Statistical Analysis Plan
(SAP)

Placebo-controlled, double-blind, randomized study of Aerucin® as adjunct therapy to antibiotics in the treatment of *P. aeruginosa* pneumonia

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SAP APPROVAL FORM

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABG	arterial blood gas
ADA	anti-drug antibody
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
APACHE II	acute physiology and chronic health evaluation II
AST	aspartate transaminase
ATC	Anatomical therapeutic class
BAL	broncho-alveolar lavage
BMI	body mass index
BUN	blood urea nitrogen
CK	creatine kinase
CRP	c-reactive protein
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
DMC	Data Monitoring Committee
ECG	electrocardiography
eCRF	electronic case report form
EDC	electronic data capture
ETA	endotracheal aspiration
GFR	glomerular filtration rate
ICU	intensive-care units
INR	international normalized ratio
ITT	Intent-to-Treat
IWRS	interactive web-based randomization system
LDH	lactate dehydrogenase
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
micro-ITT	Microbiological Intent-to-Treat
P. aeruginosa	*Pseudomonas aeruginosa*
PK	Pharmacokinetic(s)
PP	Per-protocol Population
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	standard of cure
SOFA	sequential organ failure assessment
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TESAE	treatment-emergent serious adverse event
VABP	ventilator-associated bacterial pneumonia
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with Protocol AR-105-002 (Version 3.0, 09 November 2018). The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2. STUDY OBJECTIVES

2.1. Primary Clinical Efficacy Objective

To assess the efficacy of Aerucin®, administered as a single dose in addition to standard of care (SOC) antibiotic regimen on Clinical Cure rates (resolution of pneumonia) between SOC alone and SOC with Aerucin® at Day 21.

2.2. Primary Clinical Safety Objective

To assess the clinical safety and tolerability of Aerucin® in the study population.

2.3. Secondary Clinical Efficacy Objectives

To assess the effect of Aerucin®, administered as a single dose in combination with SOC antibiotic regimen as an adjunct therapy of *P. aeruginosa* pneumonia, as compared to standard antibiotic therapy alone, on the following parameters:

1. Clinical Cure rates at Day 28, 14 and 7, using the same criteria as for the primary efficacy objective.
2. Time to Clinical Cure.
3. Mortality and Pneumonia-related mortality post-treatment.
4. Respiratory functional assessment: Time on mechanical ventilation (including if tracheostomy is in place). Time on supplemental oxygenation. Measures of respiratory health such as changes in PaO_2/FiO_2, using arterial blood gases and/or pulse oximetry measurements.
5. Overall clinical status: Changes in sequential organ failure assessment (SOFA) score.
6. Health economics: antibiotic utilization, duration of stay in the intensive care unit (ICU), duration of hospitalization, duration of intubation with ventilation or duration of mechanical ventilation if tracheostomy in place.

2.4. Pharmacokinetics (PK) Objective

To assess the PK Profile of Aerucin®.

2.5. Secondary Safety Objectives

To assess the immunogenicity of Aerucin®.

2.6. Microbiological Efficacy Objectives

To assess the effect of Aerucin®, administered as a single dose in combination with SOC antibiotic regimen as an adjunct therapy of *P. aeruginosa* pneumonia, as compared to standard antibiotic therapy alone, on the following parameters:

1. Eradication of index *P. aeruginosa* at Day 21 and 28 post-treatment,
2. Re-infection/new infection defined as a reoccurrence of pneumonia due to *P. aeruginosa* within the 28-day follow-up period,
3. Reduction in bacterial load related to the index *P.* aeruginosa

3. STUDY DESIGN

3.1. General Study Design and Plan

This study is an international, multicenter, prospective, double blind, randomized, placebo-controlled, parallel design protocol. It will be performed at multiple ICUs.

Patients with a documented diagnosis of pneumonia, due to *P. aeruginosa*, and require ICU care, who are intubated (or have a tracheostomy tube in place) and are mechanically ventilated, are eligible for screening.

Patients meeting all other eligibility requirements will be assessed for *P. aeruginosa* pulmonary infection on the basis of culture results (known from recent quantitative/semi-quantitative cultures) or on the basis of rapid diagnostic testing of a fresh airway specimen using methods available at the site (e.g. mass spectrometry, Polymerase Chain Reaction, etc.), or using devices such as CE marked Cepheid's GeneXpert® with "Investigational / Research Use Only" (IUO / RUO) PA Cartridge, or BioFire Diagnostics, LLC (a BioMerieux company)'s IUO FilmArray® LRTI Panel.

Acceptable airway samples are broncho-alveolar lavage (BAL), mini-BAL, or endotracheal aspiration (ETA) (ETA sample with <10 squamous epithelial cells and >25 polymorphonuclear cells per low power field). It is expected that some subjects will have a positive rapid diagnostic test result that will not be confirmed by standard microbial culture (quantitative, or semi-quantitative). These subjects will be followed according to all the procedures described in this protocol but will not accrue toward the target microbiologically evaluable intent to treat population (micro-ITT). Subjects with a positive diagnosis of *P. aeruginosa* pulmonary infection will be randomized to receive either investigational product or matching placebo (more than one pathogen allowed, if *P. aeruginosa* is regarded a key pneumonia causing pathogen). In total, approximately 154 microbiologically evaluable subjects will be randomized 1-1 to be treated with placebo plus SOC or Aerucin® (20 mg/kg) plus SOC in this Phase 2/3 study.

The randomization procedure will account for the fact that many study sites will enroll only a few patients. Randomization will account for existence of sub-populations regarding oxygen status at baseline (PaO2/FiO2 ≤200 or >200).

Study subjects will receive a single treatment dose (at Day 0) in addition to SOC antibiotic treatment, and then enter a safety, efficacy and PK follow-up study period for a total study duration of 28 days. The selection of SOC antibiotics is made in accordance with local best practices at the discretion of the investigator and should not exceed a duration of 14 days.

The clinical course of pneumonia will be assessed daily by the investigator. Once Clinical Cure has been determined, the clinical status of the subject will be monitored to confirm continuation of Clinical Cure, re-infection (pneumonia due to *P. aeruginosa*), or new infection (pneumonia due to an unknown pathogen or a pathogen other than *P. aeruginosa*). "Clinical Cure" can be declared at any time during the study by the PI provided, that the required criteria are met either based on documented improvements in signs and symptoms, +/- changes documented by chest X-ray (if performed as part of SOC), as interpreted by the investigator.

The assessment of Clinical Cure (resolution of pneumonia) by the site investigator will be used for the primary analysis. An adjudication committee will apply newly defined Clinical Cure criteria post hoc in a secondary analysis. "Clinical Cure" will be assessed for analytical purposes on Day 7, 14, 21 (primary efficacy endpoint) and 28.

Clinical safety assessments will be performed on an ongoing basis while predefined laboratory assessments will be performed at baseline, and thereafter at Day 4, 7, 14, 21, and 28. Test results obtained for medical reasons between these mandatory time points will be assessed for adverse events and documented accordingly.

Secondary efficacy endpoints will be assessed in a similar manner during the 28-day period, when appropriate, daily when possible (e.g., time on mechanical ventilation including if tracheostomy is in place, time on supplemental oxygenation, measures of respiratory health such as changes in PaO_2/FiO_2 using arterial blood gases and/or pulse oximetry measurements), or upon occurrence (e.g., antibiotic utilization, duration of stay in the ICU, duration of hospitalization, duration of intubation with ventilation, or duration of mechanical ventilation if tracheostomy in place).

Microbiological endpoints of eradication and re-infection/new infection will be determined based on quantitative/semi quantitative cultures performed by the local laboratory and testing of isolates performed by a central microbiology laboratory.

Two PK analyses will be performed to assess the PK profile of Aerucin® in the target patient population. The pharmacokinetics of Aerucin® will be assessed using a population PK (compartmental modeling) approach as well as a non-compartmental analysis approach. A PK sub-study ("Full PK") will be included, wherein more extensive sampling will be performed in a small number of patients (from select sites) who provide consent (i.e., 16 patients to obtain 8 patients on active treatment). In the remaining patients, a sparse sampling strategy will be implemented with only a few samples obtained from each patient at varying time points ("Sparse PK"). A compartmental population PK model will be developed using the PK data collected from the sub-study and the sparse samples. PK parameters will be estimated as well as between-subject or inter-individual variability and residual variability. The effects of select factors describing the characteristics of sub-populations of interest (e.g. high or low bacterial load, cause of admission [trauma or non-trauma], and type of pneumonia) on the PK of Aerucin® will be assessed via covariate analysis. In addition to the population PK evaluation, non-compartmental analysis of the PK sub-study data will be performed.

The investigational therapy will be studied as an adjunct to antibiotic therapy as prescribed by the study investigator according to the SOC in his/her institution. The duration and nature of the initial and any subsequent antibiotic therapy related to the baseline pneumonia event and other infections will be recorded. Duration of antibiotic treatment for the index pneumonia should not exceed 14 days.

3.2. Randomization and Blinding

This is a double-bind, placebo-controlled study. Study subjects will be first stratified as follows:

- Stratum 1: ventilator-associated bacterial pneumonia (VABP) or non-VABP
- Stratum 2: PaO_2/FiO_2 ≤200 or >200
- Stratum 3: Americas, Eastern EU, Western EU and Asia

Randomization will proceed in a 1:1 ratio, in blocks of 4, for the study overall.

A computer-generated randomization schedule will be used to allocate study treatment according to the above randomization scheme. Upon confirmation of eligibility, the study personnel will be prompted to randomize the study subject using the electronic data capture (EDC) / interactive web-based randomization system (IWRS) system.

3.3. Breaking the Blind

The Investigator will be allowed to break the blind if, in his/her opinion, this is necessary to provide proper medical care to his/her patient. In general, study drug unblinding should not impact any necessary treatment decisions by the investigator. Prior to breaking the blind, the Investigator will confer with the Medical Monitor to confirm the necessity of such action.

In the absence of the Investigator, the Medical Monitor may break the blind for a specific study subject under such urgent circumstances and after assessing the necessity of such action with a sub-investigator.

Members of the Data Monitoring Committee (DMC) will be allowed to break the blind if it is deemed necessary to assess specific adverse events.

The circumstances leading to breaking the blind will be fully documented in detail in a memo to file and as required, in the EDC system.

3.4. Study Drug Administration

Upon randomization, the number of vials of study drug based on subject's weight required for treatment will be displayed by the EDC / IWRS system, and access will be given to the inventory corresponding to the treatment allocation of the subject. Study personnel will then select the specific vials required, up to a maximum of 20 vials from the inventory available on site. Subjects weighing over 120 kg will receive the amount of Aerucin® or placebo corresponding to 120 kg, i.e. 20 vials.

The entire content of the bag must then be administered intravenously at room temperature in approximately 2 hours. The study drug will be administered once, intravenously, in a strictly monitored setting.

3.5. Study Assessments

Table 1 presents the schedule of assessments of the study.

Table 1. Schedule of Assessments

Visit	Screening, Baseline, and Randomization	Treatment	Follow-up (Daily until index pneumonia is considered resolved)	Follow-up Any setting	End of Study[14] or Early Termination[17]
Day	-1	0	1 to 28 Daily	4, 7, 14, 21	28 or Day of Termination
Informed Consent	X				
Eligibility	X				
Demographics	X				
Type of Pneumonia[10]	X				
Medical history	X				
Surgical History	X				
Case history	X				
Concomitant medications	X	X	X	X	X
Physical exam	X			X	X
Vital signs[11]	X	X	X	X	X
12-lead ECG	X				
Safety laboratory tests	X		X[1]	X	X
Sampling: ADA	X[3]				X
Sampling: Future Biomarkers (where applicable)				X	X
Sampling: PK	X[4]	X[5,6]	X[5,6]	X[5,6]	X[5,6]
Microbiology: rapid testing	X				
Microbiology: classic	X		X[1]	X[1]	X[1]
Sampling: microbiology	X		X[1]	X[1]	X[1]
Respiratory data	X	X[2]	X[1]	X	X
Arterial gases or pulse oximetry[16]	X	X		X	X
PaO_2/FiO_2 ratio	X	X	X	X	X
APACHE II	X				
SOFA	X	X	X[2]		
Randomization	X[7]				
Treatment		X			
Assessment of Clinical Cure			X[8]	X	X
Adverse events		X	X	X	X
Chest X-Rays	X[12]				
Pregnancy Test (Urine or Serum)	X[13]				
Discharge data					X[9]
Study Follow-Up Phone Call				X[15]	X[15]

Visit	Screening, Baseline, and Randomization	Treatment	Follow-up (Daily until index pneumonia is considered resolved)	Follow-up Any setting	End of Study[14] or Early Termination[17]
Day	-1	0	1 to 28 Daily	4, 7, 14, 21	28 or Day of Termination

1. To be performed if medically necessary. Follow-up airway specimens to be obtained as medically necessary and prior to extubation and at Day 28 (if not extubated prior to then) for quantitative or semi-quantitative culture.
2. SOFA and respiratory data to be collected on Day 0, 12 hours after treatment initiation and on Day 4, 7, 14, 21, 28 while intubated and mechanically ventilated. Parameters for SOFA score calculation should not be older than 72 hours.
3. ADA only at screening / baseline and Day 28, or at early termination.
4. Pre-dose PK sample to be obtained prior to treatment initiation.
5. PK samples to be obtained for the FULL PK sub-study at the following times after initiation of treatment: 2 hours (end of infusion), 4h, 12h, and 24 hours and 1 sample at each of the following visits: Day 4, 7, 14, 21, and 28.
6. PK samples for the SPARSE PK sub-study at the following times after initiation of treatment: 1 sample at 2 hours (end of infusion), 1 sample at either 4h, 12h, or 24 hours post-treatment initiation (inclusive) and 1 sample at any of the following visits: Day 4, 7, 14, 21, or 28.
7. Eligible subjects are randomized on Day -1, Treatment day is Day 0 for the purpose of monitoring and collecting the required samples over the first 24 hours.
8. Clinical Cure will be assessed at Day 7, 14, 21, 28 for the analytical purposes.
9. Discharge data to be obtained when discharge occurs or Day 28, whichever occurs first.
10. Patients with pneumonia who are intubated are eligible for screening regardless of the type of pneumonia, which will be recorded at the time of screening for all study subjects.
11. Vital signs will be recorded at baseline prior to treatment (time 0) and then at 1, 2, 4, 12, and 24 hours post treatment. Vital signs will also be recorded daily thereafter.
12. In addition to the screening timepoint, chest x-ray(s) are to be taken at any time as medically indicated.
13. Women of child bearing potential must take a urine or serum pregnancy test at the time of Screening.
14. For subjects with early discharge, effort must be made to perform all protocol defined procedures outlined for End of Study/Early Termination.
15. Subjects who decide to discontinue study assessments prior to Day 28 will receive a study exit safety follow-up phone call on key days (Day 4, 7, 14, 21, 28) until Day 28 (+7 days) to assess Clinical Cure, survival and the status of any adverse events.
16. Changes in PaO_2/FiO_2 ratio (e.g. by arterial blood gases), if available and whenever possible OR changes in non-invasive measures of oxygenation (e.g. by pulse oximetry)
17. A few days before or after the specified date is acceptable (± 2 days)

4. SAMPLE SIZE DETERMINATION

The primary efficacy endpoint is the proportion of subjects with Clinical Cure at Day 21.

It is assumed that the proportion of subjects with Clinical Cure will be 65% in the placebo group, and 85% in the 20 mg/kg dose group. With 69 subjects per group, there will be >90% power for a statistically significant difference at a two-sided 0.05 level of significance. Sample size calculation was performed based on Fisher's Exact test using binomial enumerations (PASS version 14). Assuming a 10% drop-out rate, approximately 154 subjects (77 per group) will be randomized.

5. STUDY ENDPOINTS

5.1. Primary Clinical Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with Clinical Cure at Day 21 in patients treated with Aerucin® versus the placebo group as assessed by the investigator. The investigators' assessment will be the primary analysis of the primary endpoint.

Additionally, newly defined Clinical Cure criteria (Table 2) will be applied post-hoc by an independent adjudication committee.

Table 2 Criteria for Clinical Cure

1. The subject must be alive through the index day visit
2. The patient must have **improved respiratory function** evaluated at the index day, because: • The patient is now off the ventilator and extubated or 3. if the patient entered the study with mechanical ventilation due to reasons other than pneumonia and was assessed "*likely ventilated beyond day 28"* at screening, criteria #1 (survival) and #4 (no signs and symptoms of pneumonia) are sufficient to establish Clinical Cure (*presumed not ventilated*)
4. The subject must show **no clinical signs and symptoms of bacterial pneumonia** at the index day, which is determined by • Not receiving any antibiotic therapy active against the initial *P. aeruginosa* strain or against persisting pulmonary bacterial infection for 48 hours (antibiotic therapy for documented extra-pulmonary infection permitted) **and** • Resolution of signs and symptoms of bacterial pneumonia, **as determined by the PI based on their clinical assessment**. Parameters to be considered may include: o Absence of lung abscess or empyema o Fever > 38°C or hypothermia (< 35°C) attributable to the primary bacterial pneumonia o Tachypnea or shortness of breath (> 22 respirations/min) if off the ventilator and/or back to baseline respiratory rate

- Tachycardia (> 100 bpm) or bradycardia (< 60 bpm) and/or back to baseline heart rate
- Improvement of hypoxemia (ABG or PaO_2/FiO_2 > 200 or pulse oximetry > 90%)
- If patient still produces sputum - negative *P. aeruginosa* culture from sputum, blood or pleural fluid

5.2. Secondary Clinical Efficacy Endpoints

The secondary clinical efficacy endpoints are the following:

1. Proportion of patients with Clinical Cure at Day 28
2. Proportion of patients with Clinical Cure at Day 14
3. Proportion of subjects who died (All-cause mortality) at Day 28
4. Proportion of subjects who died due to pneumonia (Pneumonia-related mortality) at Day 28
5. Proportion of patients with Clinical Cure at Day 7
6. Change from baseline in respiratory functional assessment: Time on mechanical ventilation (including if tracheostomy is in place). Time on supplemental oxygenation. Measures of respiratory health such as changes in PaO_2/FiO_2, using arterial blood gases and/or pulse oximetry measurements.
7. Mean change from baseline in overall clinical status measured by SOFA scores.
8. Health economics: antibiotic utilization, duration of stay in the ICU, duration of hospitalization, duration of intubation with ventilation or duration of mechanical ventilation if tracheostomy is in place.

5.3. Microbiological Endpoints

The microbiological endpoints have the following:

1. Microbiological outcome as measured by the proportion of subjects with the index *P.* aeruginosa pneumonia based on the data provided by the local microbiology laboratory and central microbiology laboratory.
2. Proportion of subjects achieving the eradication of *P.* aeruginosa at Day 21 and 28. Eradication is considered as obtained when a specimen of respiratory secretions is obtained between the visit day and Day 28 and is negative. When no specimen is obtained within this time frame, microbiological outcome will be assessed as "Eradicated" only if the study subject is not receiving any antibiotic active against the initial strain after the study drug administration visit day and displays no signs and symptoms of pneumonia.
3. Change in bacterial load related to the index *P.* aeruginosa on the basis of quantitative or semi-quantitative cultures by the local microbiological laboratory.

5.4. Pharmacokinetic Endpoints

The pharmacokinetic endpoints are the following:

- Assessment of the PK parameters during full PK sub-study.
- Assessment of the PK parameters during sparse PK sub-study.

5.5. Safety Endpoints

The safety endpoints are the following:

1. Assessment of clinical adverse events
2. Assessment of clinical laboratory safety tests
3. Assessment of immunogenicity to Aerucin®

6. STATISTICAL METHODOLOGY

6.1. General Considerations

6.1.1. Definition of Baseline

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

6.1.2. General Analysis Approach

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

The comparisons for the endpoints will be between the 20 mg/kg dose group and the placebo and will be performed at a two-sided 0.05 level of significance.

6.1.3. Hypotheses

1. Treatment of *P. aeruginosa* pneumonia with Aerucin® improves the rate of Clinical Cure of the index pneumonia.
2. Treatment of *P. aeruginosa* pneumonia with Aerucin® results in an increase in survival rate in the target population
3. Treatment of *P. aeruginosa* pneumonia with Aerucin® improves microbiological, functional and health economic outcomes overall.
4. Aerucin® at the proposed dose level is safe based on clinical observation, standard laboratory tests, and frequency and nature of related adverse events.
5. Aerucin® does not trigger an adverse immunogenic response (i.e., anti-Aerucin® immunogenicity).

6.1.4. Multiplicity

The study has one primary efficacy endpoint. The secondary efficacy endpoints will be tested sequentially at the 0.05 level to control the overall Type I error rate. Each key secondary endpoint will be tested in pre-specified order.

6.1.5. Handling of Dropouts and Missing Data

Missing data will be handled as follows:

- For clinical outcome at Day 7, 14, 21, and 28, missing data will be handled using the nearest clinical data available prior to that day, i.e. last observation carried forward (LOCF) approach.
- For microbiological outcome at Day 7, 14, 21, and 28, missing data will be handled using the nearest microbiological data available prior to that day, i.e. LOCF approach.
- In cases of missing or incomplete dates [e.g. adverse event (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 will be presented in the data listings.
- A conservative approach will be taken to assess the relationship of an AE to study drug: if the relationship of an event is missing, it will be considered treatment-related. Missing severity for an AE will not be imputed.
- Missing values for other variables will not be imputed and only observed values will be used in data analyses and summaries.

6.2. Analysis Populations

6.2.1. Safety Population

The Safety Population is defined as all subjects who have received the study drug. All safety data will be analyzed using the Safety Population. In the event that a subject took the wrong study drug (i.e., did not take the randomized study drug), the actual treatment received will be used for analysis.

6.2.2. Intent-to Treat Population (ITT)

The ITT Population is defined as all subjects who have been randomized and treated with any amount of study drug, regardless of microbiological documentation. Subjects will be analyzed by randomized treatment group.

6.2.3. Microbiological Intent-to-Treat Population (micro-ITT)

The micro-ITT Population is defined as all ITT subjects for whom microbiological documentation of pneumonia due to *P.* aeruginosa at screening/baseline has been obtained.

The micro-ITT population will be used for efficacy analyses. Subjects will be analyzed by randomized treatment group.

6.2.4. Per-protocol Population (PP)

The PP Population is defined as all micro-ITT subjects who completed the study without any major protocol deviation. Major protocol deviations may include but are not limited to:

- Have major inclusion or exclusion violations
- Take the wrong study drug (i.e., did not take the randomized study drug)
- Do not have Day 21 assessment unless deemed a treatment failure at an earlier time point
- Receive non-study potentially-effective concomitant antibiotic therapy against *P.* aeruginosa except in case of treatment failure

Based on the above criteria, the validity listings will be provided to identify which subjects to be excluded from the Per-protocol Population (PP). After the study team's review in a blinded manner, the decision to exclude a subject from the PP Population will be finalized and a list of subjects with major protocol deviations leading to exclusion from the PP Population will be finalized and documented prior to unblinding the randomized treatment assignments..

6.3. Subject Data and Study Conduct

6.3.1. Subject Disposition

Subject disposition will be summarized by treatment group and in total for all randomized subjects. The following subject disposition categories will be included in the summary:

- Subjects who were randomized,
- Subjects who received study drug,
- Subjects who did not receive study drug,
- Subjects who completed the study, and
- Subjects who did not complete the study.

For subjects who did not complete the study, a summary will be provided by reason for discontinuation. Counts and percentages of subjects in each defined analysis population will be tabulated by treatment group and in total based on all randomized subjects.

6.3.2. Protocol Deviations

The number of subjects with reportable protocol deviations in each category will be summarized by treatment group and in total for the ITT Population.
All protocol deviations will be listed by subject.

6.3.3. Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years or ≥65 years);
- Sex;
- Race;
- Ethnicity;
- Height (cm);
- Weight (kg);
- Body mass index (BMI) (kg/m^2) ;
- Randomization stratum 1: VABP or non-VABP;
- Randomization stratum 2: PaO_2/FiO_2 ≤200 or >200;
- Randomization stratum 3: Americas, Eastern EU, Western EU or Asia;
- Baseline APACHE score: ≥20 and <20;
- Baseline pathogen status: Monopathogen (*P. aeruginosa* only) or Multiple pathogens in baseline culture;
- Baseline pathogen susceptibility for P. aeruginosa: Multi Drug Resistant (MDR) or Susceptible for *P. aeruginosa*;
- Reason for admission to ICU at baseline (Trauma or Non-trauma);
- Randomization confirmed method: Rapid test only or Culture confirmed randomization; and
- Time from Pneumonia Diagnosis (days).

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment group and in total for the ITT, micro-ITT, and PP Populations.

6.3.4. Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1). Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment group and in total based on the ITT Population.

6.3.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization Drug Dictionary (WHO DDE B2 September 1, 2016).

Prior medications are medications used before the administration of the study drug. Concomitant medications are medications that were taken on or after the administration of the study drug.

The counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment group and in total based on the micro-ITT Population. In addition, the number and percentage of subjects taking prior antibiotics within 48 hours of study treatment will be summarized by ATC class and preferred term for each treatment group.

All prior and concomitant medications and procedures will be listed by subject.

6.3.6. Compliance to Study Drug

Compliance with study drug will be summarized and will be defined as the actual dose of study drug taken divided by intended dose multiplied by 100. Percent compliance as a continuous variable and the proportion of patients with <90% and ≥90% compliance will be summarized by treatment group for the Safety and micro-ITT Populations.

6.4. Efficacy Analyses

6.4.1. Primary Clinical Efficacy Endpoint

6.4.1.1. Primary Analysis

The primary efficacy endpoint is the proportion of patients with clinical cure at Day 21 in patients treated with Aerucin® versus the placebo group as assessed by the investigator. The investigators' assessment will be the primary analysis of the primary endpoint.

The proportion of patients with clinical cure rate at Day 21 will be summarized by randomized treatment based on the micro-ITT Population and will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test based on baseline randomization strata (stratum 1: VABP or non-VABP, stratum 2: PaO2/FiO2 ≤200 or >200, and stratum 3: Americas, Eastern EU, Western EU and Asia). The P-value from the stratified CMH test will be presented. Prior to the unblinding, the assessment of each strata and strata combinations with respect to the sample size and the corresponding number of endpoints if any or some strata need to be combined to be able to process with the analysis or an alternative method is called for (e.g. Fisher's Exact test).

For the primary analysis, subjects who dropped out or had missing outcome data will be included in the denominator. Missing data will be imputed using the nearest clinical data available prior to that day, i.e. LOCF approach.

Sensitivity Analyses

Sensitivity analyses of the primary efficacy endpoint will be conducted as follows:

- The proportion of patients with clinical cure at Day 21 will be analyzed based on the PP Population.
- The proportion of patients with clinical cure at Day 21 will be analyzed with missing data imputed as the following. If the last observation of clinical outcome assessment prior to Day 21 is a failure, failure will be carried forward to Day 21. Otherwise, missing outcome at Day 21 will be imputed as 'Indeterminate'.
- The proportion of patients with clinical cure at Day 21 will be analyzed based on observed case.

6.4.1.2. Secondary Analyses

The clinical cure at Day 21 assessed by an independent adjudication committee based on newly defined clinical cure criteria post hoc will be the secondary analysis. The secondary analysis will be performed based on the micro-ITT and PP Populations in the same manner as the primary analysis.

6.4.2. Secondary Clinical Efficacy Endpoints

Secondary endpoints will be analyzed using a hierarchical sequential testing procedure in the following predefined order.

1. Proportion of patients with Clinical Cure at Day 28
2. Proportion of patients with Clinical Cure at Day 14
3. All-cause mortality at Day 28
4. Pneumonia-related mortality at Day 28
5. Proportion of patients with Clinical Cure at Day 7
6. Change from baseline in respiratory functional assessment: Time on mechanical ventilation (including if tracheostomy is in place). Time on supplemental oxygenation. Measures of respiratory health such as changes in PaO_2/FiO_2, using arterial blood gases and/or pulse oximetry measurements.
7. Mean change from baseline in overall clinical status measured by SOFA scores.
8. Health economics: antibiotic utilization, duration of stay in the ICU, duration of hospitalization, duration of intubation with ventilation or duration of mechanical ventilation if tracheostomy is in place.

6.4.2.1. Clinical Cure

The proportion of subjects with clinical cure at Day 7, Day 14, and Day 28 will be analyzed using stratified CMH test. The P-value will be presented. The number and percentages of subjects with the clinical cure at the different timepoints will be summarized by treatment group for the micro-ITT Population.

Time to clinical cure is defined as the number of days from the administration of the study drug to the date of the first clinical cure assessed by the investigator plus 1.

Time to clinical cure will be evaluated by the Kaplan-Meier method and compared using the stratified log-rank test based on the stratification factors at randomization. The stratified log - rank P-value will be presented. In addition, the Kaplan-Meier estimate of Q1, Q3, and the median time to the event and the associated 95% confidence interval will be presented for each treatment group. Subjects without clinical cure will be censored to the last assessment date.

The number and percentage of subjects with clinical cure and subjects censored will be tabulated by treatment group for the micro-ITT Population.

6.4.2.2. Mortality

All-cause mortality and pneumonia-related mortality rate by Day 7, 14, 21, and 28 will be tabulated by treatment group for the micro-ITT Population and analyzed using a stratified CMH test based on the stratification factors at randomization. The P-value from the stratified CMH test will be presented. In addition, plots of the Kaplan-Meier estimate of the survival distribution function over time will be presented by treatment group.

6.4.2.3. Respiratory Functional Assessments and SOFA Scores

The following respiratory functional assessment endpoints will be summarized by treatment group based on the micro-ITT Population:

- Time on mechanical ventilation (including if tracheostomy is in place);
- Time on supplemental oxygenation; and
- Measures of respiratory health such as changes in PaO_2/FiO_2, using arterial blood gases and/or pulse oximetry measurements.

Time on mechanical ventilation is defined as the total number of days on mechanical ventilation after the administration of the study drug.

Time on supplemental oxygenation is defined as the total number of days on supplemental oxygenation after the administration of the study drug.

Time on mechanical ventilation and time on supplemental oxygenation will be summarized by treatment group.

PaO_2/FiO_2 ratio and SOFA score at baseline, post-baseline visits, and change from baseline will be summarized by treatment group based on the micro-ITT Population.

Time on mechanical ventilation, time on supplemental oxygenation, change from baseline in PaO_2/FiO_2 ratio and SOFA scores will be analyzed using an Analysis of Variance (ANOVA) model, with treatment as a main effect, site and baseline randomization strata as factors. Treatment by site interaction will be evaluated separately. The least squares (LS) mean, standard errors, and the 2-tailed 95% confidence intervals of the change for each treatment group will be estimated. For the between-treatment group comparisons, the differences in LS means, corresponding standard errors, 95% confidence intervals, and p-values will be obtained from the ANOVA model and presented.

6.4.2.4. Health Economics Assessments

The following health economics endpoints will be summarized by treatment group for the micro-ITT Population:

- Duration of antibiotic utilization;
- Duration of stay in the ICU; and
- Duration of hospitalization.

Duration of antibiotic utilization is defined as the number of days that the subjects received antibiotic therapy after the administration of the study drug.

Duration of stay in the ICU is defined as the total number of days of ICU stay after the administration of the study drug.

Duration of hospitalization is defined as the total number of days of hospitalization after the administration of the study drug.

Duration of antibiotic utilization, duration of stay in the ICU, and duration of hospitalization will be analyzed using an ANOVA model, with treatment as a main effect, site and baseline

randomization strata as factors. The treatment differences in LS means, corresponding standard errors, 95% confidence intervals, and p-values will be obtained from the ANOVA model and presented.

6.4.3. Microbiological Endpoints

Microbiological endpoints include the following:

- Eradication of index *P. aeruginosa* at Day 21 and 28;
- Re-infection/new infection defined as a reoccurrence of pneumonia due to *P.* aeruginosa within the 28-day follow-up period; and
- Change in bacterial load related to the index *P. aeruginosa* on the basis of quantitative or semi-quantitative cultures by the local microbiological laboratory.

Microbiological endpoints of eradication and re-infection/new infection will be determined based on quantitative/semi quantitative cultures performed by the local laboratory and testing of isolates performed by a central microbiology laboratory.

For microbiological outcome of eradication of index *P. aeruginosa,* if no specimen of respiratory secretions is obtained at the specific time point, the nearest microbiological data available prior to that day (Day 7, 14, 21, or 28) will be used, i.e. using LOCF approach. When there is no specimen obtained prior to that day, microbiological outcome will be assessed as "Eradicated" only if the study subject is not receiving any antibiotic active against the initial strain after the study drug administration and prior to that day and displays no signs and symptoms of pneumonia.

The eradication rate of index *P. aeruginosa* and reinfection rate of pneumonia due to *P. aeruginosa* will be summarized by treatment group based on the micro-ITT Population and analyzed using a stratified CMH test based on the stratification factors at randomization. The P-value from the stratified CMH test will be presented.

Change in bacterial load (log_{10}cfu/mL) related to the index *P. aeruginosa* based on the local microbiological laboratory will be presented by treatment group for the micro-ITT Population.

6.4.4. Subgroup Analysis

The following selected subgroups may be performed for subgroup analysis for the primary efficacy endpoint, i.e. the proportion of patients with clinical cure rate at Day 21 as assessed by the investigator based on the micro-ITT Population.

- Randomization stratum: Geographic regions (Americas, Eastern EU, Western EU, versus Asia)
- Randomization stratum: PaO2/FiO2 >200 versus ≤200
- APACHE score ≥20 versus <20 at baseline
- Monopathogen (*P. aeruginosa* only) versus multiple pathogens in baseline culture
- Multi Drug Resistant (MDR) versus susceptible for *P. aeruginosa* at baseline
- Reason for admission to ICU at baseline (Trauma versus Non-trauma)
- Rapid test only versus culture confirmed randomization
- Age (<65 years versus ≥65 years)

In addition, the above subgroup analysis will also be performed for the selective secondary efficacy endpoints, i.e. the proportion of patients with clinical cure rate at Day 7, Day 14, and Day 28 as assessed by the investigator based on the micro-ITT Population.

6.5. Pharmacokinetic Analyses

Pharmacokinetic endpoints include the assessment of the PK parameters during full PK sub-study and during sparse PK sub-study.

For full PK sub-study, for each patient participating in the FULL PK sub-study, a total of ten (10) PK samples will be obtained. Sampling times are as follows:

- Prior to the beginning of infusion (pre-dose, time 0)
- 2 hours (end of infusion),
- 4 hours,
- 12 hours,
- 24 hours,
- 96 hours (Day 4 visit),
- 168 hours (Day 7 visit),
- 336 hours (Day 14 visit),
- 504 hours (Day 21 visit),
- 672 hours (Day 28 visit).

A non-compartmental analysis will be performed to characterize the PK of Aerucin® for the full PK sub-study.

For sparse PK sub-study, for subjects participating in the SPARSE PK sub-study, four (4) PK samples will be obtained for each at the following times:

- Prior to the beginning of infusion (pre-dose, time 0)
- 2 hours (end of infusion),
- at any one of the following timepoints: 4h 12h, or 24h post-dose initiation (inclusive),
- at any of the following visits: Day 4, 7, 14, 21, or 28.

A population PK (compartmental modeling) approach will be used to characterize the PK of Aerucin® for the sparse PK population.

All pharmacokinetic analyses will be performed by another vendor and described in a standalone PK analysis plan.

6.6. Safety Analyses

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

6.6.1. 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. Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of randomization until 28 days after last dose. Adverse events will be coded using MedDRA (Version 19.1). Treatment-emergent adverse events (TEAEs) are defined as AEs that start on or after the administration of the study drug.

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

- Any AEs
- Any TEAEs (overall and by maximum severity)
- Any drug-related TEAEs (overall and by maximum severity)
- Any serious AEs (SAEs) (overall and by maximum severity)
- Any drug-related serious AEs (overall and by maximum severity)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study drug
- Any AEs leading to death

The number and percentage of subjects with at least one TEAE will be presented by system organ class and preferred term. Drug-related TEAE, SAEs, Drug-related SAEs, and TESAEs will be summarized in the same manner. In the case of multiple occurrences of the same AE within the same subject, each subject will be counted only once for each SOC and preferred term.

Summaries will be provided by maximum severity for the number and percentage of subjects with TEAEs by system organ class and preferred term. For this summary, subjects with multiple adverse events will be counted only once by the maximum severity with in an SOC and preferred term.

Subject listings of SAEs, TEAEs leading to discontinuation of study drug, and AEs leading to death will be provided. All adverse events will be listed.

6.6.2. Clinical Safety Laboratory Evaluations

Standard safety laboratory tests

Standard safety laboratory tests are required at screening/baseline, Day 4, 7, 14, 21 and 28, except pregnancy testing (screening/baseline only). All the following tests will be performed by the local laboratory.

- Chemistry:
    - Miscellaneous: glucose, osmolality, bicarbonate, total protein, albumin
    - Electrolytes: sodium, potassium, chloride, calcium

  - Liver function: total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), alkaline phosphatase
  - Miscellaneous enzymes: creatine kinase (CK), amylase, C-reactive protein (CRP)
  - Renal function: blood urea nitrogen (BUN), creatinine, serum glomerular filtration rate (eGFR), phosphorus
- Hematology & coagulation
  - Red blood cell (RBC), hemoglobin, hematocrit
  - WBC, neutrophils, lymphocytes, basophils, eosinophils, and monocytes (absolute counts or %)
  - INR, fibrinogen, platelets
- Urine: glucose, protein, RBC, WBC
- Pregnancy test for women of childbearing potential (serum or urine, screening only)

Laboratory test results (Chemistry, Hematology, and Coagulation) at each scheduled visit and change from baseline will be summarized by treatment group and in total.

Shift tables, showing individual subject changes from baseline to each post baseline time point will be presented for each laboratory parameter, by treatment group, using the normal, abnormal categorization noted below.

- Normal: result is within the local lab normal range
- Abnormal: result is either higher or lower than the normal range

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

Immunogenicity (ADA)

Immunogenicity (ADA) samples will be obtained at screening/baseline and Day 28. Assays will be performed by a central laboratory.

6.6.3. Vital Signs

Vital signs include heart rate, arterial blood pressure, respiratory rate, and temperature.

Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method but limited to oral, tympanic, rectal or core measurements and will be recorded in the appropriate electronic case report form (eCRF). The same method of measuring a patient's body temperature should be used throughout the study.

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

All vital sign assessments will be listed by subject.

6.6.4. Electrocardiograms (ECG)

A standard 12-lead ECG will be obtained at baseline for reference. Abnormal ECG finding that would be observed during the course of the study will be duly documented and if appropriate, reported as adverse events.

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

6.6.5. Physical Examinations

A standard physical exam by body systems (General Appearance, Head and Neck, Lymph Nodes, Cardiac, Pulmonary, Abdominal, Genitourinary, Osteoarticular, Extremities, Cutaneous, Neurological) will be performed at baseline, then at Day 4, 7, 14, 21, and 28 or in case of early termination. Changes from baseline will be assessed and if appropriate, reported as adverse events.

Physical exam findings by body systems will be tabulated using counts and percentages at baseline and each scheduled post-baseline visit.

6.7. Interim Analyses

No interim analysis is planned.

7. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject as applicable. Detailed Programming Specifications will be provided in a separate document.