages administered from [redacted] phage types = total number of doses administered * [redacted], since each dose has [redacted] phage types.

A dose with incomplete infusion will be assumed as a missed dose in compliance calculation for both compliance for each phage type and total compliance.

The following categories for study drug will be summarized:

- Descriptive statistics for days of exposure to study drug
- Descriptive statistics for the total number of doses administered
- Counts and percentages of subjects with at least one dose interruption
- Study drug compliance (%)

All study drug administration data will be listed based on randomized subjects.

3.4 Efficacy Assessment

Efficacy data will be analyzed for ITT population, Per Protocol MITT population, Phage Persistence and Clearance population, and Phage-Sensitivity ITT population (if needed):

- Efficacy analysis performed using ITT population and Phase-Sensitivity ITT population (if needed) will be summarized by pooled treatment versus pooled placebo for Phase 1b and Phase 2a:
  - Phase 1b (uncomplicated SAB) vs Phase 1b placebo
  - Phase 2a (complicated SAB) vs Phase 2a placebo
- Efficacy analysis performed using Per Protocol MITT population will be summarized by pooled treatment versus pooled placebo for Phase 2a:
  - Phase 2a vs Phase 2a placebo.
- Efficacy analysis performed using Phage Persistence and Clearance population will be summarized by following:
  - Combination of Phase 1b (excluding cohort 1) and Phase 2a Persistence vs Combination of Phase 1b (excluding cohort 1) and Phase 2a Clearance vs Combination of Phase 1b placebo (excluding cohort 1) and Phase 2a placebo
  - Phase 2a Persistence vs Phase 2a Clearance vs Phase 2a placebo

Combination of Phase 1b placebo (excluding cohort 1) and Phase 2a placebo includes Phase 1b placebo (excluding cohort 1) and Phase 2a placebo in the ITT population. Phase 2a placebo includes Phase 2a placebo in the ITT population.

Phage Persistence and Phage Clearance Population and Phage-Sensitivity ITT population (if needed) will be reported by the Sponsor separately. Subject lists for Phage Persistence and Phage Clearance Population and Phage-Sensitivity ITT population (if needed) will be provided by Sponsor for analysis.

The endpoints in section 3.4.1 for Phase 1b and Phase 2a may be assessed as secondary endpoints.

3.4.1 Efficacy Endpoints Assessments

A National Early Warning Score 2 (NEWS2) score will be recorded once per day (and should be repeated if there is a change in clinical status) from Day 1 through Day 7 and TOC for study drug (Day 12). NEWS2 is an aggregate scoring system derived from 6 physiologic parameters: respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, temperature.

Table 1 per protocol section 7.4 presents the NEWS2 scoring system. NEWS2 scores will be calculated programmatically.

Table 1. National Early Warning Score 2 Scoring System

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Note: **CVPU** = Confusion, Voice, Pain, Unresponsive; SpO_2 = oxygen saturation. SpO_2 Scale 2 (%) is meant to be used for specific population-COPD subjects with hypercapnic respiratory failure.

Time to reach a NEWS2 score ≤2 maintained for at least 24 hours or hospital discharge (whichever comes first) will be analyzed.

Time-to-event (days) = Censoring date/event date – date of first dose of study drug + 1

The Kaplan-Meier method will be used to estimate the 25%, median and 75% times. The hazard ratio, 95% confidence interval (CI) of hazard ratio, and p-value from Cox regression model will be provided to compare AP-SA02 and placebo. Cox regression will include treatment (AP-SA02 and placebo) as factor. All assessments from scheduled and unscheduled visits will be included in the time-to-event analysis. Censoring rules for the endpoint are summarized in Table 2.

The Kaplan-Meier plot of time to reach a NEWS2 score ≤2 maintained for at least 24 hours or hospital discharge (whichever comes first) will be provided.

Table 2. Time-to-event Endpoint

Endpoint: time to reach a NEWS2 score ≤2 maintained for at least 24 hours or hospital discharge		
Situation	**Date of event or censoring**	**Outcome**
NEWS2 score ≤2 maintained consecutive 2 days while hospitalized	Earlier date of these two consecutive 2 days	Event
Hospital discharge (i.e., Discharge to home, transferred to long term acute care – LTAC, transferred to long term care facility – LTCF) and no NEWS2 score ≤2 maintained consecutive 2 days while hospitalized	Date of hospital discharge	Event
No occurrence of hospital discharge to home and no NEWS2 score ≤2 maintained consecutive 2 days	Date of last visit	Censored

In Table 2, the hospital discharge types include discharge to home, transferred to long term acute care – LTAC, and transferred to long term care facility – LTCF.

Proportion of subjects reaching a NEWS2 score ≤2 maintained for at least 24 hours or hospital discharge (whichever comes first) at Day 2, Day 3, Day 4, Day 5, Day7, and TOC for study drug (Day 12) will be analyzed. The hospital discharge types include discharge home, transferred to long term acute care – LTAC, and transferred to long term care facility – LTCF. The responders will be subjects reaching a NEWS2 score ≤2 maintained for at least 24 hours or hospital discharge. Proportion of responders will be provided. Chi-square test p-value will be provided to compare AP-SA02 and placebo.

The proportion of subjects reaching a NEWS score ≤2 maintained for at least 24 hours or hospital discharge (whichever comes first) will be plotted by AP-SA02 and placebo at Day 2, Day 3, Day 4, Day 5, Day7, and TOC for study drug (Day 12).

NEWS2 score while hospitalized will be summarized with descriptive statistics by study day and changes from baseline for each study day will be summarized. A paired t-test p-value will be used to compare the baseline value with each scheduled post-baseline values. An unpaired t-test p-value will be used for the change from baseline at each scheduled study day to compare AP-SA02 and placebo.

NEWS2 score while hospitalized and changes from baseline will be plotted by AP-SA02 and placebo at each scheduled study day for each subject.

Clinical improvement or response (meets all criteria on Table 2 in section 7.3 of protocol) at TOC for study drug (Day 12), TOC for BAT (7 days [±1 day] after the end of BAT) and EOS (28 days after the end of BAT) will be assessed by both investigator and Clinical Efficacy Adjudication Committee (CEAC).

Based on both investigator and CEAC assessments, proportion of subjects who experience clinical improvement or response will be provided. Chi-square test p-value will be provided for clinical improvement or response to compare AP-SA02 and placebo.

The proportions of responders (including clinical improvement or response) will be plotted by AP-SA02 and placebo at TOC for study drug (Day 12), TOC for BAT (7 days [±1 day] after the end of BAT) and EOS (28 days after the end of BAT) by both investigator and CEAC.

Microbiological outcome at Day 5, Day 7, TOC for study drug (Day 12), TOC for BAT, and EOS will be determined programmatically based on blood culture results tested by local microbiology laboratories per Table 3 as 1 of the outcomes: Eradication, Presumed eradication, Persistence, Presumed persistence, Recurrence. The microbiological outcome at Day 5, Day 7, TOC for study drug (Day 12), TOC for BAT, and EOS will be summarized with counts and percentages of subjects based on categories in Table 3.

The Chi-square test p-value will be provided for the counts of microbiological eradication (including presumed eradication) and microbiological persistence (including presumed persistence) compare AP-SA02 and placebo.

Table 3. Microbiological Outcome

Category	Criteria
Eradication	Blood cultures negative for SA for 2 consecutive days.
Presumed eradication	Follow-up blood cultures were not done (or were technically uninterpretable) and the subject has responded clinically, as defined in Table 2 of protocol.
Persistence	Follow-up blood cultures do not meet the criteria for eradication and are positive for SA either daily or every other day.
Presumed persistence	Follow-up blood cultures were not done (or were technically uninterpretable) and the subject has not responded clinically, as defined in Table 2 of protocol.
Recurrence	A positive blood culture for SAB at any time after documented eradication or presumed eradication.

In Table 3, "the subject has responded clinically" indicates that the subject experiences clinical improvement or response per investigator's assessment at EOT for study drug. Any 2 consecutive assessments with blood cultures negative for SA is assigned as Eradication programmatically, no matter if these 2 assessments are consecutive days or consecutive visits.

Time to first resolution of any signs/symptoms related to focal site of SA infection (e.g., joint pain; redness; swelling; weight-bearing, back pain; weight-bearing, skin redness; drainage) from randomization on Day 1 will be analyzed. If all signs/symptoms are absent, the subjects will be considered achieving the resolution of signs/symptoms related to focal site of SA infection. If any signs/symptoms are present during the study assessments, the subjects will be censored at the date of latest assessment of signs/symptoms assessments for focal site of SA infection.

Time-to-event (days) = Censoring date/date of first resolution assessment – date of first dose of study drug + 1

The Kaplan-Meier method will be used to estimate the 25%, median and 75% times. The hazard ratio, 95% confidence interval (CI) of hazard ratio, and p-value from Cox regression model will be provided to compare AP-SA02 and placebo. Cox regression will include treatment (AP-SA02 and placebo) as factor. All assessments from scheduled and unscheduled visits will be included in the time-to-event analysis.

The Kaplan-Meier plot of time to first resolution of any signs/symptoms related to focal site of SA infection will be provided.

Late composite efficacy will be assessed programmatically based on the blood cultures tested by local microbiology laboratories per the definition in section 2.3.2 at EOS. Proportion of subjects who experience late composite efficacy will be provided. Chi-square test p-value will be provided for the counts of subjects who experience late composite efficacy to compare AP-SA02 and placebo.

Microbiological failure or relapse will be assessed programmatically based on the blood cultures tested by local microbiology laboratories per the definition in section 2.3.2. Proportion of subjects who experience microbiological failure or relapse at TOC for study drug (Day 12), TOC for BAT (7 days [±1 day] after the end of BAT) and EOS (28 days after the end of BAT) will be provided.

If subjects have microbiological failure or relapse at TOC for study drug (Day12) and negative blood cultures after Day 12, then subjects will not be included as microbiological failure or relapse at TOC for BAT (7 days [±1 day] after the end of BAT) or EOS (28 days after the end of BAT). If subjects have microbiological failure or relapse at TOC for BAT (7 days [±1 day] after the end of BAT) and negative blood cultures after TOC for BAT, then subjects will not be included as microbiological failure or relapse at EOS (28 days after the end of BAT). Chi-square test p-value will be provided for the counts of subjects who experience microbiological failure or relapse to compare AP-SA02 and placebo.

Time to death will be analyzed. Subject alive will be censored at the last date to be known alive.

Time to death (days) = Censoring date/death date – date of first dose of study drug + 1

The Kaplan-Meier method will be used to estimate the 25%, median and 75% times. The hazard ratio, 95% confidence interval (CI) of hazard ratio, and p-value from Cox regression model will be provided to compare AP-SA02 and placebo. Cox regression will include treatment (AP-SA02 and placebo) as factor.

Time to hospital discharge (and time to hospital discharge readiness) will analyzed. The subjects who will be in the hospital during the study will be censored at the date of last visit.

- Time to hospital discharge (days) = Censoring date/first hospital discharge date – date of first dose of study drug + 1
- Time to hospital discharge readiness (days) = Censoring date/first hospital discharge readiness date – date of first dose of study drug + 1

The Kaplan-Meier method will be used to estimate the 25%, median and 75% times. The hazard ratio, 95% confidence interval (CI) of hazard ratio, and p-value from Cox regression model will be provided to compare AP-SA02 and placebo. Cox regression will include treatment (AP-SA02 and placebo) as factor.

The Kaplan-Meier plot of time to hospital discharge (and time to hospital discharge readiness) will be provided.

Need for ICU stay will be summarized with counts and percentages of subjects. Chi-square test p-value will be provided for the counts of subjects who need ICU stay to compare AP-SA02 and placebo.

Duration of ICU stay during the study period from the Day 1 will be summarized with descriptive statistics for subjects who need for ICU stay.

The duration of ICU stay can be calculated as sum of each ICU stay from date of admission to date of discharge when the type of hospitalization is "*ICU*" in eCRF.

A t-test p-value will be provided for duration of ICU stay to compare AP-SA02 and placebo.

Need for endotracheal mechanical ventilation will be summarized with counts, and percentages of subjects. Chi-square test p-value will be provided for the counts of subjects who need endotracheal mechanical ventilation to compare AP-SA02 and placebo.

The type of oxygen delivery methods will be collected in eCRF, and the endotracheal mechanical ventilation will include types "*mechanical ventilation via tracheotomy*" and "*endotracheal tube*" in eCRF.

Duration of endotracheal mechanical ventilation will be summarized with descriptive statistics for subjects who need for endotracheal mechanical ventilation during the study.

Need for noninvasive pressure ventilation (e.g., continuous positive airway pressure, bilevel positive airway pressure) will be summarized with counts, and percentages of subjects. Chi-square test p-value will be provided for the counts of subjects who need noninvasive pressure ventilation to compare AP-SA02 and placebo. Noninvasive pressure ventilation includes oxygen delivery methods, i.e., nasal cannula, high-flow nasal cannula, nonrebreather face mask, CPAP mask, BiPAP mask, BiPAP hood and other which are collected in eCRF.

Duration of noninvasive pressure ventilation will be summarized with descriptive statistics for subjects who need for noninvasive pressure ventilation during the study.

The analysis of SA isolate sensitivity to AP-SA02, SA isolate susceptibilities to anti-staphylococcal antibiotics, and SA isolate susceptibility to BAT will be reported by the Sponsor separately.

3.4.2 Subgroups Analysis

Subgroup analyses will be performed for two endpoints clinical response and microbiological response:

- MRSA subjects
- Blood cultures positive for SA on Day -1 prior to study drug administration (blood cultures are tested by local microbiology laboratories)
- Persistent SAB on 2 blood cultures obtained over 72 hours prior to study drug administration (blood cultures are tested by local microbiology laboratories)
- Source control achieved (e.g., abscess drainage, catheter or intravascular device removal, washout of infected joint, other)
- Foci of infection present at Screening

3.5 Pharmacokinetic Assessment

PK samples for AP-SA02 will be collected prior to and post study drug.

The PK analysis will be described by a separate PK Analysis Plan and the PK Population will not be included in this SAP analyses. Calculation and analysis of PK parameters will be described and reported by the Sponsor separately.

3.6 Pharmacodynamic Assessment

Pharmacodynamic assessment will be conducted for ITT population, Per Protocol MITT population, Phage Persistence and Clearance population, and Phage-Sensitivity ITT population (if needed):

- Efficacy analysis performed using ITT population and Phase-Sensitivity ITT population (if needed) will be summarized by pooled treatment versus pooled placebo for Phase 1b and Phase 2a:
    - Phase 1b (uncomplicated SAB) vs Phase 1b placebo

  - Phase 2a (complicated SAB) vs Phase 2a placebo.
- Efficacy analysis performed using Per Protocol MITT population will be summarized by pooled treatment versus pooled placebo for Phase 2a:
  - Phase 2a vs Phase 2a placebo.
- Efficacy analysis performed using Phage Persistence and Clearance population will be summarized by following:
  - Combination of Phase 1b (excluding cohort 1) and Phase 2a Persistence vs Combination of Phase 1b (excluding cohort 1) and Phase 2a Clearance vs Combination of Phase 1b placebo (excluding cohort 1) and Phase 2a placebo
  - Phase 2a Persistence vs Phase 2a Clearance vs Phase 2a placebo

Combination of Phase 1b placebo (excluding cohort 1) and Phase 2a placebo includes Phase 1b placebo (excluding cohort 1) and Phase 2a placebo in ITT population. Phase 2a placebo includes Phase 2a placebo in ITT population.

Phage Persistence and Phage Clearance Population and Phage-Sensitivity ITT population (if needed) will be reported by the Sponsor separately. Subject lists for Phage Persistence and Phage Clearance Population and Phage-Sensitivity ITT population (if needed) will be provided by Sponsor for analysis.

Time to initial resolution of SAB will be analyzed using the Kaplan-Meier method, and the resolution will be defined as "2 consecutive days with negative SA blood cultures" based on blood cultures tested by the local microbiology laboratories. Blood cultures collected at Day 1 prior to first dose of study drug will be considered for initial resolution of SAB.

If Day 12 blood culture is positive, the subject will not be considered have initial resolution of SAB although there may be 2 or more consecutive negative blood cultures before Day 12. If EOS or BAT blood culture is positive, the subject will be considered as initial resolution of SAB when there are 2 or more consecutive negative blood cultures before EOS or BAT, and the initial resolution date and time will be the first date and time with 2 consecutive negative blood cultures. The subjects who do not experience the resolution will be censored at the last collection date and time of blood culture.

- Time to initial resolution of SAB (days) = (Censoring date and time/first date and time of 2 consecutive days with negative SA blood culture – date and time of first dose of study drug) /3600/24

The Kaplan-Meier method will be used to estimate the 25%, median and 75% times. The hazard ratio, 95% confidence interval (CI) of hazard ratio, and p-value from Cox regression model will be provided to compare AP-SA02 and placebo. Cox regression will include treatment (AP-SA02 and placebo) as factor.

The Kaplan-Meier plot of time to initial resolution of SAB will be provided.

Time to resolution of any signs and/or symptoms of bacteremia present at Screening will be analyzed using the Kaplan-Meier method as other time-to-event endpoints.

- Time to resolution of signs/symptoms of bacteremia (days) = Censoring date/date of first resolution of any signs/symptoms of bacteremia - date of first dose of study drug + 1

The Kaplan-Meier method will be used to estimate the 25%, median and 75% times. The hazard ratio, 95% confidence interval (CI) of hazard ratio, and p-value from Cox regression model will be provided to compare AP-SA02 and placebo. Cox regression will include treatment (AP-SA02 and placebo) as factor.

The Kaplan-Meier plot of time to resolution of any signs and/or symptoms of bacteremia present at Screening will be provided.

The signs and symptoms of SAB will be determined programmatically based on the following:

- Documented temperature ≥38.0°C (100.4°F) or ≤36.0°C (96.8°F) measured orally, ≥38.5°C (101.3°F) or ≤36.5°C (97.7°F) measured tympanically, or ≥39°C (102.2°F) or ≤37°C (98.6°F) measured rectally;
- Heart rate >90 beats per minute;
- Respiratory rate >20 breaths per minute;
- White blood cell count ≥12.0 × 10^9 cells/L or ≤0.4 × 10^9 cells/L, or ≥10% immature neutrophils;
- Systolic blood pressure <90 mmHg; and/or
- Pain associated with focal site of infection.

CRP and Interleukin-10 results will be summarized with descriptive statistics at baseline, each scheduled post-baseline visits. Changes from baseline for each scheduled post-baseline visit, the minimum, maximum, last post-baseline value. Both scheduled and unscheduled post-baseline values will be considered for the summaries. A paired t-test p-value will be used to compare the baseline value with each scheduled post-baseline values. An unpaired t-test p-value will be used for the change from baseline at each scheduled study day to compare AP-SA02 and placebo.

Changes from baseline will be plotted by AP-SA02 and placebo at each scheduled study day for each subject.

3.7 Safety Assessment

Safety data will be analyzed based on the Safety Population for both Phase 1b and Phase 2a and summarized by pooled treatment and pooled placebo: Phase 1b (uncomplicated SAB) vs Phase 1b placebo, and Phase 2a (complicated SAB) vs Phase 2a placebo.

Safety data will be summarized by actual treatment received based on the Safety Population.

3.7.1 Adverse Events

AEs will be captured from the date of informed consent through EOS.

All AEs will be coded to system organ class (SOC) and preferred term (PT) using MedDRA. The Investigator will grade all AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

TEAEs are defined as AEs occurring after the first dose of study drug through TOC for study drug (Day 12) or through EOS for SAEs.

An overview of AEs will be provided including counts and percentages of subjects with the following:

- Any AEs
- Any TEAEs
- Any study drug related TEAEs
- Any BAT related TEAEs
- Any SAEs
- NCI CTCAE grade 3/4/5 AEs
- NCI CTCAE grade 3/4/5 TEAEs
- Any TEAEs leading to interruption of study drug

- Any TEAEs leading to withdrawal of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death

Counts and percentages of subjects will also be presented by SOC and PT for each of the categories in the overview. Chi-square test p-value will be provided to compare AP-SA02 and placebo.

Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug based on randomized subjects.

3.7.2 Clinical Laboratory Tests

Blood samples for chemistry, hematology, coagulation, urinalysis, and serology testing will be obtained based on schedule of procedures (Appendix A). Descriptive statistics will be provided for chemistry, hematology, coagulation parameters using the International System of Units at baseline, each scheduled post-baseline visit, the minimum post-baseline value, the maximum post-baseline value, last post-baseline value and changes from baseline for each scheduled post-baseline visit, minimum, maximum, and last post-baseline values. Both scheduled and unscheduled post-baseline values will be considered for the summaries.

A paired t-test p-value will be used to compare the baseline value with each scheduled post-baseline values. An unpaired t-test p-value will be used for the change from baseline at each scheduled post-baseline visit to compare AP-SA02 and placebo.

All clinical laboratory data will be listed by subject based on randomized subjects. Laboratory values outside the normal ranges will be flagged in the data listings.

3.7.3 Vital Signs

Descriptive statistics will be provided for the vital signs measurements (e.g., systolic blood pressure, diastolic blood pressure, heart rate, SpO_2 (%), respiratory rate, temperature) at baseline, each scheduled post-baseline visit, the minimum post-baseline value, the maximum post-baseline value, last post-baseline value. Average values and average changes from baseline for each scheduled post-baseline visit, minimum, maximum, and last post-baseline values will be summarized. Both scheduled and unscheduled post-baseline values will be considered for the summaries.

A paired t-test p-value will be used to compare the baseline value with each scheduled post-baseline values. An unpaired t-test p-value will be used for the change from baseline at each scheduled post-baseline visit to compare AP-SA02 and placebo.

The counts and percentages of subjects with the following potentially abnormal vital signs at any post-baseline visits will be summarized:

- Heart rate >90 beats per minute;
- Respiratory rate >20 breaths per minute;
- Systolic blood pressure ≤ 90 mmHg and decrease ≥ 20 mmHg from baseline
- Systolic blood pressure ≥ 140 mmHg and increase ≥ 20 mmHg from baseline
- Diastolic blood pressure ≤ 50 mmHg and decrease ≥ 10 mmHg from baseline
- Diastolic blood pressure ≥ 90 mmHg and increase ≥ 10 mmHg from baseline

All vital sign data will be listed by subject based on randomized subjects.

3.7.4 Electrocardiograms

Descriptive statistics will be provided for the electrocardiogram measurements (heart rate, ventricular rate, PR interval, RR interval, QRS duration, QT interval) at any post-baseline visit, the minimum post-baseline value, the maximum post-baseline value, last post-baseline value and changes from baseline for each scheduled post-baseline visit, minimum, maximum, and last post-baseline values. Both scheduled and unscheduled post-baseline values will be considered for the summaries.

The Fridericia-corrected QT interval (QTcF) will be calculated as:

- QTcF (msec) = QT(msec)/(RR(msec)/1000)^1/3

Counts and percentage of subjects with QTcF intervals in the categories below will be provided at any post-baseline visits:

- Absolute QTcF interval ≥450 msec and ≤480 msec
- Absolute QTcF interval >480 msec and ≤500 msec
- Absolute QTcF interval >500 msec
- Change from baseline QTcF interval increase >30 msec
- Change from baseline QTcF interval increase >60 msec

The overall interpretation (Abnormal, Indeterminate, Normal, Not evaluable, Unknown) will be summarized via counts and percentage of subjects at each scheduled visit.

All electrocardiogram data will be listed by subject based on randomized subjects.

3.7.5 Acute Kidney Injury

AKI will be measured at Day 1 and EOS. AKI will be defined as stage 1 or higher using modified RIFLE criteria (Appendix D of protocol) at any time within the first 7 days or new need for renal replacement therapy between Day 1 and EOS.

For Day 1 and EOS assessment per RIFLE criteria, the counts and percentage of subjects will be summarized based on categories: None, Risk (R), Injury (I), Failure (F), Loss (L), ESKD (E).

Proportion of subjects with AKI between Day 1 and EOS will be provided. Chi-square test p-value will be provided to compare AP-SA02 and placebo.

AKI will be derived based on any of below assessments:

1) AKI assessments with results RIFLE within first 7 days from the first dose date, or
2) New need for renal replacement therapy.

All AKI assessments will be listed by subject based on randomized subjects.

3.7.6 Physical Examinations

A complete physical examination will be performed at Screening, Day 7, TOC for study drug (Day 12), TOC for BAT, and EOS. A targeted physical examination will be performed daily from Day 1 through Day 6.

All physical examination data will be listed by subject based on randomized subjects.

3.7.7 Other Safety Assessments

Other assessments about echocardiogram, ultrasound assessments, and pregnancy test will be listed by subject based on randomized subjects.

Subjects with adverse events of endocarditis or endocarditis reported on echocardiogram will be listed by subject based on randomized subjects.

4 DATA REVIEW COMMITTEE

The DRC will convene throughout the study to review blinded safety data to recommend if it is safe and appropriate to continue the study as planned. The DRC will convene to recommend if dose selection and/or dose duration are appropriate prior to dose escalation during or after Phase 1b. Additionally, the DRC can receive unblinded data, if requested and deemed necessary to adequately complete their review. Further details regarding the roles, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

5 INTERIM ANALYSIS

No interim analysis is planned.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

1) 'Time to resolution of SAB' is updated to 'Time to initial resolution of SAB' in Section 2.3.2.
2) The definitions of ITT, MITT, PK population, and Phage-Sensitive ITT Population are updated in Section 3.2.
3) 'Phage Persistence and Clearance Population' is added in Section 3.2.
4) The efficacy analysis and PD analysis conducted in Phase 1b based on ITT Population are added in Section 3.4 and Section 3.6
5) The efficacy analysis and PD analysis conducted based on Persistence and Clearance Population are added in Section 3.4 and Section 3.6.
6) 'Persistent SAB on 2 blood cultures obtained over 72 hours prior to study drug administration' and 'Foci of infection present at Screening' are added for subgroup analysis in Section 3.4.2.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A. SCHEDULE OF PROCEDURES

	Screening	Treatment Period[a]							TOC for Study Drug	TOC for BAT	EOS[b]	ETOT Visit
Day (±Visit Window)	-3 to -1[c]	1	2	3	4	5	6	7	12 (±1 day)[d]	18-60 (±1 day)[e]	39-81 (±1 day)	U
Informed consent[f]	X											
Inclusion/exclusion criteria[g]	X											
Demographic information	X											
Medical/surgical history[h]	X											
Prior/concomitant medications	X[i]	X	X	X	X	X	X	X	X	X	X	X
Weight and height[j]	X											
Complete physical examination[k,l]	X							X	X	X	X	X
Targeted physical examination[l, m]		X	X	X	X	X	X					
Vital signs[n]	X	X[o]	X[o]	X[o]	X[o]	X[o]	X	X	X	X	X	X
NEWS2 score[p]		X	X	X	X	X	X	X	X			X
Blood cultures[q]	X	X	X[r]	X[r]	X[r]	X	X[r]	X	X	X	X	X[r]
Sterile site cultures	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]
Infectious disease consultation		X[t]										
Signs/symptoms of SA infection[u]	X	X	X	X	X	X	X	X[v]	X	X	X	X
Assessment of clinical outcome									X	X	X	X
Ultrasound		X[w]										
ECHO		X[x]										
Source control[y]		X										
AKI assessment[z]		X									X	
Serum for AP-SA02 anti-phage antibodies		X[aa]						X	X		X	
IL-10	X	X[ff]	X	X	X	X	X	X	X			X
Serology testing[bb]	X											
Pregnancy test[cc]	X	X								X	X	X
12-lead ECG	X	X[dd]		X		X			X	X	X	X
Clinical laboratory evaluations[ee]	X	X[ff]	X	X	X	X		X	X	X	X	X
Urinalysis[kk]	X	X				X		X	X	X	X	X
PK blood sampling[gg]		X	X	X	X	X	X					
Urine samples for phage CL[hh, kk]		X						X	X	X		X
Randomization		X										
Study drug administration[ii]		X	X	X	X	X						
Adverse events[jj]	X	X	X	X	X	X	X	X	X	X	X	X

Note: Blood samples may be collected and stored for future assessments.

a. Daily visits will be performed at an inpatient location. Study days may not correspond exactly with calendar days during the Treatment Period. Additional dosing days will repeat procedures on Days 2 to 4, depending on the number of days added. The final day of dosing will mirror Day 5.

b. EOS will occur 28 days after the end of BAT.

c. The screening period will be up to 3 days. Subjects should be randomized as soon as possible after confirmation of study eligibility and can be randomized on the same calendar day as Screening.

d. TOC for study drug will occur on Day 12. A ±1 day window will be allowed if the subject is discharged.

e. TOC for BAT will occur 7 days (±1 d) after the end of BAT.

f. Signed informed consent by the subject (or LAR) must be obtained before any study-related procedures are performed.

g. Subjects must continue to meet eligibility criteria at randomization.

h. Relevant medical/surgical history will be collected. Any updates since the Screening Visit will be assessed at randomization.

i. All relevant medications received in the 28 days prior to randomization must be recorded.

j. Height will be collected at the Screening Visit only and will be used to calculate body mass index.

k. A complete physical examination will include evaluation of HEENT, neck, lungs, heart, chest, abdomen, extremities, neurologic status, skin for evidence of emboli, palpation for signs of pain, and any other notable conditions.

l. Pain on a physical examination should trigger diagnostic testing for metastatic foci of infection.

m. A targeted physical examination will include evaluation for complications of bacteremia, HEENT, lungs, heart, skin for any evidence of septic emboli, and palpation for signs of pain.

n. Vital signs will include temperature, heart rate, and blood pressure. Vital signs will be obtained at every visit unless the subject has been discharged and visits are being performed remotely. Wherever possible, vital signs will be obtained after at least 5 minutes resting in a supine or sitting position. If more than 1 measurement is taken on a given day, the highest value for temperature should be recorded in the eCRF.

o. During the Treatment Period, vital signs should be obtained prior to each infusion (-1 hour window).

p. A NEWS2 score will be recorded once per day (and should be repeated if there is a change in clinical status) from Day 1 through Day 7 and TOC for study drug (Day 12). NEWS2 is an aggregate scoring system derived from 6 physiologic parameters: respiration rate; oxygen saturation; systolic blood pressure; pulse rate; level of consciousness or new confusion, and temperature. The NEWS2 score will be calculated programmatically from the NEWS2 parameters entered in the eCRF; additional NEWS2 assessments should be repeated that day if indicated due to a change in clinical status.

q. Two sets of blood cultures, preferably from 2 different sites, 30 minutes apart will be drawn on Day 1 as close to the start of study drug administration as possible, unless blood cultures have already been sent that day for Screening or clinical care. Thereafter, 1 set of blood cultures is acceptable. Blood cultures should be collected from a peripheral venipuncture site when possible until 2 consecutive days of negative blood cultures are obtained or otherwise clinically indicated. Repeat blood cultures will also be obtained at EOT for study drug (Day 5), Day 7, each of the TOC (BAT and study drug) and the EOS Visits, regardless of clinical indication, to evaluate for microbiological cure and sustained cure. See Section 7.7 for additional details.

r. Blood cultures will be drawn on these days, only if necessary, until 2 consecutive days of negative blood cultures are obtained or if clinically indicated.

s. Sterile site cultures will be collected on these days as clinically indicated.

t. All subjects will receive an infectious disease consultation within 2 days of randomization unless consultation was obtained prior to enrollment. If consultation can only be obtained after 2 days of randomization, this is permissible, but must be documented. Sites without access to an infectious diseases specialist must discuss with the Medical Monitor or Sponsor if the subject can be included in the study. If the Investigator specialty is infectious disease, a separate consultation is not required.

u. Signs/symptoms related to focal site of SA infection (eg, joint pain; redness; swelling; weight-bearing, back pain; weight-bearing, skin redness; drainage) will be assessed at Screening, daily from Day 1 through Day 7, at TOC for study drug (Day 12), TOC for BAT, and EOS.

v. Investigator will provide an assessment of whether additional imaging is needed for potential metastatic infection based on clinical signs/symptoms of SA infection.

w. All subjects with an intravascular catheter present at admission that is not thought to be infected and is not planned on being removed within 3 days of randomization should receive an ultrasound to evaluate for the presence of an intravascular clot within 2 days of randomization unless this was done within 7 days prior to Screening.

x. All subjects will receive a TTE and/or TEE ECHO within 3 days of randomization unless this was done within 7 days prior to Screening. Subjects with endocarditis should have a follow-up TTE or TEE between Days 7 and 14. All effort should be made to perform this before administration of study drug.

y. All work-up for distant sites of metastatic infection and all decisions regarding source control procedures will be performed as per primary team. IV catheters known or suspected to be infected must be removed or changed as soon as possible within 72 hours after randomization. Sites should identify source control within 3 days; potential source or evidence of ongoing infection after 7 days may be considered a clinical failure.

z. AKI will be defined as stage 1 or higher using modified RIFLE criteria at any time within the first 7 days or new need for renal replacement therapy between Day 1 and EOS

aa. Serum for AP-SA02 anti-phage antibodies will be performed prior to the first dose.

bb. HIV antibody, HBsAg, and HCV antibody testing will be performed at Screening, only if status is unknown.

cc. FCBPs only must have a negative serum pregnancy test within 72 hours prior to randomization. Results can be from a local laboratory and will be confirmed at the central laboratory.

dd. A 12-lead ECG will be performed post first dose of the day.

ee. Assessments include chemistries, hematology, coagulation, CRP, and procalcitonin. See Appendix B of protocol for a list of clinical laboratory analytes.

ff. Clinical laboratory assessments and IL-10 will be performed post-dose after the second infusion.

gg. Venous blood samples for PK analysis of AP-SA02 levels will be collected from subjects enrolled at predetermined/qualified PK sites on Day 1 (pre-dose [-60 minutes], 0.5 hours [±15 minutes], 1 hour [±15 minutes], 3 hours [±15 minutes]post first dose of the day), Days 2 to 4 (1 sample 1 hour [30 minutes] post first dose of the study day, Day 5 (1 hour [±15 minutes] post last dose of the day), Day 6 (24 hours [±30 minutes] post last dose).

hh. Urine for phage CL will be collected prior to the first dose on Day 1, Day 7, TOC for study drug (Day 12), TOC for BAT, and ETOT. Date and time will be recorded for each urine sample collection at the designated time points.

ii. AP-SA02 or placebo will be administered via IV bolus infusion every 6 hours for 5 consecutive days in an inpatient location, unless the dose, frequency, or duration is modified after DRC review. In addition, all subjects will receive at least 14 days (uncomplicated SAB) or 28 days (complicated SAB) and up to 56 days of BAT. BAT will be administered at the discretion of the Investigator. Subjects must be directly observed during study drug/placebo administration by clinical personnel. The first dose of study drug on Day 1 must occur as close as possible to the time of randomization.

jj. Adverse events will be collected from the time of informed consent.

kk. It is expected that subjects enrolled who are also receiving dialysis (hemodialysis or peritoneal dialysis) may produce little or no urine. In such cases, urine for urinalysis or urine for phage clearance may not be available for collection at some or any of the timepoints listed in the protocol. Protocol deviations will not be issued for missed urine collections due to anuria.

AKI = acute kidney injury; BAT = best available therapy; CL = clearance; CRP = C-reactive protein; DRC = Data Review Committee; ECG = electrocardiogram; ECHO = echocardiogram; eCRF = electronic case report form; EOS = End of Study; ETOT = Early Termination of Treatment; FCBP = female of childbearing potential; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEENT = head, eyes, ears, nose, and throat; HIV = human immunodeficiency virus; IL = interleukin; IV = intravenous(ly); LAR = legally authorized representative; NEWS2 = National Early Warning Score 2; PK = pharmacokinetic(s); RIFLE = Risk-Injury-Failure-Loss-End-stage renal disease; SA = Staphylococcus aureus; SAB = Staphylococcus aureus bacteremia; TEE = transesophageal; TOC = Test of Cure; TTE = transthoracic; U = unscheduled.