STATISTICAL ANALYSIS PLAN

(Protocol No. ASN100-201)

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of a Single Dose of ASN100 for the Prevention of *Staphylococcus aureus* Pneumonia in Heavily Colonized, Mechanically Ventilated Subjects

DEVELOPMENT PHASE: 2

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CONFIDENTIAL

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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ASN-1	Broadly cross-reactive anti-toxin monoclonal antibody that targets alpha-hemolysin (Hla) and 3 F-components (HlgB, LukF, LukD) involved in forming 4 of the 5 bi-component leukocidins of *Staphylococcus aureus*
ASN-2	Anti-toxin monoclonal antibody that targets the fifth bi-component leukocidin of *Staphylococcus aureus*, LukGH
ASN100	A combination of the 2 fully human monoclonal antibodies ASN-1 and ASN-2
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the serum concentration-time curve
BAL	Bronchoalveolar lavage
BMI	Body mass index
C_{max}	Maximum serum concentration
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form
ELF	Epithelial lining fluid
ET	Early Termination
ETA	Endotracheal aspirate
HABP	Hospital-acquired bacterial pneumonia
ICU	Intensive care unit
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
LLN	Lower limit of normal
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

MITT	Modified Intent-to-Treat
PK	Pharmacokinetic
POP	Population and outcome plan
PP	Per Protocol
PT	Preferred term
PTT	Partial thromboplastin time
RBC	Red blood cell
S. aureus	*Staphylococcus aureus*
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDO	Sponsor-defined outcome
SOC	System organ class
SUSARS	Serious unexpected suspected adverse reactions
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum serum concentration
ULN	Upper limit of normal
VABP	Ventilator-associated bacterial pneumonia
WBC	White blood cell
WHO	World Health Organization

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for Protocol ASN100-201: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of a Single Dose of ASN100 for the Prevention of *Staphylococcus aureus* Pneumonia in Heavily Colonized, Mechanically Ventilated Subjects. The SAP is based on the protocol dated May 2, 2017 (Version 4.0).

3. PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to support the completion of the Clinical Study Report (CSR) for Protocol ASN100-201. This SAP may be modified and finalized before the study data are unblinded.

4. STUDY SUMMARY

4.1. Study Objectives

4.1.1. Primary Objective

The primary objective of this study is to evaluate the safety, tolerability, and efficacy of a single dose of ASN100 (administered as a 1:1 ratio of the ASN-1 and ASN-2 components) versus placebo for the prevention of *Staphylococcus aureus* (*S. aureus*) pneumonia in mechanically ventilated subjects who are heavily colonized with *S. aureus*.

4.1.2. Secondary Objectives

The secondary objectives of this study are the following:

- To compare the duration of mechanical ventilation post-treatment in subjects treated with ASN100 versus placebo;
- To compare the length of stay in the intensive care unit (ICU) post-treatment for subjects treated with ASN100 versus placebo;
- To determine the serum pharmacokinetics (PK) (i.e. maximum serum concentration [C_{max}], time to maximum serum concentration [T_{max}], area under the serum concentration-time curve [AUC], and terminal elimination half-life [$t_{1/2}$]) of ASN-1 and ASN-2 in mechanically ventilated subjects heavily colonized with *S. aureus*; and
- To compare 28-day all-cause mortality in subjects treated with ASN100 versus placebo.

4.1.3. Exploratory Objectives

The exploratory objectives of this study are the following:

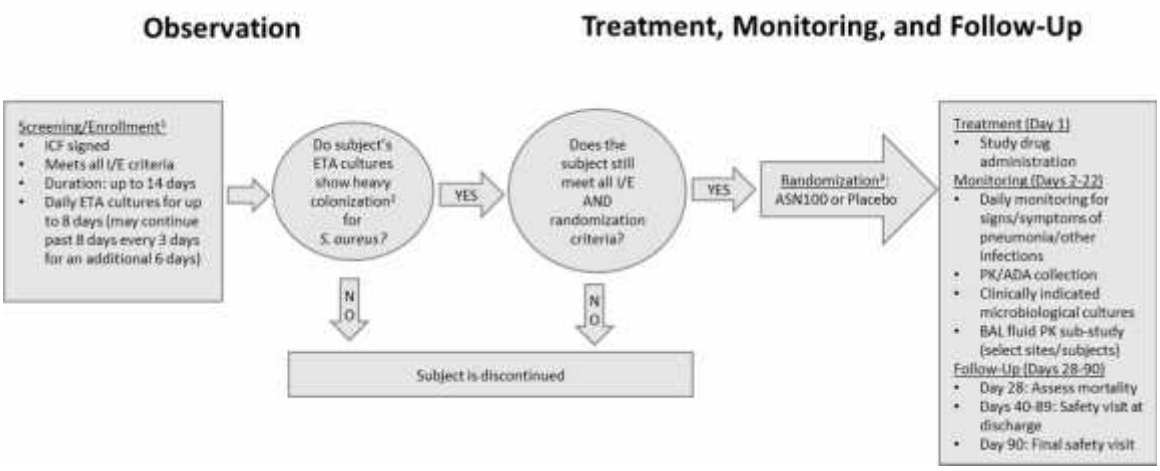
- To compare the incidence of hospital-acquired bacterial pneumonia (HABP) occurring >48 hours post-extubation up to, but not including, Day 22 in extubated subjects treated with ASN100 versus placebo;
- To compare the incidence of ventilator-associated bacterial pneumonia (VABP) up to, but not including, Day 22 in intubated subjects treated with ASN100 versus placebo;
- To determine the immunogenicity of a single dose of ASN100;
- To compare the incidence of other *S. aureus*-associated infections which occur after dosing up to, but not including, Day 22 in subjects treated with ASN100 versus placebo; and
- To assess ASN-1 and ASN-2 levels in bronchoalveolar lavage (BAL) fluid and to calculate a blood to epithelial lining fluid (ELF) ratio in those subjects participating in the BAL fluid PK sub-study.

4.2. Overall Study Design and Plan

This is a double-blind, randomized, single-dose, placebo-controlled study of ASN100 for the prevention of *S. aureus* pneumonia in mechanically ventilated subjects who are heavily colonized with *S. aureus*.

This will be a global study conducted at approximately 70 sites. Subjects will be screened for eligibility; once an Informed Consent Form is signed (or, in countries where it is applicable, a decision is made by a council of independent physicians), and all entry criteria are met, a subject is considered to be enrolled in the study. All enrolled subjects will undergo an observational stage evaluating endotracheal colonization. Subjects who are randomized will undergo a treatment, monitoring, and follow-up period. A schematic of the study is presented in Figure 1.

Figure 1. Study Schematic



1. Subjects do not need to be colonized to be enrolled.
2. For the purposes of this study, heavy colonization with *S. aureus* will be defined as a quantitative threshold of $\geq 10^5$ CFU/mL or 3+ to 4+ by semi-quantitative culture from endotracheal aspirates.
3. Once a subject has an ETA culture result signifying heavy colonization with *S. aureus*, they must be randomized within 48 hours (or up to 60 hours with Medical Monitor approval) of specimen collection or be discontinued from the study.

ADA = anti-drug antibody; BAL = bronchoalveolar lavage; ETA = endotracheal aspirate; ICF = Informed Consent Form; I/E = inclusion/exclusion; PK = pharmacokinetic; *S. aureus* = *Staphylococcus aureus*.

Approximately 2250 eligible subjects who meet all of the inclusion criteria and none of the exclusion criteria will be screened daily (while mechanically ventilated) for up to 8 days to identify those subjects who are heavily colonized with *S. aureus*.

Screening for heavy *S. aureus* colonization by ETA culture will continue on Day 11 and Day 14 provided the subject remains mechanically ventilated, for a total Screening Period of up to 14 days. Additional ETA screening may occur on Days 9, 10, 12, and 13 at the discretion of the Investigator and provided the subject remains mechanically ventilated.

ETA specimens collected during Screening/Enrollment will be cultured by quantitative or semi-quantitative methods as required by the protocol. Sites are encouraged to perform semi-quantitative cultures using a chromogenic media selective for all *S. aureus* (e.g., CHROMagar™ *Staph aureus*) for more rapid and specific detection of *S. aureus*.

Semi-quantitative cultures using chromogenic media are preferred for determination of eligibility for randomization; however, any quantitative or semi-quantitative culture performed that indicates that a subject is heavily colonized with *S. aureus* is permitted if the culture results are available to randomize the subject within 48 hours (or up to 60 hours with Medical Monitor approval) from the time the ETA specimen was collected.

Once an enrolled subject has an ETA culture reported positive for heavy *S. aureus* colonization and meets all of the inclusion and none of the exclusion criteria, they are eligible for randomization. If they are not randomized on this occasion according to the protocol, they are no longer eligible for continued ETA sampling or randomization, and will be discontinued from the study; however, if subjects are extubated and subsequently re-intubated/mechanically ventilated, they are eligible for re-screening as a new subject enrollment, provided all entry criteria continue to be met. Subjects who were previously randomized are not eligible to be re-consented and re-screened.

At the time of randomization, if a subject's screening ETA culture also shows heavy colonization of a Gram-negative organism (i.e. heavy co-colonization of both Gram-positive and Gram-negative organisms), the subject will not be randomized into the study; however, randomization should not be delayed while waiting for Gram-negative results if heavy colonization with *S. aureus* has been confirmed. Testing for Gram-negative colonization is however not a requirement of the study protocol and would apply to centers that routinely test for both Gram-positive and Gram-negative organisms as part of standard of care.

Nasal swab specimens (one from each nostril) will be obtained at the Randomization Visit and will be cultured by the central microbiology laboratory. Results from the nasal swab specimen cultures will be used to assess correlation with results of the qualifying ETA culture.

Upon determination of eligibility, approximately 354 subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups:

- ASN100 administered as 2 separate intravenous (IV) infusions of ASN-1 and ASN-2 either sequentially or simultaneously, or
- Placebo administered as 2 separate IV infusions either sequentially or simultaneously.

To ensure balance among the treatment groups, randomization for this study will be stratified by receipt or non-receipt of concomitant anti-staphylococcal antibiotics at the time of randomization that are potentially active against *S. aureus* pneumonia, including, but not limited to, nafcillin, oxacillin, vancomycin, linezolid, telavancin, ceftaroline, ceftobiprole, and teicoplanin.

Following randomization on Day 1, subjects will receive either a single IV dose of 3600 mg of ASN100 (comprised of separate infusions each of 1800 mg ASN-1 and 1800 mg ASN-2) or matching placebos, per their assigned randomization scheme.

If, as part of routine standard of care, additional respiratory and/or other microbiological specimens are collected for culture during the study, results will be documented within the electronic Case Report Form (eCRF). As described within the study laboratory manual, bacterial isolates recovered from these specimens that are deemed pathogens by the

Investigator (if retained and available at the study site's local microbiology laboratory) will be sent to the central microbiology laboratory for confirmation of pathogen identification (all isolates) and susceptibility testing (*S. aureus* isolates only).

Randomized subjects will be monitored daily for the signs and symptoms of pneumonia and other *S. aureus*-associated infections while hospitalized up to up to but not including Day 22.

All randomized subjects will undergo a study visit on Day 22 (+2 days) for treatment efficacy evaluation. A follow-up visit will occur on Day 28 (+2 days) to assess mortality. This visit may be conducted via telephone if the subject is no longer hospitalized.

For subjects who remain hospitalized between Day 40 and Day 90 at the institution where they received study treatment, a follow-up safety visit will be performed on the day of discharge from the hospital during this period.

All randomized subjects will return for a Safety Visit on Day 90 (±7 days) (if the subject is unable to return to the site, this visit may be conducted by telephone). Subjects who discontinue the study prior to Day 22 will undergo an Early Termination Visit. The end of the study will occur upon completion of the last Day 90 visit by the last subject.

Safety assessments for this study will include adverse event monitoring, clinical laboratory assessments (including chemistry, hematology, coagulation, and urinalysis), physical examinations, vital sign measurements, 12-lead ECGs, chest X-rays and/or thoracic CT scans, and the determination of the presence of ASN-1 and ASN-2 anti-drug antibodies (ADAs). Additional safety assessments may be performed throughout the duration of the study if clinically indicated.

4.3. Study Procedures

Table 1 presents the visit schedule and procedures to be conducted at each visit.

Table 1: SCHEDULE OF PROCEDURES

Study Period	Screening/ Enrollment	Randomization	Treatment	Monitoring Period			Follow-Up Period			ET
Study Day Study Procedures	Up to Day -14[a]	Day 1 pre-dose	Day 1	Day 2/3[b] (BAL PK sub-study)	Day 2 to Day 21[c]	Day 22 (+2 days)	Day 28 (+2 days)[d]	Day 40 to Day 89[e]	Day 90 (±7 days) Safety Visit[f]	Unsched[g]
Informed consent	X									
Inclusion/exclusion/ randomization criteria	X[h,i]	X[j]								
Medical history	X[h]	X[k]								
Demographics	X[h]									
Antibiotic/medication history[l]	X	X								
Height/weight	X[h]									
Physical examination[m]	X[h]	X			X	X		X	X	X
Vital signs[n]	X[h]	X	X	X	X	X		X	X	X
Pregnancy test[o]	X[h]					X				X
Clinical laboratory assessments (chemistry, hematology, and coagulation)		X			X[p]	X				X[q]
Urinalysis		X			X[r]	X				X[q]
Procalcitonin (analysis performed at central lab)		X			X[s]	X				X
Ventilator device status	X	X	X	X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]
Chest X-ray/thoracic CT scan	X[u]	X[v]		X	X[w]	X[w]				
Nasal swab specimens for culture		X								
ETA for culture[x]	X									
Collection/culture of additional microbiological specimens[y]					X	X				X
Clinical assessment of signs/symptoms of pneumonia		X	X	X	X	X				X
Other *S. aureus* infection assessment	X	X	X	X	X	X				X

Footnotes begin on the next page.

Table 1: SCHEDULE OF PROCEDURES (Continued)

Study Period	Screening/ Enrollment	Randomization	Treatment	Monitoring Period			Follow-Up Period			ET
Study Day Study Procedures	Up to Day -14[0]	Day 1 pre-dose	Day 1	Day 2/3[b] (BAL PK sub-study)	Day 2 to Day 21[c]	Day 22 (+2 days)	Day 28 (+2 days)[d]	Day 40 to Day 89[e]	Day 90 (±7 days) Safety Visit[f]	Unsched[g]
Randomization		X								
Blood collection for ADA and anti-*S. aureus* toxin antibodies		X			X[z]	X		X	X	X
12-lead ECG		X				X		X	X	X
Assess survival and discharge disposition						X	X	X	X	X
Study drug administration[aa]			X							
BAL for PK[bb]				X						
Blood collection for PK sampling and anti-*S. aureus* toxin antibodies			X[cc]	X[dd]	X[ee]	X[ee]		X[ee]	X	X
Track days on ventilator from randomization			X	X	X	X		X	X	X
Track days in ICU (or other observation area)			X	X	X	X		X	X	X
Concomitant medications[l]		X	X	X	X	X		X	X	X
Adverse event assessment	X[ff]	X	X	X	X	X		X	X	X

a. Eligible subjects will be screened daily (while mechanically ventilated) for up to 8 days to identify those subjects who are heavily colonized with *S. aureus* (see Protocol Section 3.1). Screening for heavy *S. aureus* colonization by ETA culture will continue on Day 11 and Day 14 provided the subject remains mechanically ventilated, for a total Screening Period of up to 14 days. Additional ETA screening may occur on Days 9, 10, 12, and 13 at the discretion of the Investigator and providing the subject remains mechanically ventilated.

b. Procedures are to be performed 48 hours (±36 hours) post-dose on approximately Day 2 or Day 3, depending on time of study drug administration, for those subjects participating in the BAL fluid PK sub-study only or if BAL fluid is collected as part of a standard of care procedure for any subject at any other time post-randomization for any other reason.

c. Procedures are to be performed daily (unless otherwise indicated) from Day 2 to Day 21 while the subject is hospitalized. For subjects participating in the BAL fluid PK sub-study, procedures noted for the Day 2 visit only need to be performed 1 time.

d. A follow-up visit will occur on Day 28 (+2 days) to assess mortality. This visit may be conducted via telephone if the subject is no longer hospitalized.

e. For subjects who remain hospitalized between Day 40 and Day 90 at the institution where they receive study treatment, a follow-up safety visit will be performed on the day of discharge.

f. If the subject is unable to return to the site, this visit may be conducted by telephone, with procedures performed as appropriate (i.e., concomitant medications and adverse events collected).

g. An ET visit will be conducted for subjects who are withdrawn from the study prior to Day 22.

h. To be performed at the initial Screening Visit only.
i. At the Screening Visit, subjects must meet all of the inclusion criteria and none of the exclusion criteria in order to be eligible to return for the Randomization Visit.
j. At the Randomization Visit, subjects must continue to meet all of the inclusion criteria and none of the exclusion criteria. Subjects must also meet all randomization criteria to be eligible to be randomized into the study.
k. Review and record medical history (if changes occurred since the Screening Visit).
l. All prior medications received by the subject within 14 days prior to study drug administration and any concomitant medications used throughout the duration of the study will be recorded in the source documents and on the appropriate eCRF.
m. A complete physical examination will be performed at the Screening Visit and as deemed necessary by the Investigator and will include, at a minimum, a pulmonary examination (including auscultation) and assessments of the skin, abdomen, cardiovascular, gastrointestinal, and neurological systems. A limited physical examination will be performed at the Randomization Visit, daily during the Monitoring Period (if the subject is hospitalized), on Day 22 (if the subject is hospitalized), at the time of hospital discharge (if discharge occurs between Day 40 and Day 90), at the Safety Visit (Day 90) if the visit occurs onsite, and at ET (if applicable). The limited physical examination will include, at a minimum, a pulmonary examination (including auscultation).
n. Vital sign measurements will include temperature, systolic and diastolic blood pressure, pulse, respiratory rate, and oxygenation status. Blood pressure and pulse will be assessed via an automated device. Manual techniques are only to be used if an automated device is not available. Oxygenation status will be determined via measurement of arterial blood gas, provided the subject has an arterial line placed. If no arterial line is present, pulse oximetry may be used.
o. Female subjects of childbearing potential must have a documented negative pregnancy test at the Screening Visit. Female subjects may be enrolled on the basis of a negative urine pregnancy test, pending the result of a negative serum pregnancy test prior to randomization. A pregnancy test will also be performed on Day 22 or ET (if applicable). Additional pregnancy testing may occur throughout the duration of the study, per applicable country requirements.
p. Blood samples for chemistry, hematology, and coagulation will be obtained on Days 2 (+1 day), 4 (±1 day), and 6 (±1 day) of the Monitoring Period, and twice weekly during Week 2 (Day 8 through Day 14) and/or Week 3 (Day 15 through Day 21) of the Monitoring Period while the subject remains hospitalized.
q. To be obtained if clinically indicated.
r. Urinalysis to be obtained on Day 6 (±1 day) of the Monitoring Period only.
s. Procalcitonin testing to occur on the day of diagnosis of pneumonia, if applicable.
t. If applicable.
u. A chest X-ray or thoracic CT scan is to be obtained 1 time at the initial Screening Visit. A chest X-ray or thoracic CT scan obtained as part of standard of care within 24 hours prior to the initial Screening Visit is sufficient provided there are no changes in the subject's clinical status (e.g., no change in ventilation status, secretions, or signs/symptoms that may be suggestive of pneumonia) within the 24 hours following imaging.
v. A chest X-ray or thoracic CT scan obtained within 24 hours of the Randomization Visit is sufficient, provided there are no changes in the subject's clinical status (e.g., no change in ventilation status, secretions, or signs/symptoms that may be suggestive of pneumonia) since the time of imaging.
w. A chest X-ray or thoracic CT scan is required during the Monitoring Period for those subjects presenting with signs and symptoms of a respiratory infection such as dyspnea, tachypnea, fever, or cough.
x. ETA specimens collected during Screening/Enrollment will be cultured by quantitative or semi-quantitative methods as required by the protocol. Sites are encouraged to perform semi-quantitative cultures using a chromogenic media that tests for both the presence of MSSA and MRSA (e.g., CHROMagar™ *Staph aureus*) for more rapid and specific detection of *S. aureus*. If the site is not able to obtain chromogenic media for *S. aureus*, appropriate chromogenic media may be supplied by the Sponsor. Semi-quantitative cultures using chromogenic media are preferred for determination of eligibility for randomization; however, any quantitative or semi-quantitative culture performed that indicates that a subject is heavily colonized with *S. aureus* is permitted if the culture results are available to randomize the subject within 48 hours (or up to 60 hours with Medical Monitor approval) from the time the ETA sample was collected. If subjects are extubated and subsequently re-intubated/mechanically ventilated, they are eligible for re-screening as a new subject enrollment. Subjects who were previously randomized are not eligible to be re-consented and re-screened. Subjects with a screening ETA culture that also shows heavy colonization of a Gram-negative organism (i.e., heavy co-colonization of both Gram-positive and Gram-negative organisms), will not be randomized into the study; however, randomization should not be delayed while waiting for Gram-negative results if heavy colonization with *S. aureus* has been confirmed.
y. Adequate respiratory specimen or other microbiological specimens to be obtained if clinically indicated. If, as part of routine standard of care, additional respiratory and/or other microbiological specimens are collected for culture during the study, results will be documented within the eCRF.
z. Obtain sample for ADA (to be obtained only upon discharge from the ICU, if discharge occurs prior to Day 22).

aa. Study drug will be administered in a double-blind manner. Subjects will receive ASN100 or matching placebo via 2 IV infusions over a duration of approximately 50 to 60 minutes per infusion. Both ASN100 and placebo will be administered as 2 separate infusions (either sequentially or simultaneously). The last infusion will be completed within 5 hours from initiation of drug preparation in the pharmacy.
bb. Obtain BAL fluid 48 hours (±36 hours) post-dose to determine ASN-1 and ASN-2 levels and blood to ELF ratio. If BAL fluid is collected as part of a standard of care procedure from any subject enrolled in the sub-study at any other time post-randomization for any other reason, if possible, a sample for PK analysis will also be obtained.
cc. Blood samples for PK analysis will be collected immediately following the completion of the second infusion (+15 minutes) and at 6 hours (±4 hours) and 24 hours (±6 hours) post-dose.
dd. Obtain a blood sample for PK measurement ±1 hour relative to BAL fluid collection (including scheduled BAL fluid collection or if BAL fluid is collected as part of a standard of care procedure from any subject enrolled in the sub-study at any time post-randomization).
ee. A PK sample will be obtained from all subjects on Days 4 (±1 day), 7 (±1 day), 14 (±2 days), and 22 (+2 days) of the Monitoring Period. Additional PK samples will be collected on the day of discharge (if discharge occurs between Day 40 and Day 90).
ff. Adverse events that occur between the time the subject signs the ICF and the Randomization Visit will only be recorded if related to a study-specific procedure.

ADA = anti-drug antibody; BAL = bronchoalveolar lavage; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic Case Report Form; ELF = epithelial lining fluid; ET = Early Termination; ETA = endotracheal aspirate; ICF = Informed Consent Form; ICU = intensive care unit; IV = intravenous; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; PK = pharmacokinetic; *S. aureus* = *Staphylococcus aureus*; Unsched = unscheduled.

4.4. Selection of Study Population

Male and female subjects 18 years of age who are heavily colonized with *S. aureus* as determined by either quantitative or semi-quantitative culture of an ETA specimen, mechanically ventilated, and, in the Investigator's opinion, will require ongoing ventilator support for at least 48 hours, will be enrolled.

4.5. Randomization and Blinding

Randomization will occur at the Randomization Visit following determination of the subject's eligibility. Subjects will be randomized via a centralized Interactive Response Technology (IRT) system in a 1:1 ratio to receive a single dose (2 infusions) of either ASN100 or matching placebo. Randomization will be stratified by receipt or non-receipt of concomitant anti-staphylococcal antibiotics at the time of randomization that are potentially effective for the treatment of *S. aureus* pneumonia.

The study follows a double-blind, placebo-controlled design. All study personnel, including investigators, site personnel, site pharmacist, Sponsor and contract research organization (CRO) staff involved in the conduct of the study (e.g., clinical research associate [CRA]/monitor), and subjects will be blinded to treatment assignment, except as described below. ASN100 and placebo will be identical in appearance to preserve blinding.

Randomization data will be kept strictly confidential until the time of unblinding and will not be accessible by subjects, Investigators, or anyone performing assessments and having access to study data until unblinding occurs. An independent Data Review Committee (as described in Section 7.6) will conduct a single interim analysis of futility assessment and will receive unblinded study data. Sponsor and CRO staff who are involved in the conduct of the study will not have access to unblinded Data Review Committee materials. The details of the interim analysis are described in the Data Review Committee Charter dated 8-June-2018. Individual subject unblinding will only occur in the case of subject emergencies or as required by regulations when reporting serious unexpected suspected adverse reactions (SUSARs), with complete unblinding at the conclusion of the study.

Emergency breaking of the assigned treatment code should only be undertaken when it is essential that knowledge of the treatment assignment is necessary to treat the subject's emergency safely and effectively. Emergency treatment code breaks will be performed using the IRT. When the Investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject's identifying information and confirm the necessity to break the treatment code for the subject. The Investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Sponsor and Medpace study personnel that the code has been broken.

Should the assignment of the subject be needed to fulfill regulatory reporting requirements for SUSARs as noted above, the person designated at the CRO/Sponsor for unblinding needed to fulfill regulatory reporting requirements should contact IRT, for the study drug information. The IRT documentation indicating the blind break at the site, must be retained

with the subject's source documentation in such a way as to avoid unblinding the treatment assignment to other site or Sponsor blinded personnel.

5. STUDY METHODS

5.1. Analysis Populations

The following analysis populations will be used for analyses.

5.1.1. Intent-to-Treat Population (ITT)

The ITT Population includes all subjects who are randomized to receive study drug.

5.1.2. Modified Intent-to-Treat Population (MITT)

The MITT Population includes all subjects in the ITT Population who receive study drug and who are heavily colonized with *S. aureus* as determined by quantitative or semi-quantitative culture of an ETA specimen. Exclusion from the MITT Population will be determined programmatically for each ITT subject. Programmatically determined assignment into the MITT Population will be evaluated for confirmation or Sponsor Override as applicable during a Review Meeting of the Population and Outcome Plan (POP) Review Group, as described in the POP.

Review Meetings will be held on a regular basis throughout the conduct of the study. The number of subjects included in each Review Meeting will vary depending on the number of subjects included in a data review cycle per the Medpace Rolling Data Lock Plan.

The final MITT Population classification will be performed in a blinded fashion and prior to final database lock and unblinding. After the Review Group's review, any Sponsor overrides of the MITT Population flags will be finalized and documented. The MITT Population flags and the reasons for Sponsor Override will also be included in the analysis datasets.

5.1.3. Per Protocol (PP) Population

The PP Population includes all subjects in the MITT Population who also meet the following criteria:

- Did not have any major protocol violations that would affect assessment of efficacy,
- Randomized in a timely manner following collection of an ETA specimen showing heavy *S. aureus* colonization;
- Was mechanically ventilated at randomization;
- Had an appropriate chest image performed at randomization;
- Did not have a change of oxygenation and onset of purulent secretions at randomization;
- Was not diagnosed with pneumonia at randomization or within 24 hours of receiving study drug;
- Received an adequate dose of study drug administered in a timely manner following study drug preparation,

- Did not die within 24 hours of receiving study drug,
- Did not have Investigator Diagnosis of Pneumonia within 24 hours of receiving study drug, and
- Complete an adequate number of Monitoring Period assessments through Day 22 based on medical review of available data.

Exclusion from the PP Population will be determined programmatically for each MITT subject. Programmatically determined assignment into the PP Population will be evaluated for confirmation or Sponsor Override as applicable during a Review Meeting.

The final PP Population classification will be performed in a blinded fashion and prior to final database lock and unblinding. After the Review Group's review, any Sponsor Overrides of the PP Population flags will be finalized and documented. The PP Population flags and the reasons for Sponsor Override will also be included in the analysis datasets.

5.1.4. Pharmacokinetic (PK) Population

The PK Population includes all subjects in the MITT Population with at least 1 serum PK sample collected post-dose.

5.1.5. Safety Population

The Safety Population includes all subjects who receive any amount of study drug and have at least 1 post-treatment safety assessment.

5.2. Study Endpoints

5.2.1. Microbiological and Clinical Assessments

ETA specimens will be collected for culture during Screening/Enrollment to determine randomization eligibility, including identification of heavy *S. aureus* colonization. Additional respiratory specimens may be collected for culture throughout the Monitoring Period or at Early Termination (if applicable) if clinically indicated according to routine standard of care.

If, as part of routine standard of care, additional respiratory and/or other microbiological specimens are collected for culture during the study, results will be documented within the eCRF. As described within the study lab manual, bacterial isolates recovered from these specimens that are deemed pathogens by the Investigator (if retained and available at the study site local microbiology laboratory) will be sent to the central microbiology laboratory for confirmation of pathogen identification (all isolates) and susceptibility testing (*S. aureus* isolates only).

During the Monitoring Period, a diagnosis of *S. aureus* pneumonia will be determined if subjects have *S. aureus* identified at any level from an adequate respiratory specimen by the local microbiology laboratory or central microbiology laboratory if the local microbiological sample was either not done, cultured improperly, or no growth. For a diagnosis of *S. aureus* pneumonia, the collection of an adequate respiratory specimen culture that is positive for *S. aureus* must occur within ±2 days from the time of the

development of clinical signs and symptoms of pneumonia or chest imaging results indicative of pneumonia:

- A respiratory specimen obtained by BAL, non-bronchoscopic BAL, or protected specimen brush will be considered an adequate respiratory specimen; or
- For extubated subjects, an adequate expectorated/induced sputum specimen is defined as one that does not have either 10 squamous epithelial cells or 25 PMNs/100× field will also be an adequate respiratory specimen; and
- For both intubated and extubated subjects, adequate respiratory specimens will undergo either semi-quantitative or quantitative culture in accordance with the local laboratory's standard procedure.

Subjects will be assessed daily throughout the Monitoring Period for the following clinical signs and symptoms:

Clinical Signs and Symptoms

Mechanically Ventilated Subjects	Non-Mechanically Ventilated Subjects	
· Cough, · Rales, · Dullness on percussion,* · Bronchial breath sounds, · Egophony,* · Need for suctioning, · Need for ventilator support, and · Fever ³ 38°C (³ 100.4°F).	· Cough, · Rales, · Dullness on percussion,* · Bronchial breath sounds, · Egophony,*	· Dyspnea, · Tachypnea, · Respiratory rate, · Hypoxemia, and · Fever ³ 38°C (³ 100.4°F).
*If routinely performed.		

A diagnosis of pneumonia will be determined by the Investigator based on their clinical expertise and experience.

Each pneumonia diagnosis will be categorized programmatically as HABP or VABP using the definitions below. Programmatically determined assignments as HABP and VABP will be evaluated for confirmation or Sponsor Override as applicable by the Review Group. The final categorizations will be performed in a blinded fashion and prior to final database lock and unblinding. After the Review Group's review, the decision to override a programmatic determination will be finalized and documented. The reasons for Sponsor Overrides will be included in the analysis datasets.

Definition of Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia

Indication	Definition
HABP	· A chest image showing new or progressive infiltrates suggestive of pneumonia; · Subject has been off of mechanical ventilation via an endotracheal or nasotracheal tube for >48 hours; · At least ONE of the following: o Has been hospitalized for >48 hours; or o Developed clinical signs and symptoms within 7 days following hospital discharge; · At least ONE of the following: o New onset or worsening pulmonary signs/symptoms such as cough, dyspnea, tachypnea (e.g., respiratory rate >25 breaths per minute), expectorated sputum production, or the requirement for mechanical ventilation (if subject is not already ventilated); o Need for acute changes in ventilator support to enhance oxygenation or to the amount of PEEP; or o New onset of suctioned respiratory secretions; AND · At least ONE of the following clinical signs/symptoms: o Temperature >38°C or <35°C; o WBC count ^{3} 10,000 cell/mm^3 or ≤4500 cell/mm^3; or o >15% immature neutrophils (bands) on peripheral blood smear.
VABP	· A chest image showing new or progressive infiltrates suggestive of pneumonia; · Subject has received mechanical ventilation via an endotracheal or nasotracheal tube for ^{3} 48 hours; · At least ONE of the following: · Currently receiving mechanical ventilation via an endotracheal or nasotracheal tube; or · Discontinued receiving mechanical ventilation via an endotracheal or nasotracheal tube within the last 48 hours (i.e. 48 hours); · At least ONE of the following: o New onset or worsening pulmonary signs/symptoms such as cough, dyspnea, tachypnea (e.g., respiratory rate >25 breaths per minute), expectorated sputum production, or the requirement for mechanical ventilation (if subject is not already ventilated); o Need for acute changes in ventilator support to enhance oxygenation or to the amount of PEEP; or o New onset of suctioned respiratory secretions; AND · At least ONE of the following clinical signs/symptoms: o Temperature >38°C or <35°C, o WBC count ^{3} 10,000 cell/mm^3 or ≤4500 cell/mm^3, or o >15% immature neutrophils (bands) on peripheral blood smear.
HABP = hospital-acquired bacterial pneumonia; PEEP = positive end-expiratory pressure; VABP = ventilator-associated bacterial pneumonia; WBC = white blood cell.	

5.2.2. Sponsor-Defined Outcome of *S. aureus* Pneumonia

Sponsor-Defined Outcome (SDO) of *S. aureus* pneumonia will be determined programmatically based on the data and the manual review conducted at Review Meetings per the POP.

Each randomized subject will be evaluated for the occurrence of *S. aureus* pneumonia between Randomization and up to, but not including, Day 22. In order to assign a SDO, the following assessments will be made based on available data:

1. Microbiological Assessment
2. Chest Imaging Assessment
3. Clinical Assessments
    a. Respiratory
    b. Signs and Symptoms
4. Operational Assessments

There will be 2 SDO definitions for data analysis: SDO1 and SDO2. The 2 definitions will need to satisfy the 4 assessments above and differ only on the clinical assessments. SDO1 will meet either respiratory OR signs and symptoms requirements while SDO2 will meet both respiratory AND signs and symptoms requirements.

The individual assessments for each randomized subject will be collapsed to assign an SDO1/SDO2 of Yes, No, Indeterminate (i.e. insufficient data to assign a SDO of Yes or No), or Censored (i.e. subject died prior to the Day 22 assessment) based on the mutually exclusive, hierarchical rules specified in the POP.

5.2.3. Pharmacokinetic Assessments

Blood samples will be obtained for the measurement of ASN-1 and ASN-2 in serum. Blood samples for PK analysis will be collected immediately following the completion of the second infusion (+15 minutes) and at 6 hours (±4 hours) and 24 hours (±6 hours) post-dose following the second infusion. In addition, a PK sample will be obtained from all subjects on Days 4 (±1 day), 7 (±1 day), 14 (±2 days), and 22 (+2 days) of the Monitoring Period. Additional PK samples will be collected on the day of discharge (if discharge occurs between Day 40 and Day 90), on Day 90 (if hospitalized or if the subject is able to return to the clinic), or Early Termination (if applicable).

Select sites will be invited to participate in a BAL fluid PK sub-study. Approximately 25 to 35 subjects who volunteer will participate in this sub-study and will have BAL fluid collected 48 hours (±36 hours) post-dose (on approximately Day 2 or Day 3, depending on time of study drug administration) to determine ASN-1 and ASN-2 levels and blood to ELF ratio. Subjects participating in the BAL fluid PK sub-study will have a blood sample collected for PK measurement ±1 hour relative to BAL fluid collection.

If BAL fluid is collected as part of a standard of care procedure from any subject enrolled in the sub-study at any other time post-randomization for any other reason, if possible, a sample for PK analysis will also be obtained. Additionally, attempts will be made to collect a serum sample for PK measurement ±1 hour relative to BAL fluid collection.

5.2.4. Primary Efficacy Endpoint

The primary efficacy endpoint is whether the subject has developed an SDO1 of *S. aureus* pneumonia up to, but not including, Day 22. The summary measure for efficacy is the proportion of subjects in the MITT Population who develop an SDO1 of *S. aureus* pneumonia up to, but not including, Day 22.

Analyses of the primary efficacy endpoint will also be performed separately for the ITT and PP Populations.

5.2.5. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Duration of mechanical ventilation during the first 21 days post-randomization for subjects in the MITT, ITT, and PP Populations;
- Length of ICU stay during the first 21 days post-randomization for subjects in the MITT, ITT, and PP Populations;
- The C_{max}, T_{max}, AUC, and $t_{1/2}$ of ASN-1 and ASN-2 in serum following a single dose of ASN100 in the PK Population; and
- 28-day all-cause mortality in the MITT, ITT, and PP Population.

5.2.6. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- Proportion of subjects in the MITT and PP Populations with a diagnosis of HABP >48 hours post-extubation up to, but not including, Day 22 in extubated subjects;
- Proportion of subjects in the MITT and PP Populations with development of VABP up to, but not including, Day 22;
- Incidence of all bacterial pneumonias in the MITT, ITT, and PP Populations;
- Incidence of other non-*S. aureus* bacterial pneumonias up to, but not including, Day 22 in the MITT, ITT, and PP Populations; and
- Incidence of other *S. aureus* infections acquired up to, but not including, Day 22 in the MITT, ITT, and PP Populations.

5.2.7. Safety Endpoints

Safety endpoints are as follows:

1. Treatment-emergent adverse events (TEAEs)
2. Vital signs
3. Electrocardiograms (ECGs)
4. Laboratory parameters
5. Physical examinations

6. Radiographs and Imaging
7. Immunogenicity and anti-drug antibodies

6. SAMPLE SIZE DETERMINATION

The estimated incidence of progression to *S. aureus* pneumonia in mechanically ventilated subjects with heavy endotracheal colonization of *S. aureus* is approximately 25% within 22 days of randomization.

Assuming a 2-sided significance level of 0.05 and a desired power of 80% to detect a significant difference between *S. aureus* pneumonia incidence rates of 25% in the placebo group and 12.5% in the ASN100 treatment group (50% reduction), 152 evaluable subjects are required in each treatment group. A sample size of 304 subjects (152 subjects per treatment group) will yield 80% power to detect a 50% reduction in the incidence of *S. aureus* pneumonia with ASN100 treatment when assuming a 25% incidence rate of *S. aureus* pneumonia in placebo-treated subjects. Assuming a 14% non-evaluable rate, approximately 354 subjects (177 subjects per treatment group) will be randomized. Assuming the screen failure rate is about 84%, approximately 2250 subjects will be screened.

7. STATISTICAL ANALYSIS

7.1. General Statistical Considerations

Summary statistics will be presented by treatment group. For continuous variables, the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g., standard deviation) will be displayed to two decimal places greater than the original value.

All statistical tests will be performed at the 0.05 significance level using 2-sided tests, except where otherwise noted. All confidence intervals will have a confidence level of 95%.

7.2. Treatment Misallocations

If subjects were randomized but were not treated, the subjects will be included in the ITT Population, but not included in the MITT, PP, PK, and Safety Populations consistent with their definitions.

If subjects were randomized but received incorrect study medication, they will be reported under their randomized treatment group for all efficacy analyses for the ITT, MITT, and PP Populations, but will be reported under the treatment they actually received for all safety analyses for the Safety Population.

7.3. Handling of Missing Data

7.3.1. Missing Dates

In cases of missing or incomplete dates (e.g., AE and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.

7.3.2. Missing Assessment

Randomized subjects discontinued from the study due to any cause prior to Day 22 will be considered as not developing *S. aureus* pneumonia by SDO1 for the primary efficacy analysis.

Randomized subjects that are non-informative (i.e. a subject that does not develop SDO1 or SDO2 of *S. aureus* pneumonia, indeterminate, or dies before Day 22) will be censored for the Kaplan-Meier analysis unless it is noted otherwise.

7.3.3. Other Missing Data

Other missing values will not be imputed and only observed values will be used for reporting of descriptive statistics unless otherwise stated.

7.4. Baseline Definition

For all efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to the first and only dose of study drug.

7.5. Relative Day

The date of the initiation of study drug administration will be considered relative day 1, relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days before the initiation of study drug administration:

Relative Day = Date of Assessment – Date of the initiation of study drug administration

For days on or after the initiation of study drug administration:

Relative Day = Date of Assessment – Date of the initiation of study drug administration + 1

7.6. Interim Analysis

One interim analysis will be conducted during the study, when approximately 125 subjects have reached Day 22. The interim analysis is for futility assessment of the study, and for a potential study sample size adjustment. The futility assessment is based on an unblinded efficacy evaluation while any sample size adjustment result from a review of blinded data pooled across the treatment arms. The interim analysis of futility assessment will be reviewed by an independent Data Review Committee. The details of the interim analysis are described in the Data Monitoring Committee Charter dated 25-June-2018.

7.7. Subject Disposition

Subject disposition will be summarized for the ITT Population for each treatment group and in total. The following subject disposition categories will be included in the summary for the ITT Population:

- Subjects who randomized,
- Subjects who received any study drug,
- Subjects who completed the study assessments through Day 22,
- Subjects who did not complete the study assessments through Day 22,

- Subjects who completed the study assessments by Day 28,
- Subjects who did not complete the study assessments by Day 28,
- Subjects who completed the study assessments through Day 90,
- Subjects who did not complete the study assessments through Day 90, and
- Subjects who completed assessments through Day 22, but did not complete the study assessments through Day 90.

For subjects who did not complete the study assessments through Day 90, a summary will be provided by reason of discontinuation. In addition, the total number of subjects for each defined population will be tabulated.

7.8. Demographic and Baseline Characteristics

Demographic information including sex, race, ethnicity, corrected randomization stratification factor (receipt or non-receipt of concomitant anti-staphylococcal antibiotics at the time of randomization that are potentially active against *S. aureus* pneumonia), age (as a continuous variable and categorized as <55, 55 - <65, 65 - <75 and 75 years), height, weight, and BMI will be summarized by treatment group for the ITT, MITT, PP, PK, and Safety Populations.

7.9. Medical History

Medical history will be collected at the screening visit and randomization visit if changes occurred since the Screening Visit. Only adverse events that were considered to be study procedure related were to be reported between the first study screening visit and randomization. Therefore, any changes in the subject's medical condition during this period were captured as medical history.

All reported medical history conditions will be listed by subject.

7.10. Prior and Concomitant Medications/Procedures

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Sept 2016E B2). Concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1).

Prior medications are medications used before the initiation of study drug administration. Any medications used on or after the initiation of study drug administration will be included as concomitant medications. Hence medications ongoing at start of study medication will be counted as both prior and concomitant medication.

The number and percentage of subjects taking prior medications will be summarized for the ITT Population by anatomic therapeutic chemical (ATC) class and preferred term for each treatment group and overall.

The number and percentage of subjects taking concomitant medications will be summarized for the ITT Population by anatomic therapeutic chemical (ATC) class and preferred term for each treatment group and overall.

The number and percentage of subjects receiving concomitant procedures will also be summarized for the ITT Population by system organ class (SOC) and preferred term for each treatment group and overall.

Prior and concomitant medications/procedures will be listed by subject.

7.11. Analysis of Efficacy

For all efficacy analyses, subjects will be analyzed in the group to which they were randomized.

7.11.1. Primary Efficacy Endpoint

The primary efficacy endpoint is whether the subject has or has not developed *S. aureus* pneumonia up to, but not including, Day 22 in the MITT Population. For the primary analysis, whether the subject has or has not developed *S. aureus* pneumonia will be based on sponsor defined outcome (SDO1).

The primary analysis is based on comparing two proportions of subjects who develop *S. aureus* pneumonia by SDO1 up to, but not including, Day 22. For each arm, the empirical proportion is defined by a ratio, which is the number of *S. aureus* pneumonia events divided by the total number of subjects in the arm. The inference about the difference of two population rates is based on the empirical counterpart. Specifically, the point estimate, 95% confidence interval and p-value for the rate difference. If subjects discontinued from the study due to any cause prior to Day 22, it will be considered as not developing *S. aureus* pneumonia by SDO1 for the primary efficacy analysis.

7.11.2. Additional Analyses for *S. aureus* Pneumonia

Analyses of the primary efficacy endpoint will also be performed based on the ITT and PP Populations.

The following additional analyses will be performed in the MITT and PP Populations:

- The primary efficacy analysis, based on comparing two proportions of subjects who develop *S. aureus* pneumonia by SDO2 up to, but not including, Day 22. If subjects discontinued from the study due to any cause prior to Day 22 it will be considered as not developing *S. aureus* pneumonia for this analysis by SDO2.
- The primary analysis is based on comparing two proportions of subjects who develop *S. aureus* pneumonia by SDO1 up to, but not including, Day 22. For each arm, the empirical proportion is defined by a ratio, which is the number of *S. aureus* pneumonia events divided by the total number of subjects in the arm. The inference about the difference of two population rates is based on the empirical counterpart. Specifically, the point estimate, 95% confidence interval and p-value for the rate difference. If subjects discontinued from the study due to any cause prior to Day 22, it will be considered as developing *S. aureus* pneumonia by SDO1 and SDO2.
- The Kaplan-Meier analysis will be performed for the proportion of subjects who develop *S. aureus* pneumonia by Day 21 as determined by SDO1. The proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 will

be obtained from Kaplan-Meier estimates for each treatment group. The inference about the difference of two rates will be made via the Kaplan-Meier estimates and their corresponding variance estimates in the MITT population. The treatment difference of two rates, the corresponding 95% confidence intervals and p-value will be presented. In addition, the number and percentage of subjects who developed *S. aureus* pneumonia or were censored will be summarized. The Kaplan-Meier estimate of event rates evaluated at Day 21 and the corresponding 95% confidence intervals will be presented for each treatment group. Subjects who did not develop *S. aureus* pneumonia, discontinued from the study, or died prior to Day 22 will be considered censored. For the censored subjects, the last assessment date on which the subject did not develop *S. aureus* pneumonia based on the Investigator's assessment will be used as the date of censoring.

- The Kaplan-Meier analysis will be performed for the proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by SDO1 and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen.
- The Kaplan-Meier analysis will be performed for the proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by SDO2 and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen
- The Kaplan-Meier analysis will be performed for the proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen.
- An additional Kaplan-Meier analysis will be conducted for subjects with *S. aureus* pneumonia and presumed *S. aureus* pneumonia by SDO1 and SDO2. The presumed *S. aureus* pneumonia population includes those subjects with microbiologic results "Not Done" up to and including Day 7 (presumed *S. aureus* pneumonia).
- A third Kaplan-Meier analysis will be conducted for subjects with *S. aureus* pneumonia including those subjects with microbiologic results "Not Done" up to and including Day 10 (presumed *S. aureus* pneumonia) for both SDO1 and SDO2 populations.
- The proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen will be obtained from Kaplan-Meier estimates for each treatment group. Discontinuation from the study due to any cause up to but not including Day 22 will be considered as an 'Event'.
- The proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen will be

obtained from Kaplan-Meier estimates for each treatment group incorporating censoring. Discontinuation from the study due to any cause up to but not including Day 22 will be considered censored.

- The proportion of subjects who develop either *S. aureus* pneumonia up to but not including Day 22 as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia or another *S. aureus* infection up to but not including Day 22 will be obtained from Kaplan-Meier estimates for each treatment group. Discontinuation from the study due to any cause up to but not including Day 22 will be considered as an 'Event'.
- The proportion of subjects who develop either *S. aureus* pneumonia as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia or another *S. aureus* infection up to but not including Day 22 will be obtained from Kaplan-Meier estimates for each treatment group incorporating censoring. Discontinuation from the study due to any cause up to but not including Day 22 will be considered censored.
- The proportion of subjects who develop *S. aureus* pneumonia by Day 90 as determined by the Investigator's judgement will be obtained from Kaplan-Meier estimates for each treatment group. Discontinuation from the study due to any cause prior to Day 90 will be considered as an 'Event'.
- The proportion of subjects who develop *S. aureus* pneumonia by Day 90 as determined by the Investigator's judgement will be obtained from Kaplan-Meier estimates for each treatment group incorporating censoring. Discontinuation from the study due to any cause prior to Day 90 will be considered censored.
- In addition, the two-sided statistical test with 5% false positive rate for the treatment difference will be conducted based on the difference of two observed proportions of subjects who develop S. *aureus* pneumonia before Day 22 by both SDO1 and SDO2 populations. The treatment difference of two proportions, the corresponding 95% confidence intervals and p-values will also be provided based on a Wald test on equality of proportions.

The number and percentage of subjects with SDO1 and SDO2 of *S. aureus* pneumonia, no *S. aureus* pneumonia, indeterminate, and censored in each treatment group will be summarized descriptively.

7.11.3. Secondary Efficacy Endpoints

Duration of mechanical ventilation and length of hospital ICU stay during the first 21 days post-randomization will be summarized descriptively and compared between treatment groups using a Wilcoxon rank sum test in the MITT, ITT, and PP Populations.

The other secondary endpoint, 28-day all-cause mortality in the ITT, MITT and PP Population, will be descriptively summarized by treatment group. All-cause mortality rate at Day 28 based on Kaplan-Meier estimates along with the 95% confidence interval will also be presented for each treatment group. Subjects whose survival status are unknown

due to early termination or who are lost to follow up will be censored at the last day the subject was known to be alive.

7.11.4. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- Proportion of subjects in the ITT, MITT and PP Populations with a diagnosis of HABP >48 hours post-extubation up to, but not including, Day 22 in extubated subjects;
- Proportion of subjects in the ITT, MITT and PP Populations with development of VABP up to, but not including, Day 22;
- Incidence of all bacterial pneumonias up to, but not including, Day 22 in the MITT, ITT, and PP Populations;
- Incidence of other non-*S. aureus* pneumonias up to, but not including, Day 22 in the MITT, ITT, and PP Populations; and
- Incidence of other *S. aureus* infections acquired up to, but not including, Day 22 in the MITT, ITT, and PP Populations.
- Mechanical ventilation free days and ICU free days during the first 21 days, or prior to death, or early termination post randomization will be summarized descriptively and compared between treatment groups using a Wilcoxon rank sum test in the MITT, ITT, and PP Populations.
- Summary of pneumonia free days for subjects with *S. aureus* pneumonias, for subjects with bacterial pneumonias, and for subjects with any pneumonia in the MITT and PP Populations.
- Summary of All-cause mortality rate at Day 28 for subjects with any pneumonia in the MITT and PP Populations.

All exploratory efficacy endpoints will be descriptively summarized by treatment group.

7.11.5. Pharmacokinetic Endpoints

A listing of all PK serum sample collection dates and times and the PK BAL sample collection dates and times in the PK sub-study will be provided.

The statistical analyses for PK concentrations and parameters in serum and in BAL fluid in the PK sub-study will be performed by another vendor and described in a standalone PK analysis plan. The results will reside in a separate analytical report, which will be appended to the CSR.

7.12. Subgroup Analyses

The following subgroups will be used for subgroup analyses for the primary efficacy endpoint in the MITT and PP Populations, i.e. whether the subject has or doesn't have of *S. aureus* pneumonia up to, but not including, Day 22 for both SDO1 and SDO2

populations. The exploratory efficacy endpoints, the incidence of all pneumonias, and the incidence of other non-*S. aureus* pneumonias up to, but not including, Day 22 in the MITT and PP Populations, will also undergo the following subgroup analyses.

- Corrected Randomization stratification (Receipt or Non-Receipt of concomitant anti-staphylococcal antibiotics at the time of randomization that are potentially active against *S. aureus* pneumonia.)
- Type of ICU (e.g., SICU, MICU, Neuro ICU, Trauma ICU)
- Type of mechanical ventilation (Tracheotomy or Non-Tracheotomy) at Randomization
- Length of stay in the intensive care unit (ICU) post-treatment (<5, 5-12, >12-22, and >22 days)
- Duration of mechanical ventilation before randomization (48 vs. >48 hours)
- Baseline MRSA/MSSA from qualifying ETA culture
- Pneumonia MRSA/MSSA
- Reason for mechanical ventilation
- BMI categories: <25, 25-<30, 30-<35, and 35
- Age: <50, 50-<65, and >65
- WBC × 10^9/L at Baseline: <1, 1 to <2.5, 2.5 to <5, 5 to <10, and >10
- Platelet count × 10^9/L at Baseline: <50, 50 to <150; 150 to <400, and > 400
- Change in platelet count from Baseline: decrease by 50% or greater, or an increase by 50% or greater
- Male vs. female
- Smoker vs. non-smoker
- History of COPD vs. non-COPD
- History of alcohol use vs. no history of alcohol use
- Hospital readmission within 30 days after discharge
- Qualifying ETA and Screening ETA cultures: *S. aureus* only vs. co-colonized *S. aureus* and any Gram-negative at any time before randomization vs. co-colonized *S. aureus* and any other organism at any time before randomization
- Procalcitonin at Baseline for those who develop pneumonia vs. those who don't develop pneumonia: <median vs. median
- Qualifying ETA culture: *S. aureus* 3+ vs. 4+ vs. Heavy
- Cardiac events yes/no from receipt of study drug to Day 90 or early termination
- Multi organ failure yes/no from receipt of study drug to Day 90 or early termination

- Acute kidney injury defined by an absolute increase in serum creatinine of 0.3 mg/dL or a 50% increase (*viz*., 0.3 mg/dL increase if baseline 0.6 mg/dL and 50% increase if baseline is 0.6 mg/dL) within 48 hours from receipt of study drug
- Presence of renal disease at Baseline: serum creatinine <2 mg/dL and 2 mg/dl.

7.13. Analysis of Safety Data

All subjects in the Safety Population will be included in the safety analyses and analyzed based on the actual treatment received.

7.13.1. Adverse Events

Verbatim descriptions of Adverse Events (AEs) will be coded using Version 19.1 of MedDRA. Summary tables will be provided for all Treatment-Emergent Adverse Events (TEAEs). A TEAE is defined as an AE with a start date and time on or after the initiation of study drug administration. If the time of an AE is missing, it is considered treatment emergent if it starts on the same date as the initiation of study drug administration. All AEs (including non-TEAEs), Serious AEs (SAEs), and AEs leading to study drug discontinuation will be provided in listings by treatment group, subject ID, verbatim term, MedDRA system organ class (SOC) and preferred term (PT), start and end date, seriousness flag, severity, relationship to study drug, and action taken with study drug.

An overall summary of AEs will include the number and percentage of subjects in each treatment group who experienced at least one AE/TEAE in the following categories: any AE, any TEAE, any drug-related TEAE, any severe TEAE, any SAE, any drug-related SAE, any SAE leading to death, any TEAE leading to discontinuation of study drug, and any SAE leading to study drug discontinuation. Subjects with multiple events will be counted only once within each category. Severity grade and relationship will be counted using the maximum severity and the strongest relationship respectively for a subject with multiple TEAEs.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship (unrelated or related to study drug). For all analyses of TEAEs, if the same AE (based on PT) is reported for the same subject more than once, the AE is counted only once for that PT and at the highest severity and strongest relationship to study drug.

The number and percentage of subjects reporting a SAE and reporting a TEAE leading to discontinuation of study drug in each treatment group will be summarized by SOC and PT.

Listings will be provided for SAEs and AEs leading to drug discontinuation. In addition, all AEs will be listed.

7.13.2. Vital Signs

Vital sign measurements will include temperature, systolic and diastolic blood pressure, pulse, respiratory rate, and oxygenation status (as measured by pulse oximetry or arterial blood gas).

Vital sign measurements will be obtained at the Screening Visit, the Randomization Visit (Day 1 pre-dose), on Day 1 following administration of study drug, daily during the Monitoring Period (if subject is hospitalized), on Day 22, on the day of hospital discharge (for subjects who are discharged between Day 40 and Day 90), at the Day 90 Safety Visit (if the visit occurs onsite), or Early Termination (if applicable). Oxygenation status will be determined at the Screening and Randomization Visits via measurement of arterial blood gas, provided the subject has an arterial line placed. If no arterial line is present, pulse oximetry may be used.

Descriptive statistics will be used to summarize vital signs measurements and change from baseline by each scheduled time point.

All vital sign assessments will be listed by subject.

7.13.3. Electrocardiograms

A 12-lead ECG will be performed for all eligible subjects at the Randomization Visit (Day 1 pre-dose), on Day 22, on the day of hospital discharge (for subjects who are discharged between Day 40 and Day 90), at the Day 90 Safety Visit (if the visit occurs onsite), or Early Termination (if applicable).

Quantitative ECG parameters (HR, PR, QRS, QT, and RR) will be summarized with descriptive statistics for baseline, post-baseline, and change from baseline by each scheduled time point.

The number and percent of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG assessments will be tabulated.

All 12-lead ECG data will be listed by subject.

7.13.4. Clinical Laboratory Tests

Standard clinical laboratory profiles for safety assessments (including chemistry, hematology, coagulation, and urinalysis) will be collected and evaluated at the Randomization Visit (Day 1 pre-dose).

Blood samples for chemistry, hematology, and coagulation will be obtained on Days 2 (+1 day), 4 (±1 day), and 6 (±1 day) of the Monitoring Period, or Early Termination (if applicable and if clinically indicated). During Week 2 (Day 8 through Day 14) and/or Week 3 (Day 15 through Day 21) of the Monitoring Period, clinical laboratory assessments of chemistry, hematology, and coagulation will be performed twice a week while the subject remains hospitalized.

Urine for urinalysis will be obtained at the Randomization Visit (Day 1 pre-dose), on Day 6 (±1 day) of the Monitoring Period, or Early Termination (if applicable and if clinically indicated).

Below is a list of clinical laboratory analytes to be assessed:

Chemistry

Alanine aminotransferase (ALT)	Albumin
Alkaline phosphatase	Aspartate aminotransferase (AST)
Bicarbonate	Blood urea nitrogen
Calcium	Chloride
Creatinine	Direct bilirubin
Glucose	Phosphorus
Potassium	Sodium
Total bilirubin	Total protein

Hematology

Hematocrit	Hemoglobin
Platelet count	Red blood cell (RBC) count
White blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)	RBC indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), %Reticulocytes

Coagulation

Prothrombin time	Partial thromboplastin time (PTT)

Urinalysis

pH	Blood
Ketones	Specific Gravity
Leukocyte esterase	Bilirubin
Glucose	Nitrite
Protein	

Other Screening Tests as needed (for female subjects of childbearing potential only)

Urine and/or serum pregnancy test

Descriptive statistics will be provided for hematology, chemistry, urinalysis, and coagulation parameters and change from baseline by each scheduled time point.

Shift tables from baseline to the worst post-baseline value will be provided for selected chemistry parameters (Alanine aminotransferase, Aspartate aminotransferase, Total Bilirubin, Creatinine, and Alkaline phosphatase) and hematology parameters (Hematocrit, Hemoglobin, Platelets, White blood cell count and differential). Both scheduled and unscheduled visits will be considered. For chemistry parameters, the following categories will be used: <LLN, normal, >ULN and 3×ULN, >3×ULN to 5×ULN, >5×ULN, and missing. For hematology parameters, the following categories will be used: low, normal, high, and missing.

The number and percentage of subjects with the following PCS abnormal liver function test will be summarized:

- ALT 3×ULN, 5×ULN, 10×ULN, and 20×ULN
- AST 3×ULN, 5×ULN, 10×ULN, and 20×ULN
- ALT or AST 3×ULN, 5×ULN, 10×ULN, and 20×ULN

- Total bilirubin 1.5×ULN and 2×ULN
- ALP 1.5×ULN and 3×ULN
- ALT or AST 3×ULN and Total bilirubin 2×ULN
- Potential Hy's Law cases: ALT or AST 3×ULN, Total bilirubin 2×ULN, and ALP 2×ULN

A listing of subjects with any post-baseline abnormal liver function tests will be presented.

All clinical laboratory data will be listed. Values outside the normal ranges will be flagged.

7.13.5. Physical Examinations

A complete physical examination will be performed at the Screening Visit and as deemed necessary by the Investigator and will include, at a minimum, a pulmonary examination (including auscultation) and assessments of the skin, abdomen, cardiovascular, gastrointestinal, and neurological systems. Body weight and height will also be measured.

A limited physical examination will be performed at the Randomization Visit, daily during the Monitoring Period, on Day 22, on the day of hospital discharge (for subjects who are discharged between Day 40 and Day 90), at the Day 90 Safety Visit (if the visit occurs onsite), or Early Termination (if applicable). The limited physical examination will include, at a minimum, a pulmonary examination (including auscultation).

All abnormal physical examination findings will be listed by subject.

7.13.6. Radiographs and Imaging

A chest X-ray or thoracic CT scan is required on 4 occasions during the study as defined below for (1) initial Screening Visit, (2) Randomization Visit, (3) Post-BAL sampling for those subjects participating in the optional BAL sub-study, and (4) Monitoring Period (Day 2 through Day 22) for those subjects presenting with signs/symptoms suggestive of a respiratory infection.

Imaging should be conducted per institutional guidelines and assessed by the Investigator. The results of radiographs or imaging obtained at the Screening Visit and any subsequent visits should be documented on the appropriate eCRF. Radiograph or imaging reports and films will be collected for future analysis and will be uploaded within the EDC system.

All Radiographs and Imaging data will be listed by subject.

7.13.7. Immunogenicity

Samples to evaluate anti-drug antibody response, including neutralizing antibodies, to ASN-1 and ASN-2 will be collected from all subjects at the Randomization Visit (Day 1 pre-dose), upon discharge from the ICU (if discharge occurs prior to Day 22), on Day 22, on the day of hospital discharge (for subjects who are discharged between Day 40 and Day 90), and at the Day 90 Safety Visit (if the visit occurs onsite).

Subjects who discontinue early or are withdrawn from the study should also have samples collected as part of their Early Termination Visit. These samples will be sent to the central laboratory for analysis.

Samples will be screened for antibodies binding to ASN-1 and ASN-2 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the neutralizing ability of antibodies to ASN-1 or ASN-2 and/or to further characterize the immunogenicity of ASN-1 and ASN-2.

All anti-drug antibody data will be listed by subject.

The statistical analyses for ADA data will be performed by another vendor and described in a standalone analysis plan. The results will reside in a separate analytical report, which will be appended to the CSR.

8. GENERAL INFORMATION

8.1. Statistical Software

The creation of analysis datasets and statistical analyses will be done using SAS® version 9.3 or higher. The Medpace standard operating procedures (Medpace documents GL-DS-02-S2.1 and GL-DS-03-S1) will be followed for the validation of all SAS programs and outputs.

8.2. Format of Tables, Listings, and Figures

The format of tables, listings, and figures will be described in a stand-alone programming specifications document and will be finalized before database lock for the study.

9. CHANGES FROM PROTOCOL SPECIFIED ANALYSIS

The following analysis have been added which are not described in the protocol.

The primary efficacy analysis, based on comparing two proportions of subjects who develop *S. aureus* pneumonia by SDO2 up to but not including Day 22.

The Kaplan-Meier analysis will be performed for the proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by the SDO1.

The Kaplan-Meier analysis will be performed for the proportion of subjects who develop *S. aureus* pneumonia by up to but not including Day 22 as determined by the SDO1 and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen.

The Kaplan-Meier analysis will be performed for the proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by SDO2 and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen.

The Kaplan-Meier analysis will be performed for the proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen.

An additional Kaplan-Meier analysis will be conducted for subjects with *S. aureus* pneumonia and presumed *S. aureus* pneumonia by SDO1 and SDO2. The presumed *S. aureus* pneumonia population includes those subjects with microbiologic results "Not Done" up to and including Day 7 (presumed *S. aureus* pneumonia).

A third Kaplan-Meier analysis will be conducted for subjects with *S. aureus* pneumonia including those subjects with microbiologic results "Not Done" up to and including Day 10 (presumed *S. aureus* pneumonia) for both SDO1 and SDO2 populations.

The proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen will be obtained from Kaplan-Meier estimates for each treatment group. Discontinuation from the study due to any cause up to but not including Day 22 will be considered as an 'Event'.

The proportion of subjects who develop *S. aureus* pneumonia up to but not including Day 22 as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia pathogen will be obtained from Kaplan-Meier estimates for each treatment group incorporating censoring. Discontinuation from the study due to any cause up to but not including Day 22 will be considered censored.

The proportion of subjects who develop either *S. aureus* pneumonia by Day 21 as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia or another *S. aureus* infection up to but not including Day 22 will be obtained from Kaplan-Meier estimates for each treatment group. Discontinuation from the study due to any cause up to but not includingDay 22 will be considered as an 'Event'.

The proportion of subjects who develop either *S. aureus* pneumonia as determined by the Investigator's judgement and the Review Meeting's determination of *S. aureus* as a causative pneumonia or another *S. aureus* infection up to but not including Day 22 will be obtained from Kaplan-Meier estimates for each treatment group incorporating censoring. Discontinuation from the study due to any cause prior to Day 22 will be considered censored.

The proportion of subjects who develop *S. aureus* pneumonia by Day 90 as determined by the Investigator's judgement will be obtained from Kaplan-Meier estimates for each treatment group. Discontinuation from the study due to any cause prior to Day 90 will be considered as an 'Event'.

The proportion of subjects who develop *S. aureus* pneumonia by Day 90 as determined by the Investigator's judgement will be obtained from Kaplan-Meier estimates for each treatment group incorporating censoring. Discontinuation from the study due to any cause prior to Day 90 will be considered censored.

Mechanical ventilation free days and ICU free days during the first 21 days, or prior to death, or early termination post randomization will be summarized descriptively and compared between treatment groups using a Wilcoxon rank sum test in the MITT, ITT, and PP Populations.

Summary of pneumonia free days for subjects with *S. aureus* pneumonias and for subjects with all pneumonias in the MITT and PP Populations.

Summary of All-cause mortality rate at Day 28 for subjects with any pneumonia in the MITT and PP Populations.