CLINICAL STUDY PROTOCOL

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*

Investigational Product: AP-SA02

Protocol Number: AP-SA02-101

EudraCT Number: 2021-001190-22

Sponsor:
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SIGNATURE PAGE

STUDY 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*

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
	31July2024

Deborah Birx, MD
Chief Executive Officer
Armata Pharmaceuticals, Inc.

Mina Pastagia	July 31, 2024

Mina Pastagia, MD
Chief Medical Officer
Armata Pharmaceuticals, Inc.

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the protocol inclusive of the design and specific provisions of this protocol and will complete the study within the time designated in this protocol. I will provide copies of this protocol to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Armata Pharmaceuticals, Inc., that it may not be further disclosed to third parties, and is subject to the confidentiality obligations contained in the Clinical Study Agreement. I understand that the study may be terminated or enrollment suspended at any time by Armata Pharmaceuticals, Inc. with or without cause, or by my institution in accordance with the terms of the Clinical Study Agreement.

I agree to conduct this study in full accordance with all applicable laws and regulations, including Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

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*

PROTOCOL NUMBER: AP-SA02-101

INVESTIGATIONAL PRODUCT: AP-SA02

PHASE: 1b/2a

INDICATION: Bacteremia due to *Staphylococcus aureus* (SA)

OBJECTIVES:

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 SA bacteremia (SAB).

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.

POPULATION:

Subjects who meet all inclusion criteria and none of the exclusion criteria during the 3-day screening period will be considered eligible for enrollment in the study.

Inclusion Criteria

Inclusion criteria for Phase 1b and 2a

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Is able and willing to provide written informed consent or have consent provided by a legally authorized representative (LAR);
2. Is a hospitalized male or female adult subject aged 18 years or older at time of consent;
3. Has SAB identified from at least 1 blood culture or from a rapid diagnostic test within 72 hours of randomization. Time of positive blood culture starts from when specimen is collected for blood culture;

4. Has a plan for source control within 3 days after randomization to be completed within 7 days of randomization if relevant (eg, abscess drainage, washout or debridement of infected material) or has source already controlled;
5. If a female of childbearing potential (FCBP), the subject must agree to use a highly effective method of birth control (defined as those, alone or in combination, that result in a low failure rate [ie, less than 1% per year]) from Day 1 through 60 days following the last dose of study drug;

   Note: FCBP must have a negative serum pregnancy test within 72 hours prior to randomization. An FCBP is any female, regardless of sexual orientation, who meets the following criteria: has not undergone a hysterectomy or bilateral oophorectomy, or has not been naturally postmenopausal for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).
6. If a male subject, the subject must agree to use barrier contraception (ie, condoms) from Day 1 through 60 days following the last dose of study drug;

Additional inclusion criteria for Phase 2a only

7. Has at least 1 of the following signs/symptoms at or within 72 hours prior to randomization:
   a. Documented temperature ≥38.0ºC (100.4ºF) or ≤36.0°C (96.8°F) measured orally, ≥38.5ºC (101.3ºF) or ≤36.5°C (97.7°F) measured tympanically, or ≥39ºC (102.2ºF) or ≤37°C (98.6°F) measured rectally;
   b. Heart rate >90 beats per minute;
   c. Respiratory rate >20 breaths per minute;
   d. White blood cell count ≥12.0 × 10^9 cells/L or ≤0.4 × 10^9 cells/L, or ≥10% immature neutrophils;
   e. Systolic blood pressure <90 mmHg; and/or
   f. Pain associated with focal site of infection.
8. Has at least 1 of the following:
   a. At the time of positive SA blood culture was undergoing chronic intermittent hemodialysis or peritoneal dialysis;
   b. Positive blood culture for SA after 2 or more days on anti-staphylococcal antibiotic treatment;
   c. Temperature ≥38.0°C (100.4°F) at ≥72 hours after initial blood culture;
   d. SAB associated with signs or symptoms of metastatic foci and/or hematogenous seeding, including, but not limited to, septic thrombophlebitis, osteomyelitis (not including osteomyelitis associated with hardware or prosthetic joint infection), deep soft tissue abscess, septic arthritis/bacterial native joint infection, septic pulmonary emboli/infarction, visceral soft tissue abscess, or empyema confirmed by physical examination, imaging, or culture; and/or

e. Presence of right-sided SAB endocarditis (native valve) by modified Duke criteria, with no clinical evidence of cerebral foci requiring at least 28 days of anti-SA antibiotic treatment.

Exclusion Criteria

Exclusion criteria for Phase 1b and 2a

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Has concomitant growth of organisms besides SA in a blood culture, excluding coagulase-negative staphylococci (eg, *Staphylococcus epidermidis*) and other species when considered by the primary team to represent contaminants;
2. Has, in the 7 days prior to randomization, a positive culture with SA that has a known minimum inhibitory concentration to daptomycin >1 mcg/mL or vancomycin >2 mcg/mL;
3. Has received treatment with any potentially effective (anti-SA) systemic antibiotic for more than 72 hours within 7 days prior to randomization;

   Note: Subjects who have received >72 hours of antibiotics and have documented resistance to administered therapy or persistent SAB on 2 blood cultures obtained over 72 hours may be considered for the study with Sponsor or Medical Monitor approval.
4. Has known or suspected left-sided infectious endocarditis by modified Duke criteria;
5. Has a suspected endovascular source of bacteremia including, but not limited to, perivalvular abscess, left ventricular assist device (cardiac pacemaker or automatic implantable cardioverter-defibrillator [AICD]), AICD wire, arteriovenous graft, prosthetic valves, or valve rings;

   Note: A subject with a suspected endovascular source of infection may be considered if that source is planned to be removed within 72 hours of randomization.
6. Has a known or suspected brain abscess;

   Note: A subject with epidural abscess may be included if they do not require surgical intervention and have minimal neurologic deficits.
7. Community acquired pneumonia, nosocomial pneumonia due to pathogens **other than** *S. aureus*.

   Note: patients with pneumonia due to *S. aureus* are eligible for enrollment.

   ;
8. Has osteomyelitis that is associated with hardware or prosthetic joint infection;

   Note: A subject with a suspected osteomyelitis with hardware or prosthetic joint infection may be considered if that source is planned to be removed within 72 hours of randomization.
9. Has refractory shock with persistent hypotension (ie, mean arterial pressure <60 mmHg) that is unresponsive to fluids and vasopressors at Screening;

10. Has a known allergy to phage products;
11. Is a female subject who is pregnant or breastfeeding;
12. In the Investigator's opinion, the subject is unable to understand and comply with protocol requirements, instructions, and protocol-stated restrictions and is unlikely to complete the study as planned;
13. Is currently enrolled in another investigational interventional trial and has received any investigational treatment within 28 days prior to consent or will continue to receive any investigational treatment during the study;
14. Has anticipated requirement for effective systemic bacterial therapy unrelated to the treatment of SAB or other planned use of systemic antibacterial therapy (eg, treatment of acne vulgaris);

    Note: Prophylactic antibiotics for operative dental procedures and chronic suppressive oral antibiotic therapy after completion of a minimum of 14 days (uncomplicated SAB) or 28 days (complicated SAB) to 56 days of BAT are permitted.
15. Has, at Screening, 1 or more of the following laboratory abnormalities:

    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN) if total bilirubin <2 × ULN; and/or
    b. ALT or AST >2.5 × ULN if total bilirubin is >2 × ULN.
16. Has, in the opinion of the Investigator, an acute or chronic medical condition (eg, seizure disorder in status epilepticus, acute coronary syndrome, end-stage renal disease with no plan to dialyze, metastatic malignancy, chronic severe liver disease, or other disease) or other finding that is clinically significant that could put the subject at risk or harm by participating in the study;
17. Has, in the opinion of the Investigator, evidence of a concurrent medical illness that is immediately life-threatening, has life-expectancy of less than 3 months, or is likely to elect palliative care within 3 months;
18. Has any known previous exposure to AP-SA02 or prior participation in Study AP-SA02-101;
19. History of AIDS (human immunodeficiency virus positive with an AIDS-defining condition and/or CD4 count <200 cells/mm^3) or chronic severe liver disease due to hepatitis B virus (HBV) or C virus (HCV), confirmed by medical history or recent test results (within 90 days prior to Screening). If neither of these options are feasible to confirm disease status, rapid testing should be performed by the Investigator.

<u>Additional exclusion criteria for Phase 1b only</u>

20. Has all of the following signs/symptoms at or within 24 hours prior to randomization:

    a. Documented temperature ≥38.0ºC (100.4ºF) or ≤36.0°C (96.8°F) measured orally, ≥38.5ºC (101.3ºF) or ≤36.5°C (97.7°F) measured tympanically, or ≥39ºC (102.2ºF) or ≤37°C (98.6°F) measured rectally;
    b. Heart rate >90 beats per minute;

c. Respiratory rate >20 breaths per minute;

d. White blood cell count ≥12.0 × 10^9 cells/L or ≤0.4 × 10^9 cells/L, or ≥10% immature neutrophils; and

e. Systolic blood pressure <90 mmHg.

STUDY DESIGN AND DURATION:

Adult hospitalized subjects who have a positive blood culture for SA and require a minimum of 14 days (uncomplicated SAB) or 28 days (complicated SAB) and a maximum of 56 days of IV antibiotic therapy may be eligible for this study. Prior to any study screening evaluations, the subject (or LAR) must sign an informed consent form. Subjects will be assessed for all inclusion and exclusion criteria, source and distal sites(s) of infection, presence of endocarditis, significant comorbidities, and National Early Warning Score 2 (NEWS2) score. Screening assessments will be completed from Day -3 to Day -1. After all eligibility criteria are met, the subject will be randomized. Subjects not fulfilling the eligibility criteria and not randomized may be rescreened for participation if their eligibility characteristics change. Screening procedures that fall within the screening window do not need to be repeated.

Blinded study drug will be initiated on Day 1 and administered every 6 hours through Day 5. The BAT must be planned for a minimum of 14 days (uncomplicated SAB) or 28 days (complicated SAB) and a maximum of 56 days (inclusive of the days on BAT prior to study enrollment/randomization) based on the clinical presentation of the subject and the clinical judgment of the Investigator. Visits from Day 1 through Day 7 should be performed in an inpatient location.

All subjects will receive antibiotics that are chosen by the Investigator and are per local standard of care. If subjects with methicillin-susceptible SA isolates are intolerant to beta-lactam therapy, an alternative antibiotic considered to be BAT, is acceptable. The BAT will have been started before randomization in most subjects.

Summary of Study Design

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 (eg, 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.

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:

<u>Phase 1b</u>

- 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.

<u>Phase 2a</u>

- 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 the 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.

Based on these evaluations and DRC recommendation, the Sponsor will determine if additional methicillin-resistant SA (MRSA) subjects will need to be enrolled in order to ensure adequate distribution of MRSA subjects between treatment arms.

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.

DATA REVIEW COMMITTEE:

The DRC will be comprised of members with pertinent expertise who will review emerging blinded safety data at appropriate times throughout the study, as described in this protocol and as set forth in the DRC Charter.

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.

In addition, ad hoc reviews of blinded safety data will be performed throughout the study by appropriate study personnel and the Medical Monitor. The DRC can convene for ad hoc meetings if deemed necessary by the Sponsor or Medical Monitor through ongoing trend reviews or if a study stopping rule has been met.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

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

[redacted] The dose level of AP-SA02 to be administered to each subject will be determined based on the cohort assignment. Dosage (in PFU) per cohort is shown in the table below. The dose level to be tested in the Phase 1b additional cohort(s) (up to 3) and Phase 2a will be based on the observed safety and tolerability in the prior dosed subjects.

Phase Cohort	Each Dose (Approximate PFU/phage)	Each Dose (Approximate Total PFU)	Total Daily Dose (Approximate Total PFU)	Total Dose Over 5 Days (Approximate Total PFU)
Phase 1b				
1	1×10^9	2×10^9	8×10^9	4×10^{10}
2	1×10^{10}	2×10^{10}	8×10^{10}	4×10^{11}
Phase 2a	TBD	TBD	TBD	TBD
PFU = plaque-forming units; TBD = to be determined.				

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, 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.

ENDPOINTS:

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.

Phase 2a

The Phase 2a endpoints are the following:

- Time to reach a NEWS2 score ≤2 maintained for at least 24 hours or hospital discharge (whichever comes first) for subjects on active drug versus placebo in the Microbiological Intent-to-Treat (MITT) Population;
- Clinical Improvement or response at TOC for study drug (Day 12) in the MITT Population;
- 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) in the MITT Population;
- 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 (eg, 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 (eg, joint fluid, tissue) >14 days from randomization; or
  - Blood culture positive for SA >72 hours after the first blood cultures showing clearance (CL) of SAB (defined as 2 consecutive days with negative SA blood cultures).
- Time to resolution of SAB;
- Time to hospital discharge (and time to hospital discharge readiness);
- Need for and duration of intensive care unit stay;
- Need for and duration of endotracheal mechanical ventilation;
- Need for and duration of noninvasive pressure ventilation (eg, 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 (eg, 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, defined as stage 1 or higher using modified Risk-Injury-Failure-Loss-End-stage renal disease 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.

CLINICAL EFFICACY ADJUDICATION COMMITTEE:

The Clinical Efficacy Adjudication Committee (CEAC) will consist of a group of independent clinical experts blinded to treatment allocation and not associated with study conduct. Data obtained for subjects who receive study drug may be reviewed independently by CEAC members. The CEAC members will give their opinion on the diagnosis and classification of the SAB, the adequacy of BAT, the adequacy of source control, and/or the response assessment (overall success or failure). For deaths occurring during the study, a blinded assessment of the attribution of death to SAB or to another cause may be performed by the CEAC members.

STUDY EVALUATIONS:

Safety

Safety will be assessed by monitoring AEs, vital signs, laboratory data (chemistries, hematology, and coagulation), immunogenicity evaluation, physical examinations, electrocardiograms, and radiologic imaging per standard of care (eg, echocardiogram).

Pharmacokinetics

PK samples for AP-SA02 will be collected from subjects enrolled at predetermined/qualified PK sites on the following days and times, and evaluated based on AP-SA02 levels as measured by venous blood samples:

- Day 1: pre-dose (-60 minutes) and , 0.5 hours (±15 minutes), 1 hour (±15 minutes), and 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; and
- Day 6: 24 hours (±30 minutes) post last dose.

PK parameters of AP-SA02 will be assessed from subjects enrolled at predetermined/qualified PK sites with serial PK sampling, including maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), terminal elimination half-life ($t_{½}$), CL, volume of distribution (V_z), area under the plasma concentration time curve (AUC) from time 0 to the last quantifiable time (AUC_{0-t}), and

AUC from time 0 to infinity ($AUC_{0-\infty}$). Additional details regarding PK analysis methodology will be described in the Statistical Analysis Plan (SAP).

Pharmacodynamics

Pharmacodynamics will be evaluated based on the following:

- Time to resolution of signs/symptoms of bacteremia present at Screening;
- Time to resolution of bacteremia based on blood cultures; and/or
- Change in CRP from baseline.

STATISTICAL ANALYSES:

Predefined or post-hoc statistical analysis for all subjects may be performed to compare the treatment groups that are randomized based on the following:

- MRSA subjects (subgroup will be for Phase 2a only);
- Blood cultures positive for SA on Day -1 prior to study drug administration; and
- Source control achieved (eg, abscess drainage, catheter or intravascular device removal, washout of infected joint).

Note: The final SAP will finalize the subgroup analyses.

Analysis Populations

The following analysis populations will be defined for the Phase 1b and Phase 2a cohorts:

- Intent-to-Treat (ITT): all randomized subjects regardless of whether or not study drug is received;
- Phage-Sensitive ITT: all randomized subjects who receive both BAT and study drug, and whose SA isolate is sensitive to at least 1 of the phage components that comprise the study drug;
- Safety: all randomized subjects who receive at least 1 dose of study drug;
- MITT: all subjects in the ITT Population with baseline SAB and who receive at least 1 dose of study drug; and
- PK: all subjects (enrolled at predetermined/qualified PK sites) who have at least 1 PK sample drawn.

An SAP will be prepared and finalized before database lock and analyses of data. Summary data will be tabulated and presented by treatment group.

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 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.

SITES: Approximately 30 to 35 sites globally

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AICD	Automatic implantable cardioverter-defibrillator
AIDS	Acquired immunodeficiency syndrome
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the last quantifiable time
BAT	Best available therapy
CEAC	Clinical Efficacy Adjudication Committee
CFR	Code of Federal Regulations
CL	Clearance
C_{max}	Maximum observed plasma concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive protein
CTA	Clinical trial authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
EOS	End of Study
EOT	End of Treatment
ETOT	Early Termination of Treatment
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	Head, eyes, ears, nose, and throat
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

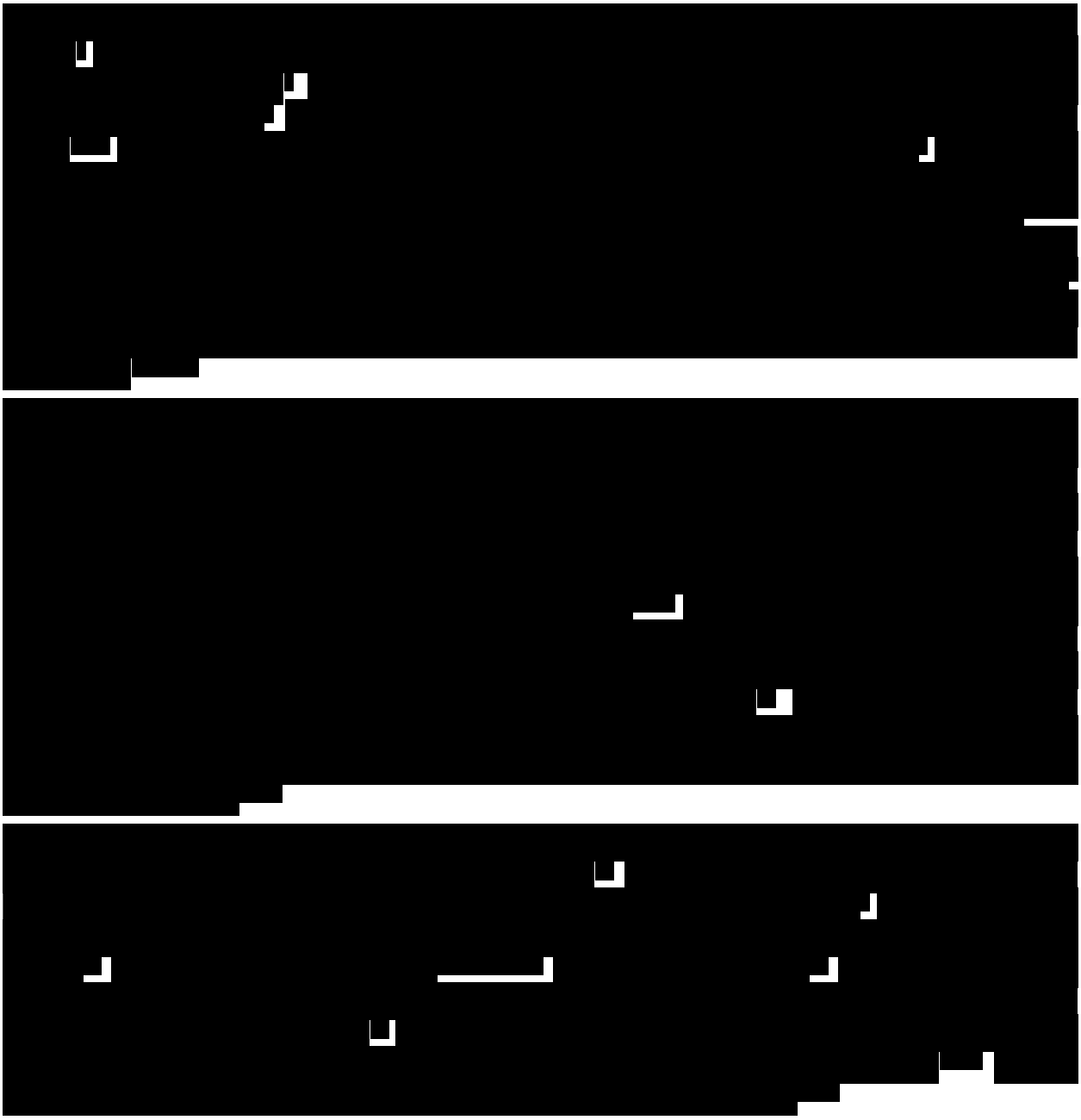
Abbreviation	Definition
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous(ly)
LAR	Legally authorized representative
MAD	Multiple ascending dose
MITT	Microbiological Intent-to-Treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NEWS2	National Early Warning Score 2
OHRO	Office of Human Research Oversight
PFU	Plaque-forming units
PK	Pharmacokinetic(s)
RIFLE	Risk-Injury-Failure-Loss-End-stage renal disease
SA	*Staphylococcus aureus*
SAB	*Staphylococcus aureus* bacteremia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum observed plasma concentration
TOC	Test of Cure
ULN	Upper limit of normal
V_z	Volume of distribution

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Introduction

Armata Pharmaceuticals, Inc. (Armata, the Sponsor) is developing a proprietary multi-phage therapeutic candidate (AP-SA02) for the treatment of *Staphylococcus aureus* (SA) bacteremia (SAB). The intended route of clinical administration is intravenous (IV) and will be administered as an adjunct to best available antibiotic therapy.

1.1.1 *Staphylococcus aureus* Bacteremia



[redacted]

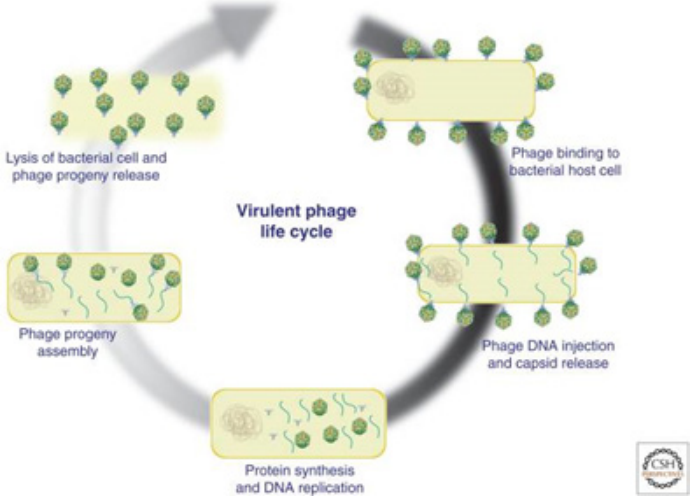
1.1.2 Phage as Antimicrobials

[redacted]

1.1.2.1 Mechanisms of action of phages

[redacted]

Figure 1. Lytic Cycle of Bacteriophages



Schematic representation of virulent phage infection, replication, and lysis of bacterial host cells.
DNA = deoxyribonucleic acid.
Source: Barbu EM, Cady KC, Hubby B. Phage therapy in the era of synthetic biology. *Cold Spring Harb Perspect Biol*. 2016;8(10):a023879

1.1.3 *Staphylococcus aureus* Phage Product, AP-SA02

Based on a comprehensive series of in vitro and in vivo studies assessing antimicrobial potential and bioavailability, AP-SA02 is an optimized product comprised of [redacted] lytic phages with desirable therapeutic properties. In addition to infecting over 95% of SA clinical isolates, AP-SA02 is highly selective for SA, active against SA biofilms, viable in relevant biological fluids, and is cooperative with current standard of care antibiotics. Please see the Investigator's Brochure for details.

1.2 Rationale

This is a Phase 1b/2a first-in-human study evaluating multiple doses of AP-SA02 as an adjunct to best available therapy (BAT) in adults with SAB. The aim of this study is to examine the safety and tolerability of multiple ascending IV doses of AP-SA02 (Phase 1b). The study is also designed to evaluate the efficacy, safety, and tolerability of multiple doses of AP-SA02 as an adjunct to BAT compared to BAT alone (Phase 2a).

These data will be used to support further clinical development of AP-SA02 for treatment of SAB.

1.3 Risk/Benefit

1.3.1 Benefits

1.3.1.1 Known benefits

The clinical benefit of AP-SA02 remains to be established.

1.3.1.2 Potential benefits

Subjects participating in this study might have a benefit regarding the clinical course of their SA infection. Results from the proposed study may be useful in developing a new antimicrobial therapy for SA infection.

1.3.2 Risks

1.3.2.1 Known risks

No clinical studies have been performed and, as a consequence, adverse drug reactions have not been identified.

1.3.2.2 Potential risks

All therapies have the potential to cause adverse experiences. The risks associated with blood sampling for safety or pharmacokinetic (PK) purposes are limited and the volume of blood needed is well below the acceptable limits for adults. Study intervention will be provided in addition to, not in replacement of, standard of care supportive and symptomatic therapy.

1.3.3 Overall Risk/Benefit Assessment

Based on the available data and proposed safety measures, the overall benefit/risk assessment for AP-SA02 clinical studies is deemed acceptable for the reasons described below.

Several safety measures will be implemented to potentially minimize the risk to subjects, including:

- Utilization of selection criteria which exclude subjects who may potentially be at higher risk of experiencing an adverse event (AE);
- Females of childbearing potential (FCBPs) must agree to use a highly effective method of birth control from Day 1 through 60 days following the last dose of study drug;
- Males must agree to use barrier contraception (ie, condoms) from Day 1 through 60 days following the last dose of study drug;
- Utilization of discontinuation and withdrawal criteria. Subjects who prematurely discontinue study intervention for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule;
- At several time points throughout the study (see the Schedule of Procedures in Appendix A), safety parameters, including AEs, vital signs, clinical laboratory evaluations (chemistries, hematology, and coagulation), immunogenicity evaluations, physical examinations, electrocardiograms (ECGs), vital signs, and radiological imaging per standard of care (eg, echocardiogram) will be assessed;
- Follow-up visits are scheduled after the last intake of study drug, or after withdrawal, for final study-related assessments; and
- A Data Review Committee (DRC) will monitor and review data on a regular basis to ensure the continuing safety of the participants enrolled in this study.

1.4 Intent to Benefit

All subjects will receive additional safety monitoring as required per the protocol, in addition to the standard of care they would receive and will still receive, if they did not participate in the clinical study. While standard of care varies by institution, the additional safety monitoring all

study subjects will receive per the AP-SA02-101 protocol includes, but is not limited to, the following:

- Daily blood cultures and use of a rapid diagnostic at sites with this capability in which it is not standard of care;
- Increased vital sign monitoring (temperature, heart rate, and blood pressure);
- Additional blood chemistry, hematology, coagulation, C-reactive protein (CRP), interleukin (IL)-10, and procalcitonin testing;
- Additional oversight from local study physician(s), nurses, and research staff, as well as physicians and medical personnel at the Sponsor and Clinical Research Organization; and
- Continued follow-up and monitoring after hospital discharge.

Due to variation in standard of care at each institution, participation in this clinical study provides every subject with a personalized and thorough hospital experience provided for by the designated study clinical team in addition to the standard of care team, with continued oversight following discharge through EOS (28 days after the end of BAT). With a clear mechanism of follow-up defined in the study protocol, subjects or legally authorized representatives (LARs) can discuss post-hospitalization status with their study physician allowing identification of SAB-related sequelae. Post-hospitalization follow-up, and close monitoring while hospitalized, may lead to better outcomes for all subjects enrolled in the study.

2 STUDY OBJECTIVES

2.1 Phase 1b

The objective of Phase 1b is to evaluate the safety and tolerability of multiple ascending IV doses of AP-SA02 or placebo as an adjunct to BAT compared to BAT alone in subjects with SAB.

2.2 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.

3 STUDY DESCRIPTION

Adult hospitalized subjects who have a positive blood culture for SA and require a minimum of 14 days (uncomplicated SAB) or 28 days (complicated SAB) and a maximum of 56 days of IV antibiotic therapy may be eligible for this study. Prior to any study screening evaluations, the subject (or LAR) must sign an informed consent form (ICF). Subjects will be assessed for all inclusion and exclusion criteria, source and distal site(s) of infection, presence of endocarditis, significant comorbidities, and National Early Warning Score 2 (NEWS2) score. Screening assessments will be completed from Day -3 to Day -1. After all eligibility criteria are met, the subject will be randomized. Subjects not fulfilling the eligibility criteria and not randomized may be rescreened for participation if their eligibility characteristics change. Screening procedures that fall within the screening window do not need to be repeated.

Blinded study drug will be initiated on Day 1 and administered every 6 hours through Day 5. The BAT must be planned for a minimum of 14 days (uncomplicated SAB) or 28 days (complicated SAB) and a maximum of 56 days (inclusive of the days on BAT prior to study enrollment/randomization) based on the clinical presentation of the subject and the clinical judgment of the Investigator. Visits from Day 1 through Day 7 should be performed in an inpatient location.

All subjects will receive antibiotics that are chosen by the Investigator and are per local standard of care. If subjects with MSSA isolates are intolerant to beta-lactam therapy, an alternative antibiotic considered to be BAT, is acceptable. The BAT may have been started before randomization in most subjects.

3.1 Summary of Study Design

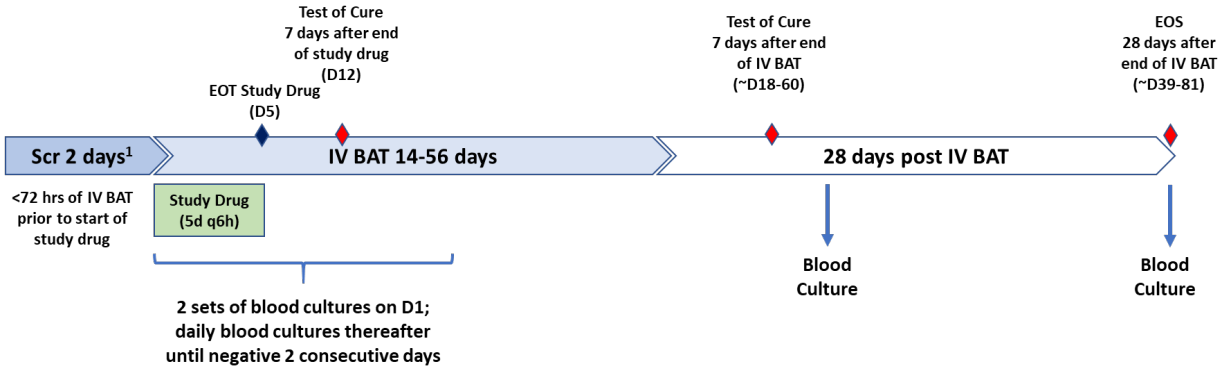
This is a first-in-human, prospective, Phase 1b/2a, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study to assess the safety, tolerability, and efficacy of multiple IV doses of AP-SA02 as an adjunctive therapy to BAT and compared to BAT alone for the treatment of SAB. This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

Figure 2 shows the study schema.

Figure 2. Study Schema



Note: EOT for IV BAT is dependent on the duration of the Investigator prespecified antibiotic therapy (14 days [uncomplicated SAB] or 28 days [complicated SAB] to 56 days).
1. The screening period will be up tp 3 days.
BAT = best available therapy; D/d = day; EOS = End of Study; EOT = End of Treatment; hrs = hours; IV = intravenous(ly); q6h = every 6 hours; SAB = *Staphylococcus aureus* bacteremia; Scr = Screening.

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:

<u>Phase 1b</u>

- 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.

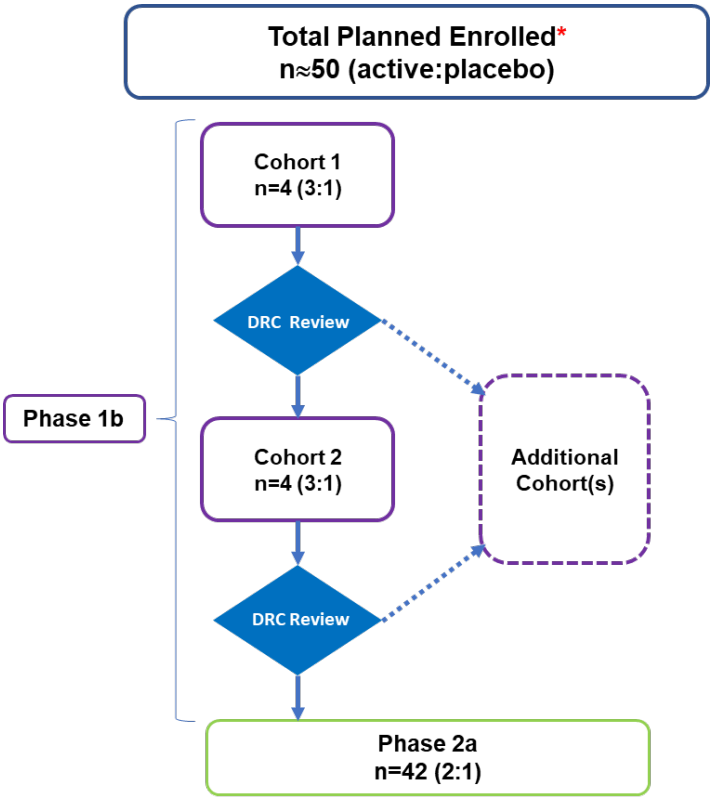
  Additional cohort(s) (up to 3) as determined after DRC review.

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.

Figure 3 shows the study cohort progression.

Figure 3. Study Cohort Progression



*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.
DRC = Data Review Committee; MRSA = methicillin-resistant *Staphylococcus aureus*; n = number.

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. 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.

Based on these evaluations and DRC recommendation, the Sponsor will determine if additional MRSA subjects will need to be enrolled in order to ensure adequate distribution of MRSA subjects between treatment arms.

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.

3.2 Data Review Committee

The DRC will be comprised of members with pertinent expertise who will review emerging blinded safety data at appropriate times throughout the study, as described in this protocol and as set forth in the DRC Charter.

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.

In addition, ad hoc reviews of blinded safety data will be performed throughout the study by appropriate study personnel and the Medical Monitor. The DRC can convene for ad hoc meetings if deemed necessary by the Sponsor or Medical Monitor through ongoing trend reviews or if a study stopping rule has been met; see Section 4.3.

3.3 Study Indication

The indication for this study is the treatment of bacteremia due to SA.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects who meet all inclusion criteria and none of the exclusion criteria during the 2-day (or 3-day upon discussion with the Medical Monitor or Sponsor) screening period will be considered eligible for enrollment in the study.

4.1 Inclusion Criteria

Inclusion criteria for Phase 1b and 2a

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Is able and willing to provide written informed consent or have consent provided by an LAR;
2. Is a hospitalized male or female adult subject aged 18 years or older at time of consent;
3. Has SAB identified from at least 1 blood culture or from a rapid diagnostic test within 72 hours of randomization. Time of positive blood culture starts from when specimen is collected for blood culture;
4. Has a plan for source control within 3 days after randomization to be completed within 7 days of randomization if relevant (eg, abscess drainage, washout or debridement of infected material) or has source already controlled;
5. If an FCBP, the subject must agree to use a highly effective method of birth control (defined as those, alone or in combination, that result in a low failure rate [ie, less than 1% per year]) from Day 1 through 60 days following the last dose of study drug;

   Note: FCBP must have a negative serum pregnancy test within 72 hours prior to randomization. An FCBP is any female, regardless of sexual orientation, who meets the following criteria: has not undergone a hysterectomy or bilateral oophorectomy, or has not been naturally postmenopausal for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).
6. If a male subject, the subject must agree to use barrier contraception (ie, condoms) from Day 1 through 60 days following the last dose of study drug;

Additional inclusion criteria for Phase 2a only

7. Has at least 1 of the following signs/symptoms at or within 72 hours prior to randomization:
   a. 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;
   b. Heart rate >90 beats per minute;
   c. Respiratory rate >20 breaths per minute;
   d. White blood cell count ≥12.0 × 10^9 cells/L or ≤0.4 × 10^9 cells/L, or ≥10% immature neutrophils;
   e. Systolic blood pressure <90 mmHg; and/or
   f. Pain associated with focal site of infection.

8. Has at least 1 of the following:
   a. At the time of positive SA blood culture was undergoing chronic intermittent hemodialysis or peritoneal dialysis;
   b. Positive blood culture for SA after 2 or more days on anti-staphylococcal antibiotic treatment;
   c. Temperature ≥38.0°C (100.4°F) at ≥72 hours after initial blood culture;
   d. SAB associated with signs or symptoms of metastatic foci and/or hematogenous seeding, including, but not limited to, septic thrombophlebitis, osteomyelitis (not including osteomyelitis associated with hardware or prosthetic joint infection), deep soft tissue abscess, septic arthritis/bacterial native joint infection, septic pulmonary emboli/infarction, visceral soft tissue abscess, or empyema confirmed by physical examination, imaging, or culture; and/or
   e. Presence of right-sided SAB endocarditis (native valve) by modified Duke criteria (Appendix C), with no clinical evidence of cerebral foci requiring at least 28 days of anti-SA antibiotic treatment.

4.2 Exclusion Criteria

Exclusion criteria for Phase 1b and 2a

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Has concomitant growth of organisms besides SA in a blood culture, excluding coagulase-negative staphylococci (eg, *Staphylococcus epidermidis*) and other species when considered by the primary team to represent contaminants;
2. Has, in the 7 days prior to randomization, a positive culture with SA that has a known minimum inhibitory concentration to daptomycin >1 mcg/mL or vancomycin >2 mcg/mL;
3. Has received treatment with any potentially effective (anti-SA) systemic antibiotic for more than 72 hours within 7 days prior to randomization;

   Note: Subjects who have received >72 hours of antibiotics and have documented resistance to administered therapy or persistent SAB on 2 blood cultures obtained over 72 hours may be considered for the study with Sponsor or Medical Monitor approval.
4. Has known or suspected left-sided infectious endocarditis by modified Duke criteria (Appendix C);
5. Has a suspected endovascular source of bacteremia including, but not limited to, perivalvular abscess, left ventricular assist device (cardiac pacemaker or automatic implantable cardioverter-defibrillator [AICD]), AICD wire, arteriovenous graft, prosthetic valves, or valve rings;

   Note: A subject with a suspected endovascular source of infection may be considered if that source is planned to be removed within 72 hours of randomization.

6. Has a known or suspected brain abscess;

   Note: A subject with epidural abscess may be included if they do not require surgical intervention and have minimal neurologic deficits.

7. Community acquired pneumonia, nosocomial pneumonia due to pathogens **other than** *S. aureus.*

   Note: patients with pneumonia due to *S. aureus* are eligible for enrollment;

8. Has osteomyelitis that is associated with hardware or prosthetic joint infection;

   Note: A subject with a suspected osteomyelitis with hardware or prosthetic joint infection may be considered if that source is planned to be removed within 72 hours of randomization.

9. Has refractory shock with persistent hypotension (ie, mean arterial pressure <60 mmHg) that is unresponsive to fluids and vasopressors at Screening;
10. Has a known allergy to phage products;
11. Is a female subject who is pregnant or breastfeeding;
12. In the Investigator's opinion, the subject is unable to understand and comply with protocol requirements, instructions, and protocol-stated restrictions and is unlikely to complete the study as planned;
13. Is currently enrolled in another investigational interventional trial and has received any investigational treatment within 28 days prior to consent or will continue to receive any investigational treatment during the study;
14. Has anticipated requirement for effective systemic bacterial therapy unrelated to the treatment of SAB or other planned use of systemic antibacterial therapy (eg, treatment of acne vulgaris);

    Note: Prophylactic antibiotics for operative dental procedures and chronic suppressive oral antibiotic therapy after completion of a minimum of 14 days (uncomplicated SAB) or 28 days (complicated SAB) to 56 days of BAT are permitted.

15. Has, at Screening, 1 or more of the following laboratory abnormalities:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN) if total bilirubin <2 × ULN; and/or
    b. ALT or AST >2.5 × ULN if total bilirubin is >2 × ULN.
16. Has, in the opinion of the Investigator, an acute or chronic medical condition (eg, seizure disorder in status epilepticus, acute coronary syndrome, end-stage renal disease with no plan to dialyze, metastatic malignancy, chronic severe liver disease, or other disease) or other finding that is clinically significant that could put the subject at risk or harm by participating in the study;
17. Has, in the opinion of the Investigator, evidence of a concurrent medical illness that is immediately life-threatening, has life-expectancy of less than 3 months, or is likely to elect palliative care within 3 months;

18. Has any known previous exposure to AP-SA02 or prior participation in Study AP-SA02-101;
19. History of AIDS (human immunodeficiency virus positive with an AIDS-defining condition and/or CD4 count <200 cells/mm^3) or chronic severe liver disease due to hepatitis B virus (HBV) or C virus (HCV) within 90 days prior to Screening.

Additional exclusion criteria for Phase 1b only

20. Has all of the following signs/symptoms at or within 24 hours prior to randomization:
    a. 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;
    b. Heart rate >90 beats per minute;
    c. Respiratory rate >20 breaths per minute;
    d. White blood cell count ≥12.0 × 10^9 cells/L or ≤0.4 × 10^9 cells/L, or ≥10% immature neutrophils; and
    e. Systolic blood pressure <90 mmHg.

4.3 Stopping Criteria

The DRC will oversee the safety and tolerability of AP-SA02 during the study and determine if it is acceptable to continue. However, safety and tolerability data will be reviewed on an ongoing basis by the Medical Monitor and stopping rules will be applicable starting with dosing of the first subject.

4.3.1 Criteria for Potential Interruption or Discontinuation of Study Drug in Individual Subjects

In the event that any of the following criteria are encountered, the Investigator should review the AE with the Medical Monitor as soon as feasible. The Investigator will hold the next infusion pending that review has been completed. The Investigator and Medical Monitor in consultation with the Sponsor will decide whether to continue to hold study treatment pending additional information or to discontinue study treatment.

- ≥Grade 3 AE or clinically significant laboratory abnormality per Common Terminology Criteria for AEs (CTCAE) version 5.0 considered attributable to AP-SA02 (confirmed by unblinding). If the event or laboratory test is not listed in the CTCAE, the event or laboratory test should be graded by applying the CTCAE guidelines detailed in Section 8.1.3; or

  Note: Clinically significant laboratory abnormalities classified per above should be confirmed with a repeat test within 24 hours.

- Clinical signs or symptoms of severe allergic or anaphylactic reaction.
- Any SAE considered to be at least possibly related to AP-SA02 (confirmed by unblinding).

Any subject who prematurely discontinues from study drug should continue to be followed per protocol for safety and key efficacy endpoints. Study staff should make every effort to complete the full panel of assessments scheduled for Early Termination of Treatment (ETOT). The reason

and date of discontinuation will be documented in the eCRF and the subject should continue to complete all safety assessments at subsequent study visits.

4.3.2 Criteria for Ad Hoc Data Review Committee Review of Study

In the event that any of the following criteria are encountered, the DRC may, as described in the DRC Charter, convene to review available data and make recommendations, including but not limited to, if the cohort should stop or pause the study, enrollment, or treatment and/or make recommendations to modify the protocol (ie, decrease or change the dose of study drug, modify safety monitoring):

Phase 1b criteria

- If any unacceptable toxicity (as determined by the Investigator or Sponsor's Medical Monitor) occurs;
- If ≥1 serious AE (SAE) considered attributable to AP-SA02 (confirmed by unblinding) occurs; or
- If ≥2 of all treated subjects experience similar SAEs or Grade 3 (CTCAE version 5.0) AEs meeting the following criteria:
  - Onset between start of dosing and 7 days after last dose; and
  - Considered attributable to AP-SA02 (confirmed by unblinding).

  Note: All ≥Grade 3 (CTCAE version 5.0) laboratory abnormalities should be confirmed with a repeat test within 24 hours.

Phase 2a criteria

- If ≥1 serious AE (SAE) considered at least possibly attributable to AP-SA02 (confirmed by unblinding) occurs; or
- If ≥2 of all treated subjects experience the same or similar adverse events that are Grade 3 or higher meeting the following criteria:
  - Onset between start of dosing and 28 days after last dose; and
  - Considered attributable to AP-SA02 (confirmed by unblinding).

  Note: All ≥Grade 3 (CTCAE version 5.0) laboratory abnormalities should be confirmed with a repeat test within 24 hours.

Further enrollment of subjects and dosing of the investigational product should be halted until a safety review of the event is completed. If the DRC recommends, and the Sponsor then implements, stopping study treatment and, subsequently, the Sponsor, independent of or following a DRC recommendation, proposes to restart the study, a substantial amendment will be submitted to regulatory agencies, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Office of Human Research Oversight (OHRO). The study will not restart until the amendment has been approved by regulatory agencies and IRB/IECs. These requirements are not applicable if the Sponsor pre-emptively pauses study treatment for subject safety pending DRC review and the DRC recommends resuming study treatments and/or any study modifications recommended do not represent substantial protocol changes.

4.4 Withdrawal or Modification of Individual Subject Study Participation

Participation of a subject in this clinical study will be discontinued if:

- The subject or LAR withdraws consent or requests discontinuation from the study for any reason; or
- The subject becomes pregnant.

The Investigator may with concurrence of Medical Monitor or Sponsor discontinue or modify a subject's study participation for any of the following reasons:

- Occurrence of any AE (whether or not attributed to study treatment), medical condition, or circumstance that does not allow the subject to adhere to the requirements of the protocol or continued participation is not in the best interest of the subject; or
- Subject failure to comply with protocol requirements or study-related procedures.

Subjects will be considered lost to follow-up if, after completing study treatment, they fail to attend a required visit or are unresponsive despite 3 attempts to reach them by telephone, text message, email, and/or regular postal mail. Such subjects may, with the concurrence of the Sponsor, be terminated from study participation and notification sent by registered mail to the last known address. These contact attempts will be documented in both the study record and the subject's medical record.

Subjects who discontinue prematurely from the study or whose participation is modified will be strongly encouraged to complete the full panel of safety assessments scheduled for the ETOT. The reason for subject withdrawal must be documented in the eCRF.

Withdrawn or lost to follow-up subjects may be replaced to ensure adequate numbers of evaluable subjects at the discretion of the Sponsor. Subjects who discontinue for study drug-related safety or tolerability reasons will not be replaced.

4.4.1 Termination of the Study

The Sponsor may terminate the study at any time and for any reason, including but not limited to recommendation by the DRC, new non-clinical information regarding the study treatment, or if required by regulatory authorities.

Depending on the circumstances, termination procedures may or may not include completion of study treatment as assigned for all subjects who have received at least 1 dose. After a subject receives their last treatment, all EOS treatment safety evaluations will be completed.

5 STUDY TREATMENTS

5.1 Treatment Groups

The dose level of AP-SA02 to be administered to each subject will be determined based on the cohort assignment. Table 1 shows the dosage (in PFU) per cohort. The dose level to be tested in the Phase 1b additional cohort(s) (up to 3) and Phase 2a will be based on the observed safety and tolerability in the prior dosed subjects.

Table 1. Dosage per Cohort

Phase Cohort	Each Dose (Approximate PFU/phage)	Each Dose (Approximate Total PFU)	Total Daily Dose (Approximate Total PFU)	Total Dose Over 5 Days (Approximate Total PFU)
Phase 1b				
1	1×10^9	2×10^9	8×10^9	4×10^{10}
2	1×10^{10}	2×10^{10}	8×10^{10}	4×10^{11}
Phase 2a	TBD	TBD	TBD	TBD
PFU = plaque-forming units; TBD = to be determined.				

5.2 Rationale for Dosing

[redacted]

[redacted]

5.3 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 (CRO) study team, and Investigators.

5.4 Breaking the Blind

Unblinding at the request of the Investigator should occur only in the event of severe AE or SAE that is reasonably assessed as treatment related and for which it is necessary to know the treatment assignment to determine an appropriate course of therapy for the subject. If the Investigator must identify the treatment assignment of an individual subject, the Investigator or qualified designee should request the treatment assignment from the centralized randomization system. They should not attempt to get this information from the site's unblinded study team. The Investigator is advised to not reveal the treatment assignment to any other site, Sponsor, or CRO personnel.

Whenever possible, prior to proceeding with unblinding, the Investigator will contact the Sponsor to discuss the need to break the blind. The Investigator will notify the Sponsor as soon as is practical in the event of the study blind being broken and will document the reason. In the event this is not possible, the Investigator should contact the Sponsor as soon as possible to discuss the event without revealing the treatment assignment. The Investigator must document the subject identification, the date and time of breaking the blind, and must clearly explain the reasons for breaking the blind.

Medically necessary care should not be delayed for unblinding information (ie, the Investigator should treat the subject based on the subject's signs/symptoms without waiting for the unblinding process to be completed).

Subjects who are unblinded and discontinue study drug should continue to complete all safety assessments at subsequent study visits.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

[redacted]

Study drug will be labeled according to local regulatory requirements.

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

5.5.2 Study Drug Preparation and Dispensing

[redacted]

5.5.3 Study Drug Administration

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. For a delayed dosing administration, if the dose is delayed by <2 hours, the original schedule, relative to the first dose of study drug should be kept. If dose administration is delayed by >2 hours, the next dose, and all subsequent doses, should be based on the timing of the delayed dose and subjects should receive all study drug doses, even if this extends the treatment period. Sites should complete dose administration within ± 30 mins of the scheduled dose administration time. 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.

5.5.4 Treatment Compliance

Details of the date and time when the study drug is administered, along with any deviation from the procedure described in this protocol, will be recorded in the subject's source documents and the eCRF.

5.5.5 Storage and Accountability

[redacted]

The Investigator will agree to not supply the study drug to any person other than the sub-Investigators, designated study staff, and the subjects participating in the study.

The Investigator will return or destroy all study drugs according to the Pharmacy Manual. The list of destroyed vials must be recorded. The Investigator must agree to neither dispense the study drug from, nor store it at, any study site other than the study site agreed upon with the Sponsor. Details on study drug accountability and destruction will be included in the Pharmacy Manual.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

The following medications and/or procedures are prohibited:

- Any investigational treatment within 28 days of Screening; and
- Anticipated requirement for effective systemic bacterial therapy unrelated to the treatment of SAB or other planned use of systemic antibacterial therapy (eg, treatment of acne vulgaris).

  Note: Prophylactic antibiotics for operative dental procedures and chronic suppressive oral antibiotic therapy after completion of a minimum of 14 days (uncomplicated SAB) or 28 days (complicated SAB) to 56 days of BAT are permitted.

5.6.2 Documentation of Prior and Concomitant Medication Use

Any treatment given in addition to the study drug during the study will be regarded as a concomitant medication and must be recorded on the appropriate eCRF.

Any relevant medications received in the 28 days prior to randomization must be recorded on the appropriate eCRF, along with the reason for use, dates of administration, and dosages.

Concomitant medications, including over-the-counter medications and herbal supplements, should be kept to a minimum during the study. However, if these are considered necessary for the subject's welfare and are unlikely to interfere with the study drug, they may be given at the discretion of the Investigator and recorded in the subject's source documents and the eCRF.

6 STUDY PROCEDURES

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

7 EFFICACY ASSESSMENTS

7.1 Phase 1b Multiple Ascending Dose Safety Endpoints

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

- Treatment-emergent AEs (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;
- Vital signs; and
- Clinical laboratory evaluations.

The endpoints listed in Section 7.2 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.

7.2 Phase 2a Endpoints

The Phase 2a endpoints are the following:

- Time to reach a NEWS2 score ≤2 maintained for at least 24 hours or hospital discharge (whichever comes first) for subjects on active drug versus placebo in the Microbiological Intent-to-Treat (MITT) Population;
- Clinical Improvement or response at TOC for study drug (Day 12) in the MITT Population;
- 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) in the MITT Population;
- 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 (eg, 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 (eg, joint fluid, tissue) >14 days from randomization; or
  - Blood culture positive for SA >72 hours after the first blood cultures showing CL of SAB (defined as 2 consecutive days with negative SA blood cultures).
- Time to resolution of SAB;
- Time to hospital discharge (and time to hospital discharge readiness);
- Need for and duration of intensive care unit stay;
- Need for and duration of endotracheal mechanical ventilation;
- Need for and duration of noninvasive pressure ventilation (eg, 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 (eg, 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 (Appendix D) 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 CRP from baseline to EOS;
- Change in IL-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.

7.3 Efficacy Outcome Assessments

Clinical outcome will be assessed at TOC for study drug, TOC for BAT, and EOS, and will be based on the definitions in Table 2. The signs and symptoms of SAB include 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.

Note: On Day 7, the Investigator will provide an assessment of whether additional imaging is needed for potential metastatic infection based on clinical signs/symptoms of SA infection.

Table 2. Definition of Clinical Outcome

Clinical Outcome	Definition
Improvement or response (meets all criteria)	• The subject is alive; • Eradication of SAB based on blood cultures obtained through Day 7; • No new metastatic foci including and after Day 7 or complications of SAB; and • Resolution of SAB-related clinical signs and symptoms that were present at baseline.
No response (meets 1 or more criteria)	• Death due to any cause; • Persistence of bacteremia based on blood cultures obtained through Day 7 or recurrence of SAB; • Development of new metastatic foci after Day 7 or other complications related to SA; or • Persistence, worsening, or recurrence of attributable signs and symptoms of SAB which were present at baseline.
Indeterminate	Study data not available for the evaluation of efficacy due to lost to follow-up, withdrawal of consent, or missing data.

SA = *Staphylococcus aureus*; SAB = *Staphylococcus aureus* bacteremia.

7.4 National Early Warning Score 2

Table 3 presents the NEWS2 scoring system. 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.

Table 3. 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	

Consciousness definitions: alert, fully awake (spontaneous opening of eyes, will to respond to voice, has motor function); CVPU: new Confusion, responds to Voice with eyes, voice or motor (event if limited response); responds to a Pain stimulus (likely only withdrawal if not respond to voice); Unresponsive (commonly referred to as unconscious) does not give any eye, voice, or motor response to voice or pain.
CVPU = Confusion, Voice, Pain, Unresponsive; SpO_2 = oxygen saturation.
Source: Royal College of Physicians. *National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS.* Royal College of Physicians; 2017. Accessed 23 March 2021. https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

Table 4 presents the NEWS2 thresholds and associated clinical risk. The aggregate score represents the risk of death from sepsis and indicates the urgency of the response:

- 0 to 4: low risk (a score of 3 in any individual parameter is low-medium);
- 5 to 6: medium risk; or
- 7 or more: high risk.

Table 4. National Early Warning Score 2 Thresholds and Clinical Risk

NEW score	Clinical risk
Aggregate score 0–4	Low
Red score Score of 3 in any individual parameter	Low–medium
Aggregate score 5–6	Medium
Aggregate score 7 or more	High

NEW = National Early Warning.
Source: Royal College of Physicians. *National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS.* Royal College of Physicians; 2017. Accessed 23 March 2021.
https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

7.5 Anti-Phage Antibodies

Serum samples will be collected prior to the first dose on Day 1, Day 7, TOC for study drug (Day 12), and EOS to determine if titers of anti-phage antibodies are detectable.

7.6 Phage Clearance

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.

7.7 Blood Cultures

Blood cultures and susceptibility testing will be performed by a local microbiology laboratory per the laboratory's standard procedures and standard of care at Screening, daily from Day 1 through Day 7 as indicated in the Schedule of Procedures (Appendix A). Blood cultures should be collected regardless of clinical indication at Day 1, EOT for study drug (Day 5), Day 7, TOC for study drug (Day 12), TOC for BAT, and EOS. Isolates of SA from positive blood cultures for standard of care blood cultures used to assess eligibility as well as from study cultures will be sent to the central microbiology laboratory for confirmations of identification and susceptibility testing.

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 as 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 to evaluate for microbiological cure and sustained cure.

Subjects' SA blood culture isolates will be classified as MSSA or MRSA.

7.7.1 Criteria for Positive Blood Culture for Eligibility

For study eligibility, subjects must have blood culture positive for SA determined by rapid diagnostic or conventional method from blood culture specimens collected within 72 hours prior to randomization. Time of positive blood culture starts from when specimen is collected for blood culture. The site microbiological laboratory is encouraged to use a Food and Drug Administration (FDA)-cleared, European Conformity-in vitro diagnostic certified, or Sponsor-approved rapid diagnostic test to identify SA if it is available at the site. Subjects may be enrolled based on a positive result from a rapid diagnostic test, but confirmation of SA by conventional culture methods will be the required objective measure for SA in the study analyses for efficacy. Subjects who are enrolled based on a positive rapid diagnostic test, but have negative blood culture result for SA, will discontinue study drug if the Investigator decides to discontinue antibiotic treatment of SAB. In the event subjects will complete the EOT for the study drug safety evaluations and have additional safety follow-up 7 days after last dose in person, if feasible, or by phone.

The study site's local microbiology laboratory will perform identification and in vitro susceptibility testing to standard of care antibiotics according to local practices for all blood cultures positive for SA. The Investigator should ensure that all SA isolates obtained from all cultures performed during the study period (and wherever possible, the isolate from the initial positive culture for SA) are sent to the central microbiology laboratory, as described in the Laboratory Manual. The local microbiology laboratory will be required to prepare SA isolates for shipment to the central microbiology laboratory as outlined in the Laboratory Manual. Although only SA isolates should be sent to the central microbiology laboratory, all organisms isolated from blood cultures performed during the study should be recorded in the electronic data capture (EDC) system. The central microbiology laboratory will confirm the identification and perform in vitro susceptibility testing and phage susceptibility of isolates in batches for the purposes of the final study analysis; the central microbiology laboratory will not be providing results to the sites. Further evaluation to identify the potential mechanism of resistance may be performed.

7.7.2 Cultures From Sterile Sites

Specimens from sterile sites (eg, joint fluid, tissue) will be collected as clinically indicated and sent to the site's local microbiology laboratory for culture and susceptibility per standard practice. Results of the cultures will be entered into the EDC system. Isolates of all SA isolates will be sent to the central microbiology laboratory for confirmation of identification and susceptibility testing as outlined in the Laboratory Manual.

7.8 Microbiological Outcome

Microbiological response will be determined programmatically as 1 of the following outcomes based on the results of blood cultures and/or urine cultures at EOT for study drug (Day 5), TOC for study drug (Day 12), TOC for BAT, and EOS. A microbiological favorable assessment will include eradication and presumed eradications, as detailed in Table 5.

Table 5. 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.
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.
Recurrence	A positive blood culture for SAB at any time after documented eradication or presumed eradication.

SA = *Staphylococcus aureus*; SAB = *Staphylococcus aureus* bacteremia.

7.9 Pharmacokinetic Assessments

PK samples for AP-SA02 will be collected from subjects enrolled at predetermined/qualified PK sites on the following days and times, and evaluated based on AP-SA02 levels as measured by venous blood samples:

- Day 1: pre-dose (-60 minutes) and , 0.5 hours (±15 minutes), 1 hour (±15 minutes), and 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; and
- Day 6: 24 hours (±30 minutes) post last dose.

PK parameters of AP-SA02 will be assessed from subjects enrolled at predetermined/qualified PK sites with serial PK sampling, including maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), terminal elimination half-life ($t_{½}$), CL, volume of distribution (V_z), area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable time (AUC_{0-t}), and AUC from time 0 to infinity ($AUC_{0-\infty}$). Additional details regarding PK analysis methodology will be described in the Statistical Analysis Plan (SAP).

7.10 Pharmacodynamic Assessments

Pharmacodynamics will be evaluated based on the following:

- Time to resolution of signs/symptoms of bacteremia present at Screening;
- Time to resolution of bacteremia based on blood cultures; and/or
- Change in CRP from baseline.

8 SAFETY ASSESSMENTS

Safety will be assessed by monitoring AEs, vital signs, laboratory data (chemistries, hematology, and coagulation), immunogenicity evaluation, physical examinations, ECGs, and radiologic imaging per standard of care (eg, echocardiogram).

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent. Subjects should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at Screening, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For AP-SA02, the reference safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The severity of all AEs should be graded according to the CTCAE version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

Assessment of severity

The severity of all AEs should be graded according to the CTCAE version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; or
- CTCAE Grade 5: Death related to the AE.

Assessment of causality

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug-

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

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

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a preexisting condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live

too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE 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 or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until end of study must be reported to [redacted] Clinical Safety within 24 hours of the knowledge of the occurrence.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, [redacted] Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] Safety at [redacted] (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, subject discharge summary or autopsy reports) to [redacted] Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a subject becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug immediately and the subject should be withdrawn from the study. ETOT procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to [redacted] Clinical Safety within 24 hours of knowledge of the event. [redacted] Clinical Safety will then

provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to [redacted] Clinical Safety.

If the female partner of a male subject becomes pregnant while the subject is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify [redacted] Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to [redacted] Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, to the Central Ethics Committee, OHRO, and other designated officials as needed (Department of Defense) and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities concerned, and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational drug product.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of subjects missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

8.7 Clinical Laboratory Evaluations

Blood samples for chemistry, hematology, coagulation, CRP, and procalcitonin will be obtained at Screening, daily from Day 1 through EOT for study drug (Day 5), Day 7, TOC for study drug (Day 12), TOC for BAT, and EOS. Clinical laboratory assessments will be performed post-dose after the second infusion on Day 1. All standard blood tests will be analyzed centrally by a certified clinical laboratory and details on the collection and processing of central laboratory samples can be found in the Laboratory Manual.

Following study drug dosing, the Investigator will review laboratory values for those outside of normal range and will be required to conduct clinically appropriate follow-up procedures. Clinical significance of the values outside of normal ranges will be assessed by the Investigator.

The analytes listed in Appendix B will be measured at Screening, daily from Day 1 through EOT for study drug (Day 5), Day 7, TOC for study drug (Day 12), TOC for BAT, and EOS.

8.8 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) at any time within the first 7 days or new need for renal replacement therapy between Day 1 and EOS.

8.9 Vital Signs

Vital signs will be measured at Screening, prior to infusion (-1 hour window) daily on Day 1 through Day 7, TOC for study drug (Day 12), TOC for BAT, and EOS. 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. During the Treatment Period, vital signs should be obtained prior to each infusion (-1 hour window). 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.

8.10 Electrocardiogram

A 12-lead ECG will be conducted at Screening, post first dose on Day 1, Day 3, EOT for study drug (Day 5), TOC for study drug (Day 12), TOC for BAT, and EOS. The Investigator will evaluate ECGs for abnormal results and document the clinical significance of these, reporting as AEs or medical history where appropriate.

8.11 Physical Examination

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.

A complete physical examination will include evaluation of head, eyes, ears, nose, and throat (HEENT), neck, lungs, heart, chest, abdomen, extremities, neurologic status, skin for evidence of emboli, palpation for signs of pain, and any other notable conditions. 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. Pain on a physical examination should trigger diagnostic testing for metastatic foci of infection.

9 STATISTICS

9.1 Analysis Populations

The following analysis populations will be defined for the Phase 1b and Phase 2a cohorts:

- Intent-to-Treat (ITT): all randomized subjects regardless of whether or not study drug is received;
- Phage-Sensitive ITT: all randomized subjects who receive both BAT and study drug, and whose SA isolate is sensitive to at least 1 of the phage components that comprise the study drug;
- Safety: all randomized subjects who receive at least 1 dose of study drug;
- MITT: all subjects in the ITT Population with baseline SAB and who receive at least 1 dose of study drug; and
- PK: all subjects (enrolled at predetermined/qualified PK sites) who have at least 1 PK sample drawn.

An SAP will be prepared and finalized before database lock and analyses of data. Summary data will be tabulated and presented by treatment group.

9.2 Statistical Methods

Predefined or post-hoc statistical analysis for all subjects may be performed to compare the treatment groups that are randomized based on the following:

- MRSA subjects (subgroup will be for Phase 2a only);
- Blood cultures positive for SA on Day -1 prior to study drug administration; and
- Source control achieved (eg, abscess drainage, catheter or intravascular device removal, washout of infected joint).

Note: The final SAP will finalize the subgroup analyses.

9.2.1 Analysis of Phase 2a Endpoints

Phase 2a endpoints will be summarized descriptively for each treatment arm using appropriate proportions and means depending on the data type along with the 95% confidence interval. No formal hypothesis testing is planned.

Additional details will be described in the SAP.

9.2.2 Analysis of Safety

Safety will be assessed by monitoring AEs, vital signs, laboratory data (chemistries, hematology, and coagulation), immunogenicity evaluation, physical examinations, ECGs, and radiologic imaging per standard of care (eg, echocardiogram).

9.2.3 Analysis of Pharmacokinetics

PK samples for AP-SA02 will be collected from subjects enrolled at predetermined/qualified PK sites per protocol and evaluated based on AP-SA02 levels as measured by venous blood samples.

PK parameters of AP-SA02 will be assessed from subjects enrolled at predetermined/qualified PK sites with serial PK sampling, including C_{max}, T_{max}, $t_{½}$, CL, V_z, AUC_{0-t}, and $AUC_{0-\infty}$. Additional details regarding PK analysis methodology will be described in the SAP.

9.2.4 Analysis of Pharmacodynamics

Pharmacodynamics will be evaluated based on the following:

- Time to resolution of signs/symptoms of bacteremia present at Screening;
- Time to resolution of bacteremia based on blood cultures; and/or
- Change in CRP from baseline.

9.2.5 Clinical Efficacy Adjudication Committee

The Clinical Efficacy Adjudication Committee (CEAC) will consist of a group of independent clinical experts blinded to treatment allocation and not associated with study conduct. Data obtained for subjects who receive study drug may be reviewed independently by CEAC members. The CEAC members will give their opinion on the diagnosis and classification of the SAB, the adequacy of BAT, the adequacy of source control, and/or the response assessment (overall success or failure). For deaths occurring during the study, a blinded assessment of the attribution of death to SAB or to another cause may be performed by the CEAC members.

9.2.6 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 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.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC and OHRO will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing of subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor and the Clinical Study Agreement has been signed by the institution.

For sites in the European Union, it is the responsibility of the Sponsor or their designee [redacted] to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements, as set forth in the Clinical Study Agreement.

The Investigator must ensure that each study subject or LAR is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject or LAR before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the subject or LAR.

11.4 Subject Card

For sites in the European Union, on enrollment in the study, the subject will receive a subject card to be carried at all times. The subject card will state that the subject is participating in a clinical research study, type of treatment, number of treatments received, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as set forth in the Clinical Study Agreement, and as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible. If planned onsite monitoring visits are not possible because of Coronavirus Disease 2019, remote monitoring may occur, if allowed by local and federal legal and regulatory requirements.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Such data may be used only as set forth in the Clinical Study Agreement. Subjects or their LAR may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms,

source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

[redacted]

11.9 Financial Disclosure

[redacted]

11.10 Insurance and Indemnity

[redacted]

11.11 Legal Aspects

[redacted]

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

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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	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	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 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] and 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.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Direct bilirubin
Estimated glomerular filtration rate [1]	Gamma-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

1. Estimated glomerular filtration rate will be calculated using the Cockcroft-Gault method.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

1. Manual microscopic review will be performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

Serology

Hepatitis B surface antigen	Hepatitis C virus antibody
Human immunodeficiency virus antibody	

Pregnancy Test

Serum β-human chorionic gonadotropin pregnancy test [1]

1. Within 72 hours prior to randomization for females of childbearing potential.

Additional Tests

C-reactive protein	Interleukin-10
Procalcitonin	

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy will be performed only as needed based on positive dipstick test results.

APPENDIX C: MODIFIED DUKE CRITERIA FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS

Table 6. Modified Duke Criteria for Diagnosis of Infective Endocarditis: Definitions of Definite, Possible, and Rejected Endocarditis

Criteria	Definition

Definite IE	• Pathologic criteria:
	  ○ Pathologic lesions – Vegetation or intracardiac abscess demonstrating active endocarditis on histology; **OR**
	  ○ Microorganism – Demonstrated by culture or histology of a vegetation or intracardiac abscess.
	• Clinical criteria:
	  ○ Using specific definitions listed in Table 7:
	  ▪ 2 major clinical criteria; **OR**
	  ▪ 1 major and 3 minor clinical criteria; **OR**
	  ▪ 5 minor clinical criteria.

Possible IE[1]	• Presence of 1 major and 1 minor clinical criteria; **OR** • Presence of 3 minor clinical criteria.
Rejected IE	• A firm alternate diagnosis is made; **OR** • Resolution of clinical manifestations occurs after ≤4 days of antibiotic therapy; **OR** • No pathologic evidence of infective endocarditis is found at surgery or autopsy after antibiotic therapy for ≤4 days; **OR** • Clinical criteria for possible or definite IE not met.

1. The category of possible IE represents a modification from the previously published Duke criteria.
IE = infective endocarditis.
Source: Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633-638

Note: Duke criteria will be captured in the eCRF data for subjects in Phase 2a.

Table 7. Modified Duke Criteria for Diagnosis of Infective Endocarditis: Definitions for Major and Minor Criteria

Criteria	Definition
Major	• Positive blood cultures for IE (1 of the following): o Typical microorganisms consistent with IE from 2 separate blood cultures: ▪ SA; ▪ Viridans streptococci; ▪ *Streptococcus gallolyticus* (formerly *Streptococcus bovis*), including nutritional variant strains (*Granulicatella* spp and *Abiotrophia defectiva*); ▪ HACEK group – *Haemophilus aphrophilus* (subsequently called *Aggregatibacter aphrophilus* and *Aggregatibacter paraphrophilus*), *Actinobacillus actinomycetemcomitans* (subsequently called *Aggregatibacter actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*; ▪ Community-acquired enterococci in the absence of a primary focus. o Persistently positive blood culture: ▪ For organisms that are typical causes of IE – at least 2 positive blood cultures from blood samples drawn >12 hours apart; ▪ For organisms that are more commonly skin contaminants – 3 or a majority of ≥4 separate blood cultures (with first and last drawn at least 1 hour apart). o Single positive blood culture for *Coxiella burnetii* or phase 1 IgG antibody titer >1:800.* • Evidence of endocardial involvement (1 of the following): o Echocardiogram positive for IE: ▪ Vegetation (oscillating intracardiac mass on a valve or on supporting structures, in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation); **OR** ▪ Abscess; **OR** ▪ New partial dehiscence of prosthetic valve. o New valvular regurgitation: ▪ Increase in or change in preexisting murmur not sufficient.
Minor	• Predisposition – IV drug use or presence of a predisposing heart condition (prosthetic heart valve or a valve lesion associated with significant regurgitation or turbulence of blood flow); • Fever – temperature ≥38.0°C (100.4°F); • Vascular phenomena – major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions; • Immunologic phenomena – glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor; • Microbiologic evidence – positive blood cultures that do not meet major criteria **OR** serologic evidence of active infection with organism consistent with IE. Note: Echocardiographic minor criteria eliminated.*

Modifications from the previously published Duke criteria are noted by an asterisk (*).
IE = infective endocarditis; IgG = immunoglobulin G; IV = intravenous(ly); SA = *Staphylococcus aureus*; spp = species.
Source: Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633-638

APPENDIX D: RISK-INJURY-FAILURE-LOSS-END-STAGE RENAL DISEASE CRITERIA

Table 8. Definition of Risk-Injury-Failure-Loss-End-Stage Renal Disease Criteria

Term	Definition
Risk (R)	Increased creatinine 1.5 × or GFR decrease >25%
Injury (I)	Increased creatinine 2 × or GFR decrease >50%
Failure (F)	Increased creatinine level 3 ×, GFR decrease >75%, or creatinine level ≥4 mg/dL
Loss (L)	Persistent acute renal failure or complete loss of function for >4 weeks
ESKD (E)	ESKD for >3 months

ESKD = end-stage kidney disease; GFR = glomerular filtration rate.
Source: Hartzell JD, Neff R, Ake J, et al. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. *Clin Infect Dis*. 2009;48(12):1724-1728