CLINICAL STUDY PROTOCOL

Study Title

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

Investigational Product: Aerucin® (aerubumab, AR-105)
Protocol Number: AR-105-002
EudraCT number: 2016-004261-10

Sponsor:
Aridis Pharmaceuticals, Inc.
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Protocol Version Number: 3.0
Date: 09NOV2018

SIGNATURE PAGE

STUDY TITLE: Placebo-controlled, double-blind, randomized study of Aerucin® as adjunct therapy to antibiotics in the treatment of *P. aeruginosa* pneumonia (Protocol Number AR-105-002).

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

Signature for Lynne Deans — Date 09 Nov 2018

Lynne Deans, MT (ASCP)
Head of Clinical Operations
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09 Nov 2018

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09NOV2018

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INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information provided by Aridis Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Aridis Pharmaceuticals, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by Aridis Pharmaceuticals, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

VERSION HISTORY

Version and Date	Author	Summary of changes
1.2 26-Dec-2016	Paul-André de Lame, M.D.	Original protocol
1.3 - Taiwan 07-Mar-2017	Paul-André de Lame, M.D.	Change to lower age limit from 18 to 20 to comply with Taiwan regulations.
1.4 - Germany 28-Jul-2017	Paul-André de Lame, M.D.	Updated exclusion criteria # 10 to specific required contraception for women of childbearing potential and precautions required from male partners of such women. Added section 12.2 regarding criteria for study termination. Minor edits.
1.5 31-Aug-2017	Paul-André de Lame. M.D.	Integrates changes made in versions 1.3 and 1.5. 5.4: clarified PI free access to unblinding 8.4: Clarified AE and SUSAR reporting per country regulations 8.6: Clarified handling of SUSARs 11.1: Specified that waivers and planned deviations form protocol are forbidden 12.1: Clarified handling of amendments Minor edits
2.0 04-May-2018	Alan Cohen, M.D.	Please refer to separate Summary of Changes document
3.0 09-Nov-2018	Wolfgang Dummer, M.D., Ph.D,	Please refer to separate Summary of Changes document

SYNOPSIS

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

PROTOCOL NUMBER: AR-105-002

INVESTIGATIONAL PRODUCT: Aerucin® (aerubumab, AR-105)

PHASE: 2/3

INDICATION(S): Aerucin® is intended for use as adjunct therapy for treatment of ventilator-associated pneumonia (VAP) due to *Pseudomonas aeruginosa* (*P. aeruginosa*) in combination with standard of care (SOC) antibiotic therapy.

OBJECTIVES:

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.

Primary Clinical Safety Objective

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

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.

Pharmacokinetics:

To assess the PK Profile of Aerucin®.

Secondary Safety Objectives: To assess the immunogenicity of Aerucin®.

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

POPULATION:

Persons of either gender who meet all of the following inclusion criteria and none of the exclusion criteria.

Inclusion Criteria

1. Written Informed Consent given by the patient or, if not possible, by a legally authorized representative and/or an independent physician as authorized by the competent ethics committee (EC) or independent review board (IRB) and local regulations.
2. To be at least 18 years of age.

   Taiwan only: To be at least 20 years of age.

   South Korea only: To be at least 19 years of age.
3. To be treated in an ICU at the time of enrollment.
4. Endotracheal tube in place (tracheostomy is allowed).
5. The patient is mechanically ventilated.
6. Diagnosis of pneumonia based on the following criteria (a, b, and c, all must be met):
   a. One definitive chest X-ray diagnostic of pneumonia,

      or

      A sequence of at least 2 chest X-rays showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia.
   b. Hypoxemia based on at least one of the following measurements/criteria:
      i. $PaO_2/FiO_2 < 250$ mmHg (at sea level or equivalent for significant elevations above sea level) while intubated and mechanically ventilated, as one or more measures within ≤ 24 hours prior to randomization, or
      ii. $PaO_2 < 60$ mmHg (at sea level or equivalent for significant elevations above sea level) while intubated and mechanically ventilated, as one or more measures within ≤ 24 hours prior to randomization, or
      iii. Respiratory failure necessitating intubation and mechanical ventilation. If tracheostomy is in place, the need for mechanical ventilation.
   c. At least one of the following signs:

i. Documented fever (e.g., body temperature greater than or equal to 38º Celsius).

ii. Hypothermia (e.g., core body temperature less than or equal to 35º Celsius).

iii. Total peripheral white blood cell (WBC) count greater than or equal to 10,000 cells/µL (or mm^3).

iv. Leukopenia with total WBC less than or equal to 4,500 cells/µL (mm^3).

v. Greater than 15 percent immature neutrophils (bands) noted on peripheral blood smear.

7. Documented pulmonary infection with *P. aeruginosa* obtained by bronchoalveolar lavage (BAL), mini-BAL, protected endotracheal tube aspiration (ETA) (collectively 'airway specimen'). For the study randomization, *P. aeruginosa* must be identified by one of the three methods below:

   a. An airway specimen culture positive by any method for *P. aeruginosa* of a specimen obtained less than 72 hours prior to randomization. A fresh airway specimen must be obtained prior to treatment initiation for baseline standard microbial culture by the local laboratory (including organism identification, quantitative/semi-quantitative culture and susceptibility testing); the corresponding culture results are NOT required prior to randomization.

   OR

   b. A rapid diagnostic test. In such case, the same sample must ALSO be used for standard microbial culture by the local laboratory (including organism identification, quantitative/semi-quantitative culture and susceptibility testing). The corresponding culture results are NOT required prior to randomization.

   OR

   c. A positive airway specimen culture by any method of *P. aeruginosa* from a specimen obtained at screening (quantitative, semi-quantitative).

8. APACHE II score ≥ 10 and ≤ 35 within 24 hours once subject has consented.

Exclusion Criteria

1. The subject is moribund. Clinical judgment by the investigator that the subject is unlikely to survive the current illness/ICU-admission/treatment period despite delivery of adequate antibiotics for treatment of *P. aeruginosa* pneumonia.
2. Effective antibacterial drug therapy for the index pneumonia administered continuously for 48 hours or more prior to initiation of study treatment. Effective antibiotics would include those typically used to treat *P. aeruginosa*.
3. Plasmapheresis (ongoing or planned) or any procedure that would remove/filter out the monoclonal antibody/study drug.
4. Immunocompromised and at risk of infection by opportunistic pathogens including, but not limited to the following:

   a. HIV / AIDS who are not stable under medication and/or most recent CD4 < 200.

b. Expected neutropenia due to chemotherapy.

c. Absolute neutrophil count less than 500/μL (mm^3).

d. Heart or lung transplant recipient within the past 6 months.

5. Known hereditary complement deficiency.
6. Liver dysfunction with a Child Pugh C score (Child Pugh score of A or B are acceptable at discretion of the Principal Investigator [PI]).
7. Pulmonary disease that precludes evaluation of a therapeutic response (such as lung cancer resulting in bronchial obstruction or on the same side as the pneumonia, active tuberculosis, cystic fibrosis, granulomatous disease, fungal pulmonary infection, lung abscess, pleural empyema or post obstructive pneumonia).
8. Patient has received intravenous (IV) immunoglobulin therapy within 3 months prior to the Screening Visit.
9. Any woman of child-bearing potential (WOCBP) who does not have a negative pregnancy test result at Screening using SERUM or URINE testing based on Beta-subunit human chorionic gonadotropin (HCG) standard tests and methods from the local laboratory. Non-pregnant and non-lactating with confirmation via local laboratory testing is required. Women who are post-menopausal as evidenced by the absence of menstruation for at least 1 year are eligible; the date of last menstruation is to be recorded in the study files unless post-menopausal status is obvious due to age.
10. Any sexually active subject who is unwilling to use acceptable methods of contraception for 120 days after dosing. WOCBP must agree to use to an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, barrier methods, abstinence) or male partner sterilization alone for the duration of the study and for at least 120 days after dosing. Males with female partners of reproductive potential must agree to practice abstinence or to use a condom (male) plus an additional barrier method (female partner) of contraception for the duration of the study and for at least 120 days after dosing.
11. Known lack of treatment compliance from prior studies or ongoing medical care based on medical records and PI's judgment and/or the capacity of the patient to comply with all study requirements.
12. Any medical, psychological, cognitive, social or legal conditions that would interfere in the ability to give an Informed Consent OR the absence of a legally valid representative of the patient or independent physician allowed and able to give consent on his/her behalf.
13. Participation as a subject in another interventional study within 30 days prior to the first dose of study treatment, or planned participation in such a study during the study or within 30 days of its completion by the patient. Patients who participate in observational or epidemiological studies are eligible provided this does not interfere with their capacity or the capacity of the study staff to comply with all study requirements.

STUDY DESIGN AND DURATION:

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, PCR, 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 BAL, mini-BAL, or 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 ($PaO_2/FiO_2 \leq 200$ 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 (IIV) and residual variability (RV). 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.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Aerucin® is provided as a sterile solution for intravenous infusion, in the amount of 4.5 mL in 10 mL vials at a concentration of 27.5 mg/mL.

STUDY ENDPOINTS:

Primary Clinical Efficacy Endpoint

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 will be applied post-hoc by an independent adjudication committee:

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
   - 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 #3 (no signs and symptoms of pneumonia) are sufficient to establish Clinical Cure (*presumed not ventilated*)

3. 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:
     - Fever > 38°C or hypothermia (< 35°C) attributable to the primary bacterial pneumonia
     - 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

Secondary Clinical Efficacy Endpoints

1. Proportion of patients with Clinical Cure at Day 28
2. Proportion of patients with Clinical Cure at Day 14
3. All-cause mortality
4. Pneumonia-related mortality
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.

Microbiological Endpoints

Microbiological outcome of the index *P. aeruginosa* pneumonia based on the data provided by the local microbiology laboratory and central microbiology laboratory.
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.
Change in bacterial load related to the index *P. aeruginosa* on the basis of quantitative or semi-quantitative cultures by the local microbiological laboratory.

Pharmacokinetic Endpoints

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

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

Safety Endpoints:

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

STATISTICAL ANALYSES:

Continuous data will be summarized by means, standard deviations, median, min, and max. Categorical data will be summarized by frequency and percentages.

The primary endpoint of Clinical Cure rate at Day 21 will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test. The CMH test will be stratified by baseline randomization strata. Time to Clinical Cure will be analyzed using a stratified log rank test. Other continuous endpoints will be analyzed using an Analysis of Covariance (ANCOVA), with treatment as a main effect, site, and baseline strata as covariates. Treatment by site interaction will be evaluated separately. Secondary endpoints will be analyzed using a sequential procedure in predefined order. Categorical variables will be analyzed using a stratified CMH test.

The primary comparisons for all endpoints will be between the 20 mg/kg dose group and placebo and will be done at 0.05 level of significance. The details of the planned analyses will be provided in the Statistical Analysis Plan.

Demographics, Baseline Characteristics, and Disposition

Demographics and baseline characteristics will be summarized by treatment group and overall. Disposition will be summarized by treatment group, and various outcomes (completed or discontinued the study, and reasons for discontinuation, etc.).

Safety analysis

Safety evaluations will include treatment emergent adverse events, vital signs, physical exam, and laboratory values. Safety will be summarized by treatment group. All treatment emergent adverse events, and serious adverse events, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Relationship to treatment, as well as severity will also be summarized. Changes in vital signs and physical exams will be summarized by group. Changes in laboratory values, as well as shifts (normal-> abnormal) will be summarized by treatment group.

Pharmacokinetic analyses

Two types of pharmacokinetic analyses will be performed to assess the PK hypothesis that the PK profile of Aerucin® in the target patient population is similar to the profile observed in healthy human volunteers (HV). The first pharmacokinetic analysis will consist of a population PK (compartmental modeling) approach using the combined concentration data collected in the PK sub-study and the sparse concentration data, pooled with the available PK data from healthy volunteers (Study ARC-11-01). A compartmental population PK model will be developed and the effects of select intrinsic and extrinsic factors, including but not limited to patient status (e.g., HV versus patient with pneumonia), high or low bacterial load, and cause of admission [trauma or non-trauma]) on the PK of Aerucin® will be evaluated via covariate analysis. The population PK model will be described by the estimation of mean structural model parameters, the magnitude of IIV in these parameters, and the magnitude of RV.

The second pharmacokinetic analysis to be performed will be a non-compartmental analysis of the extensively sampled concentration-time data collected in the PK sub-study. The pharmacokinetic parameters to be derived from the individual concentration time profiles will include: the maximum observed plasma concentration (C_{max}), the time of occurrence of C_{max} (t_{max}), the area under the plasma concentration time curve from time 0 to Day 28 (AUC_{0-28}), the terminal elimination rate constant (λz), and, if data permits, the terminal half-life ($t_{1/2}$). Parameter estimates will be summarized and tabulated by individual and overall. Graphs of plasma concentration versus time profiles will be generated for each subject and graphs of mean ± SD profiles will be generated to compare patient and HV data.

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.

SITES: Approximately 120 sites worldwide.

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABG	arterial blood gas
ADA	anti-drug antibody
AE	adverse event
ALT	Alanine transaminase
ANCOVA	analysis of covariance
APACHE II	acute physiology and chronic health evaluation II
AST	aspartate transaminase
BAL	broncho-alveolar lavage
BOCF	baseline observation carried forward
BUN	blood urea nitrogen
CABP	community-acquired bacterial pneumonia
CF	cystic fibrosis
CIP	Council of Independent Physicians
CK	creatine kinase
CRA	clinical research associate
CTA	clinical trial authorization
CRP	c-reactive protein
CMH	Cochran-Mantel-Haenszel
DNA	deoxyribonucleic acid
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiography
eCRF	electronic case report form
EDC	electronic data capture
ETA	endotracheal aspiration
FA	FilmArray
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	glomerular filtration rate
HABP	hospital-acquired bacterial pneumonia
HAP	hospital-acquired pneumonia
HCAP	healthcare-associated pneumonia
HCABP	healthcare associated bacterial pneumonia
HCG	human chorionic gonadotropin
HCO_3	Bicarbonate
HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome

Abbreviation	Definition
HV	human volunteers
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICU	intensive-care units
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
INR	international normalized ratio
IRB	Institutional Review Board, Independent Review Board
ITT	Intent to Treat
IUO	investigational use only
IV	intravenous
IWRS	interactive web-based randomization system
LDH	lactate dehydrogenase
LRTI	lower respiratory tract infection
LOCF	Last Observation Carried Forward
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MDR	multi-drug resistance
mITT	Modified Intent to Treat
micro-ITT	Microbiological Intent to Treat (microbiologically evaluable)
MRSA	methicillin-resistant *Staphylococcus aureus*
NIMP	Non-investigational Medical Product
P. aeruginosa	*Pseudomonas aeruginosa*
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PEEP	positive end-expiratory pressure
PI	Principal Investigator
PK	Pharmacokinetic(s)
PO	Per Os (orally)
PP	Per-protocol Population
RBC	red blood cell
RUO	research use only
RV	residual variability
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	standard of cure
SOFA	sequential organ failure assessment
SUSAR	suspected unexpected adverse reaction

Abbreviation	Definition
TOC	Test of Cure
VAP	ventilator-associated pneumonia
WBC	white blood cell
WOCBP	Woman of Child-Bearing Potential

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Rationale

Nosocomial infections such as hospital associated pneumonia (HAP) and particularly ventilator associated pneumonia (VAP) are a major problem for providers and payers [1,2]. Gram-negative bacteria are responsible for approximately 80% of cases of pneumonia in hospitalized patients (this contrasts with bloodstream infections, for example, which are mainly caused by Gram-positive bacteria, of which methicillin-resistant *Staphylococcus aureus* (MRSA) is the most prominent [3]. *Pseudomonas aeruginosa* (*P. aeruginosa*) causes the majority of multi-drug resistant (MDR) nosocomial infections. Pneumonia accounts for approximately 15% of all hospital-associated infections, and also 27% and 24% of all infections acquired in medical intensive-care units (ICU) and coronary care units, respectively, making it the second most common hospital-associated infection after urinary tract infections. Being intubated and attached to a mechanical ventilator are two of the most common risk factors for infection in ICU patients [4].

Mortality for hospital-associated pneumonia and ventilator-associated pneumonia in particular, is high, e.g., for hospital-associated, pneumonia-attributed mortality rates of 20% to 33% have been reported and ventilator-associated pneumonia accounted for 60% of all deaths due to hospital-associated infections [1]. Direct mortality from HAP is ~50% with about 21% of all HAP caused by *P. aeruginosa* infections [2]. The unmet medical need in VAP treatment is even more acute than in cystic fibrosis (CF), as it is increasingly clear that mortality in VAP is high despite aggressive antibiotic therapies (up to 70%) [1], leading to expensive hospitalization costs (~$150,000 per patient) [4]. VAP patients are also at a high risk of MDR *P. aeruginosa* infection [1,3].

Given the rise in naturally occurring antibiotic resistance and the widening gap between the number of drug-resistant pathogens and the number of antibiotics under development within the past 3 decades, the development of new anti-infective is clearly of increased importance. Human monoclonal antibodies (mAbs) represent a promising class of anti-infective alternatives to antibiotics, exhibiting attractive attributes such as strong safety track records, long plasma half-life (e.g. 3-4 weeks for an IgG1), and thus require much less frequent dosing than antibiotics, differentiated immunological mechanisms that do not require transport across the membrane/capsule of the bacteria and thus not susceptible to common mechanisms of antibiotic resistance. A recognized binding target of some antibacterial mAbs is the capsule surface antigens of pathogens, such as extracellular polysaccharides. Aerucin® is a fully human mAb that was discovered by screening B-cells of a volunteer that was immunized with *P. aeruginosa* extracellular polysaccharide alginate.

Alginate (also called mucoid exopolysaccharide) is an ideal epitope because it is uniquely and ubiquitously expressed on *P. aeruginosa*. It consists of β-1, 4-linked D-mannuronic acid and L-glucuronic acid and confers resistance to antibiotics [5]. It is a key virulence associated factor with the absence of detectable escape mutants (alginate negative), and it is a conserved, polymeric, high-density and high-avidity cell surface target. Alginate expression is key to colonization, biofilm growth, virulence, and immune evasion.

In support of alginate as a clinically effective target, it has been observed that alginate production is the hallmark of progressive decline in lung function in CF patients [5,6] and *P. aeruginosa* persistence and virulence [7]. Additionally, a described subpopulation of older CF patients who were not colonized with *P. aeruginosa* produced alginate specific phagocytic antibodies [8]. Patients with opsonic antibodies had a lower rate of positive cultures for *P. aeruginosa*, while those lacking these antibodies were usually infected with *P. aeruginosa* [5,6,7]. One treatment approach is the use of vaccines to generate specific mAb against *P. aeruginosa*. Vaccines studies of *P. aeruginosa*, including alginate and alginate conjugate vaccines, have not resulted in data demonstrating the ability of vaccines to generate broadly protective antibodies in humans. Thus, an approach to overcome the potential problems of active vaccination is to produce human mAbs that can be administered passively; both for prophylactic (very early in life) and therapeutic (for patients with an existing *P. aeruginosa* infection) use. This approach formed the basis for the development of Aridis' human mAb (Aerucin®).

1.2 Aerucin®

Aerucin® binds to the conserved epitope of *P. aeruginosa*, alginate, at the C6 carboxyl group of mannuronic acid and mediates complement dependent phagocytic killing of both mucoid and non-mucoid *P. aeruginosa*. Our data show that alginate is present on >90% of clinical *P. aeruginosa* isolates tested, and that there is no non-specific binding of Aerucin® against a panel of 40 normal human tissues. Opsonization is a key feature of Aerucin's mechanism of action as demonstrated in vitro: phagocytic assays showed that enabling *P. aeruginosa* killing requires the presence of phagocytes (e.g., neutrophils, macrophages) and complement. Its binding target (alginate) is a common cell surface component of *P. aeruginosa* and is critically required for host colonization and pathogenicity. Indeed, if selection pressure resulted in down regulated expression of alginate (which is not known to occur naturally), *P. aeruginosa* would become unable to colonize the host and significantly more susceptible to conventional antibiotics. Aerucin® offers additional features that may be advantageous compared to conventional small molecule antibiotics for use in pneumonia and in CF, including long systemic serum half-life of about 3 weeks, and thus requires much less frequent dosing than antibiotics. As a result, Aerucin® offers a unique profile and an entirely new mode of action, with no direct competition from antibiotics.

Aerucin® has not yet been approved for human use. Cellular and animal studies conducted with Aerucin® have confirmed the stability and efficacious quality of this antibody. Experimental tests were performed using a refrigerated stable liquid formulation of Aerucin®. These in vitro and in vivo studies have demonstrated that: 1) Aerucin® binds to more than 90% of *P. aeruginosa* strains tested, 2) Aerucin® protected against and treated infection, and 3) the delivery modalities were efficient enough to deliver the required concentration of Aerucin® to the target and to demonstrate efficacy in the animal model. Human tissue binding and mouse toxicology evaluations show no human tissue binding and no adverse toxic effects.

A Phase 1 study in healthy volunteers showed that Aerucin® has a favorable safety profile and a PK profile consistent with that of IgG immunoglobulins. The highest dose tested was 20 mg/kg, which is the dose selected for this study.

1.3 Indication

Aerucin® is being developed as adjunct therapy in combination with antibiotics for the treatment of pneumonia caused by *P. aeruginosa*.

1.4 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).

1.5 Risk/Benefit

1.5.1 Risks related to Aerucin®

Aerucin® is a fully human monoclonal antibody. It has been shown in a phase 1 study (Protocol ARC-11-01) in healthy volunteers to be safe in doses of 2.0, 8.0, and 20.0 mg/kg, administered intravenously over 1 hour. In that phase 1 study, a total of 46 AEs was reported, with a frequency that was similar across all three treatment cohorts without any pattern indicating a possible dose-related increase in frequency of the AEs or a specific safety issue. Most subjects (14/16, or 87.5%) experienced at least 1 AE. None of the reported AEs was serious. All AEs were mild in intensity.

Out of the 46 AEs that were reported, 6 were deemed related, as summarized in Table 1-1 below. Again, there was no clear pattern of dose-dependent safety issues, and as noted above, all these events were mild in intensity. A decrease in diastolic blood pressure was observed in two separate subjects in the higher dose cohort. Both occurred close to the infusion of the investigational product, were mild, were deemed possibly related by the investigator, and promptly resolved without any medical intervention.

The effectiveness of Aerucin® has not been established. Therefore, no benefit should be expected.

Table 1-1 Summary of Related AEs

System Organ Class Preferred Term	Aerucin® 2.0 mg/kg (N = 5)	Aerucin® 8.0 mg/kg (N = 6)	Aerucin® 20 mg/kg (N = 5)	Total (N = 16)
N AEs	15	15	16	46
N Related AEs	0	2	4	6
General disorders and administration site conditions				
Infusion site edema	0	1	0	1
Investigations				
Blood pressure diastolic decreased	0	0	2	2
Musculoskeletal and connective disuse disorders				
Back pain	0	0	1	1
Nervous system disorders				
Headache	0	0	1	1
Somnolence	0	1	0	1

1.5.2 Risks related to the study design and required procedures

Aerucin® will be administered in addition to standard-of-care antibiotic therapy, as determined by the investigator on the exclusive basis of the medical needs of his/her patient. Therefore, participation in this study does not affect the chances of a positive clinical outcome in any given study subject, also taking into account the favorable safety profile of the investigational product.

Except for blood sampling for PK and anti-drug antibody (ADA), and rapid testing of airway specimens for assessing the presence of *P. aeruginosa*, the procedures that are required for the study are all routine procedures, in nature and frequency, for this type of patients whose clinical status requires hospitalization in an ICU. Therefore, with the exceptions noted earlier, this study does not impose an unreasonable burden on the study subjects.

Blood sampling for PK and ADA has been reduced to the minimum necessary by allowing sparse sampling for the majority of the study subjects, on the one hand, and by limiting the required sample volume to the minimum technically necessary for the assays, thus limiting the related burden as much as possible.

Eligible study subjects will be randomized and treated either on the basis of culture results (known from recent cultures) or on the basis of rapid diagnostic testing of airway specimens using devices such as CE marked Cepheid's GeneXpert® with Investigational / Research Use Only (IUO / RUO) PA Cartridge, BioFire Diagnostics, LLC (a BioMerieux company)'s IUO FilmArray® LRTI Panel (please refer to section **14.3**). This approach is necessary to allow the study intervention to be implemented as early as possible in the course of the disease, as early treatment is a known driver of clinical outcomes. It is expected that the results of rapid testing will not be confirmed by standard microbial culture in a small number of subjects for various reasons including the possibility of rapid test false positive, inadequate samples, or sample cultures affected by an ongoing antibiotic treatment. This situation is not expected to occur in more than 5% of the randomized subjects. Considering the safety profile of Aerucin® and of similar fully human anti-infective mAbs, this risk is deemed acceptable in the context of this study protocol.

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:
    - Clinical Cure rate at Day 28, 14 and 7, using the same criteria as for the primary efficacy objective at Day 21.
    - Time to Clinical Cure
2. Mortality:
    - All-cause mortality
    - Pneumonia-related mortality post-treatment
3. Respiratory functional assessment:
    - Mechanical ventilation parameters
    - 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)
    - Use of supplemental oxygen
4. Overall clinical status:
    - Changes in sequential organ failure assessment (SOFA) score
5. Health economics
    - Antibiotic utilization
    - Duration of stay in ICU
    - Duration of hospitalization
    - Duration of intubation with ventilation
    - Duration of mechanical ventilation if tracheostomy is in place
6. Pharmacokinetics

2.4 To assess the PK Profile of Aerucin® Secondary Safety Objective

To assess the immunogenicity of Aerucin®

2.5 Microbiological Efficacy Objectives

To assess the effect of Aerucin®, administered as a single dose as adjunct therapy in addition to standard antibiotic therapy for *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 DESCRIPTION

3.1 Summary of Study Design

This study is an international, multicenter, prospective, double blind, randomized, placebo-controlled, parallel design protocol in patients with VAP caused by *P. aeruginosa*. It will be performed at multiple ICUs.

Patients with a documented diagnosis of pneumonia due to *P. aeruginosa*, and require ICU care, and 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, PCR, etc.), or using devices such as CE marked Cepheid's GeneXpert® with IUO / RUO PA Cartridge, or BioFire Diagnostics, LLC (a BioMerieux company)'s IUO FilmArray® LRTI Panel (please refer to section **14.3**). Acceptable samples are bronchoalveolar lavage (BAL), mini-BAL, or endotracheal tube aspiration (ETA, ETA sample with < 10 squamous epithelial cells and >25 polymorphonuclear cells per low power field). It is expected that a small number of subjects will have a positive rapid diagnostic test result that will not be confirmed by standard microbial culture (quantitative/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 the 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" will 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® in patients 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 (IIV) and residual variability (RV). 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. Antibiotic treatment of the index pneumonia should not exceed 14 days.

3.2 Study Indication(s)

Aerucin® is intended for use as adjunct therapy for the treatment of VAP due to *P. aeruginosa* in combination with SOC antibiotic therapy.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects of either gender who meet all inclusion criteria and no exclusion criteria are eligible for participation in the study.

4.1 Inclusion Criteria

1. Written Informed Consent given by the patient or, if not possible, by a legally authorized representative and/or an independent physician as authorized by the competent ethics committee (EC) or independent review board (IRB) and local regulations.
2. To be at least 18 years of age.

   For Taiwan: To be at least 20 years of age.

   South Korea only: To be at least 19 years of age.
3. To be treated in an ICU at the time of enrollment.
4. Endotracheal tube in place (tracheostomy is allowed).
5. The patient is mechanically ventilated.
6. Diagnosis of pneumonia based on the following criteria (a, b, c, all must be met):

   a. One definitive chest X-ray diagnostic of pneumonia,

   or

   A sequence of at least 2 chest X-rays showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia.

   b. Hypoxemia based on at least one of the following measurements/criteria:

      i. $PaO_2/FiO_2 < 250$ mmHg (at sea level or equivalent for significant elevations above sea level) while intubated and mechanically ventilated, as one or more measures within ≤ 24 hours prior to randomization, or

      ii. $PaO_2 < 60$ mmHg (at sea level or equivalent for significant elevations above sea level) while intubated and mechanically ventilated, as one or more measures within ≤ 24 hours prior to randomization), or

      iii. Respiratory failure necessitating intubation and mechanical ventilation. If tracheostomy is in place, the need for mechanical ventilation.

   c. At least one of the following signs:

      i. Documented fever (e.g., body temperature greater than or equal to 38º Celsius).

      ii. Hypothermia (e.g., core body temperature less than or equal to 35º Celsius).

      iii. Total peripheral white blood cell (WBC) count greater than or equal to 10,000 cells/µL (or mm^3).

      iv. Leukopenia with total WBC less than or equal to 4,500 cells/µL (mm^3).

      v. Greater than 15 percent immature neutrophils (bands) noted on peripheral blood smear.

7. Documented pulmonary infection with *P. aeruginosa* obtained by BAL, mini-BAL, protected ETA (collectively 'airway specimen'). For the study randomization, *P. aeruginosa* must be identified by one of the three methods below:

   a. An airway specimen culture positive by any method for *P. aeruginosa* of a specimen obtained less than 72 hours prior to randomization. A fresh airway specimen must be obtained prior to treatment initiation for standard microbial culture by the local laboratory (including organism identification, quantitative/semi-quantitative culture and susceptibility testing); the corresponding culture results are NOT required prior to randomization.

   OR

   b. A rapid diagnostic test (see section **14.3** for acceptable methods). In such case, the same sample must ALSO be used for standard microbial culture by the local laboratory (including organism identification, quantitative/semi-quantitative culture and susceptibility testing). The corresponding culture results are NOT required prior to randomization.

   OR

   c. A positive airway specimen culture by any method of *P. aeruginosa* from a specimen obtained at screening (quantitative, semi-quantitative).

8. APACHE II score ≥ 10 and ≤ 35 within 24 hours once subject has consented.

4.2 Exclusion Criteria

1. The subject is moribund. Clinical judgment by the investigator that the subject is unlikely to survive the current illness/ICU-admission/treatment period despite delivery of adequate antibiotics for treatment of *P. aeruginosa* pneumonia.
2. Effective antibacterial drug therapy for the index pneumonia administered continuously for 48 hours or more prior to initiation of study treatment. Effective antibiotics would include those typically used to treat *P. aeruginosa*.
3. Plasmapheresis (ongoing or planned) or any procedure that would remove/filter out the monoclonal antibody/study drug.
4. Immunocompromised and at risk of infection by opportunistic pathogens including, but not limited to the following:
   a. HIV / AIDS who are not stable under medication and/or most recent CD4 < 200.
   b. Expected neutropenia due to chemotherapy.
   c. Absolute neutrophil count less than 500/µL (mm^3).
   d. Heart or lung transplant recipient within the past 6 months.
5. Known hereditary complement deficiency.
6. Liver dysfunction with a Child Pugh C score (Child Pugh score of A or B are acceptable at discretion of the Principal Investigator [PI]).

7. Pulmonary disease that precludes evaluation of a therapeutic response (such as lung cancer resulting in bronchial obstruction or on the same side as the pneumonia, active tuberculosis, cystic fibrosis, granulomatous disease, fungal pulmonary infection, lung abscess, pleural empyema or post obstructive pneumonia).
8. Patient has received intravenous (IV) immunoglobulin therapy within 3 months prior to the Screening Visit.
9. Any woman of child-bearing potential (WOCBP) who does not have a negative pregnancy test result at Screening using SERUM or URINE testing based on Beta-subunit human chorionic gonadotropin (HCG) standard tests and methods from the local laboratory. Non-pregnant and non-lactating with confirmation via local laboratory testing is required. Women who are post-menopausal as evidenced by the absence of menstruation for at least 1 year are eligible; the date of last menstruation is to be recorded in the study files unless post-menopausal status is obvious due to age.
10. Any sexually active subjects who is unwilling to use acceptable methods of contraception for 120 days after dosing. WOCBP must agree to use to an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, barrier methods, abstinence) or male partner sterilization alone for the duration of the study and for at least 120 days after dosing. Males with female partners of reproductive potential must agree to practice abstinence or to use a condom (male) plus an additional barrier method (female partner) of contraception for the duration of the study and for at least 120 days after dosing.
11. Known lack of treatment compliance from prior studies or ongoing medical care based on medical records and PI's judgment and/or the capacity of the patient to comply with all study requirements.
12. Any medical, psychological, cognitive, social or legal conditions that would interfere in the ability to give an Informed Consent OR the absence of a legally valid representative of the patient or independent physician allowed and able to give consent on his/her behalf.
13. Participation as subject in another interventional study within 30 days prior to the first dose of study treatment, or planned participation in such a study during the study or within 30 days of its completion by the patient. Patients who participate in observational or epidemiological studies are also eligible provided this does not interfere with their capacity or the capacity of the study staff to comply with all study requirements.

4.3 Withdrawal Criteria

Participation of a subject in this clinical study may be discontinued, but not limited to, any of the following reasons:

- The subject withdraws consent or formally requests discontinuation from the study for any reason;
- The subject is lost to follow-up
- Improvement of pneumonia and discharge from ICU should NOT be considered withdrawal. All assessments including Clinical Cure assessment should be collected through Day 28

- Termination of the study by the Sponsor or the regulatory authority.

If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should ensure that End of Study Visit data are recorded. The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records, including whether the subject is alive at the time of contact.

Withdrawn subjects will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

After completing all screening procedures, eligible study subjects will be randomized to one of the following treatment groups:

- Control group: placebo
- Investigational Product group: Aerucin® 20 mg/kg

5.2 Rationale for Dosing

Aerucin® was shown to be safe when administered in doses up to 20 mg/kg intravenously over 1 hour in a phase 1 safety and PK study of 16 healthy volunteers. The 20 mg/kg dose, the highest dose then tested, was selected for this study because of the existence of a dose-response in animal studies, because of the severity of the target infection, and because the target for Aerucin® is specific to *P. aeruginosa*, the amount of which may affect the PK profile of the product.

5.3 Randomization and Blinding

This is a double-bind, placebo-controlled study.

Study subjects will be first stratified as follows:

- Stratum 1: VABP or non-VABP
- Stratum 2: $PaO_2/FiO_2 \leq 200$ 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.

5.4 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.

5.5 Drug Supplies

Aerucin® is a fully human IgG1 lambda monoclonal antibody that binds to alginate on the surface of all *P. aeruginosa* cells and mediates complement-dependent phagocytic killing of both mucoid and non-mucoid *P. aeruginosa*.

5.5.1 Formulation and Packaging

The Aerucin® drug product is formulated at 27.5 mg/mL in 10 mM L-histidine, 150 mM sodium chloride, pH 6.0, and 0.02% w/v Polysorbate 20. Aerucin® is a clear to slightly opalescent, colorless to pale yellow, sterile, preservative-free liquid for intravenous infusion. The composition of the Aerucin® drug product is provided in the table below.

The composition and formulation of the placebo is the same but for the absence of Aerucin®.

Table 5-1 Composition of Aerucin® Drug Product

Ingredient	Amount/mL	Function
Aerucin®	27.5 mg/mL	Active ingredient
L-Histidine	0.80 mg/mL	Buffer
L-Histidine (monohydrochloride, monohydrate)	1.01 mg/mL	Buffer
Sodium chloride	8.77 mg/mL	Tonicity, Stabilizer
Polysorbate 20	0.2 mg/mL	Stabilizer
Water for Injection, USP	q.s.	Solvent

Abbreviations: mg/mL = milligram(s) per milliliter; q.s. = quantum satis

The study drug (investigational product or control) is provided in 10 mL glass vials with butyl rubber stoppers containing no less than 4.5 mL of extractable volume at an Aerucin® concentration of 27.5 mg/mL. Each vial is labeled in the local language in compliance with local regulations. Each vial is identified with a unique vial number.

The vials are packaged in individual cartons (one per vial), similarly labeled.

5.5.2 Study Drug Preparation and Dispensing

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.

A Pharmacy Manual will describe the process in detail. In summary, to prepare the study drug for use, the corresponding volume of liquid from the study drug must first be extracted from a 100 mL normal saline infusion bag, and then the content of the selected vials must be transferred into this bag using sterile technique.

When ready for use, the infusion bag should be marked with the study subject number, the date and time of preparation, and the number of vials used, and a list of the vial numbers that were used for verification against the list assigned using the EDC / IWRS system should be provided.

5.5.3 Study Drug Administration

The entire content of the bag must then be administered intravenously at room temperature in approximately 2 hours. An in-line 0.2 μm pore filter should be used.

5.5.4 Treatment Compliance

The study drug will be administered once, intravenously, in a strictly monitored setting. Compliance will be recorded by confirming the start and stop dates and times of the infusion to show that the study drug was administered per the amount indicated by the EDC / IWRS system.

5.5.5 Storage and Accountability

The study drug must be kept refrigerated between 2 and 8º C (35.6 and 46.4º F). Storage temperature is to be monitored and the corresponding records kept on file.

Availability and usage of study drug by the study sites will be recorded using the EDC / IWRS & Inventory system.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Administration of monoclonal antibodies is forbidden for the duration of the study. Patients who received intravenous immunoglobulins (IVIG) within the last 90 days are excluded from the study.

5.6.2 Restricted Medications and/or Procedures

None.

5.6.3 Documentation of Prior and Concomitant Medication Use

All concomitant therapies which are ongoing at the time of Informed Consent signature and/or administered during the course of study through 28 days after study treatment will be recorded in the EDC. This includes both prescription and non-prescription drugs.

In addition to reporting period above, antibiotic therapies administered within 48 hours of study treatment should also be recorded in the EDC, even if they were administered prior to Informed Consent Signature.

6 STUDY PROCEDURES

An overview of the study is provided below (**Figure 6-1**). Day-by-day details are provided in (**Table 6-1**). In summary, any patient with VAP, who is intubated, older than 18 years (at least 20 years of age in Taiwan and at least 19 years of age in South Korea) and who signed an informed consent, will enter a screening phase dedicated to identifying any pathogen that is present, and in particular, verifying whether *P. aeruginosa* is present. This screening phase is critical to ensuring that no potentially eligible patient is missed. Therefore, the related activities should be organized and managed proactively. Participation of key hospital staff is very important, including personnel involved in managing infectious diseases in the institution, the local microbiology department, and any relevant personnel.

If a culture from a valid airway specimen (BAL, mini-BAL or ETA) obtained within 72 hours of randomization is positive for *P. aeruginosa*, the subject can be randomized on this sole basis provided that all eligibility criteria are met, and that a new valid airway specimen is obtained prior to treatment. This baseline airway specimen will be sent to the site's local microbiology laboratory for quantitative/semi-quantitative culture. These baseline culture results are not required prior to randomization.

The sites will obtain airway specimens for culture prior to treatment (baseline), as medically indicated, at time of extubation, and at Day 28 (if not extubated prior to Day 28). Airway specimen cultures will be sent to the local microbiology laboratory for culture, including identification of genus and species, quantification and susceptibility testing as outlined in the microbiology laboratory manual.

Isolates of unique organisms from airway specimen cultures will be sent to the central lab. The central microbiology laboratory will confirm identification and perform standardized antibiotic quantitative/semi-quantitative culture, susceptibility testing and serotyping on target pathogens as outlined in the microbiology laboratory manual.

If the results of an airway specimen obtained within 72 hours of randomization are not available, a valid airway specimen (BAL, mini-BAL or ETA) should be obtained and tested using rapid diagnostic testing (see section **14.3**) if available at site and approved to use by the Regulatory Authorities (RA) / Independent Ethics Committee (IEC). If such rapid testing is positive for *P. aeruginosa*, the subject can be randomized on this sole basis.

The same airway specimen used for rapid testing will be assessed at the site's local laboratory for baseline culture including identification of genus and species, quantitative/semi-quantitative culture and susceptibility testing as outlined in the laboratory procedure manual. These baseline culture results are not required prior to randomization.

Isolates of unique organisms will be sent to the central lab. The central microbiology laboratory will confirm identification, perform the standardized antibiotic susceptibility testing, and serotyping.

If no rapid diagnostic test is available and no culture within 72 hours of randomization has been taken, the site should make all possible efforts to have an airway specimen (BAL, mini-BAL or ETA) collected and sent to their local microbiology lab as soon as possible. The randomization cannot be done in this case until the microbiology results of a positive *P. aeruginosa* culture have been confirmed.

As soon as *P. aeruginosa* is confirmed on a valid airway specimen and all other inclusion and exclusion criteria are met, the subject should be randomized and treated (more than one pathogen allowed, if *P. aeruginosa* is regarded a key pneumonia causing pathogen). The study personnel will randomize the subject using the EDC / IWRS system to either Aerucin® 20 mg/kg or placebo.

Upon randomization, PK evaluations will be initiated as detailed in section **7.4.**

Following treatment, all patients will be assessed daily for overall clinical status, as detailed below (see Section **6.5**), based on information collected as medically required. In addition, complete assessments will be performed on Day 4, 7, 14, 21 and 28, as detailed below (see Section **6.6**).

Methods are described in detail in the Laboratory Manual.

Figure 6-1 Protocol Overview
Study Design: Protocol AR-105-002

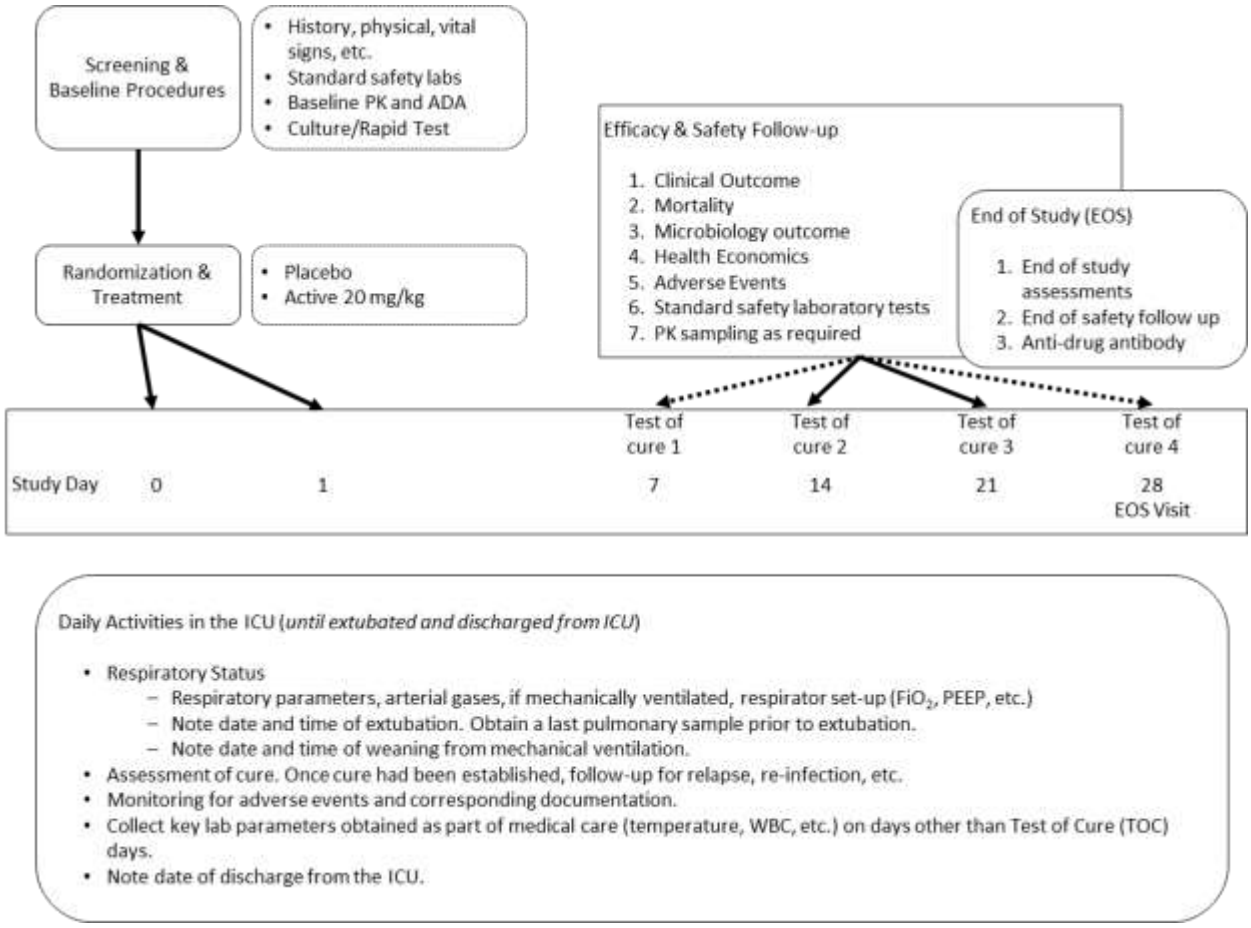


Table 6-1 Schedule of Assessments

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)

6.1 Informed Consent

Informed consent will be obtained prior to any study-related procedure or data collection according to the regulations applicable at the study site where the patient is being enrolled. Depending upon such regulations, informed consent may be given by the study subject, a legally authorized representative, an independent physician or a council of independent physicians. The informed consent process will be duly documented in the subject's study file.

Prior to signing this document, the patient and/or his/her representative must have an opportunity to read it thoroughly, ask any questions, and do so under no pressure. The Informed Consent Form (ICF) should be provided to the patients as soon as possible before the first study procedures, so that time is allowed for each patient or his/her representative to review the documents and discuss them at his/her leisure.

If for any reason, the Informed Consent Form can only be read to the patient prior to his/her signing, a witness must sign, together with the patient, to guarantee that the document has been read to and understood by the patient prior to his/her signature.

The Investigator is responsible for obtaining the Informed Consent. If this task is delegated to other study personnel, the Investigator remains responsible for ensuring that the Informed Consent process has been followed and clearly documented.

6.1.1 Russia

Subject, legally authorized representative (LAR), or council of independent physicians (CIP) has provided written informed consent.

6.2 Screening and Enrollment (Day-1)

Please refer to **Figure 6-2** for a detailed flowchart of the screening and randomization process. All patients who are at least 18 years of age (at least 20 years of age in Taiwan) for whom an informed consent has been obtained, who are diagnosed with pneumonia based on the requirements in the inclusion criteria, and who are intubated will be considered for the study. Additionally to the exclusion criteria, by way of clarification, if the subject:

a. is unlikely to survive for the study duration despite delivery of adequate antibiotics and supportive care for treatment;
b. has a diagnosis of liver dysfunction with a Child Pugh C score > 9;
c. is a WOCBP and has not agreed to use an effective method of birth control or is not post-menopausal as evidenced by the absence of menstruation for at least 1 year prior to Screening Visit;
d. is not receiving/has not received interventional study drug (e.g. placebo) or medications/procedures except for SOC within the timeframe described (subject can be included, if he/she received placebo);

he/she will be excluded from / not be enrolled in the study.

The following information will be recorded:

- Demographics
- Screening data and reason(s) for screen failure in such case
- Microbiology and Rapid Diagnostic Test for *P. aeruginosa*
    - All subjects who have given consent, have pneumonia and are intubated will enter the screening phase.

      Subjects for whom a culture from a valid airway specimen (BAL, mini-BAL or ETA) obtained within 72 hours of randomization is positive for *P. aeruginosa* can be randomized on this sole basis provided that all eligibility criteria are met, and that a new valid baseline airway specimen is obtained prior to treatment. This baseline airway specimen will be sent to the site's local microbiology laboratory for culture including identification of genus and species, quantitative/semi-quantitative culture and susceptibility testing as outlined in the microbiology laboratory manual. These baseline culture results are not required prior to randomization. Isolates of unique organisms

will be sent to a central lab. The central microbiology laboratory will perform confirmation of identification, standardized antibiotic susceptibility testing and serotyping on target pathogens as outlined in the microbiology laboratory manual. Such culture results are not required prior to randomization.

For subjects in whom a culture from a valid airway specimen (BAL, mini-BAL or ETA) obtained within 72 hours of randomization is NOT available, such valid airway specimen will be obtained and tested using rapid diagnostic testing (see section **14.3**). If such rapid testing is positive for *P. aeruginosa*, the subject can be randomized on this sole basis and should be treated. The same airway specimen will be sent to the site's local microbiology laboratory for culture including identification of genus and species, quantitative/semi-quantitative culture and susceptibility testing as outlined in the microbiology laboratory lab manual. These baseline culture results are not required prior to randomization. Isolates of unique organisms will be sent to a central lab. The central microbiology laboratory will perform confirmation of identification, standardized antibiotic susceptibility testing and serotyping on target pathogens as outlined in the microbiology laboratory manual.

If NO rapid diagnostic test is available and NO culture within 72 hours of randomization has been taken, the site should make all possible efforts to have an airway specimen (BAL, mini-BAL or ETA) collected and sent to their local microbiology lab as soon as possible. The randomization cannot be done in this case until the microbiology results of a positive *P. aeruginosa* culture have been confirmed.

- Acceptable airway specimen sampling methods are BAL, mini-BAL, and ETA for both rapid testing and standard microbial culture (quantitative or semi-quantitative). Aliquots should be reserved for assessing bioavailability. Make sure that blood urea nitrogen (BUN) or urea is recorded on or about the same time a BAL or mini-BAL sample is obtained.
- The same airway specimens will be processed by the local microbiology laboratory for identification and quantification (quantitative/semi-quantitative cultures). Isolates of all the target pathogens obtained from the culture performed at the local lab will be sent to the central microbiology lab for confirmation of identification, susceptibility testing and serotyping.
- The nature, quantity and antibiotic susceptibility of all pathogens identified by the local microbiology laboratory, and an assessment of the probability that the identified pathogen(s) are responsible for the index pneumonia will be recorded using the EDC system.

- Record type of pneumonia based on the following criteria:

a. Hospital-acquired bacterial pneumonia (HABP)
Pneumonia occurring in a patient hospitalized for more than 48 hours or developing within 7 days of discharge from a hospital or a similar institution (e.g., long-term care facility).

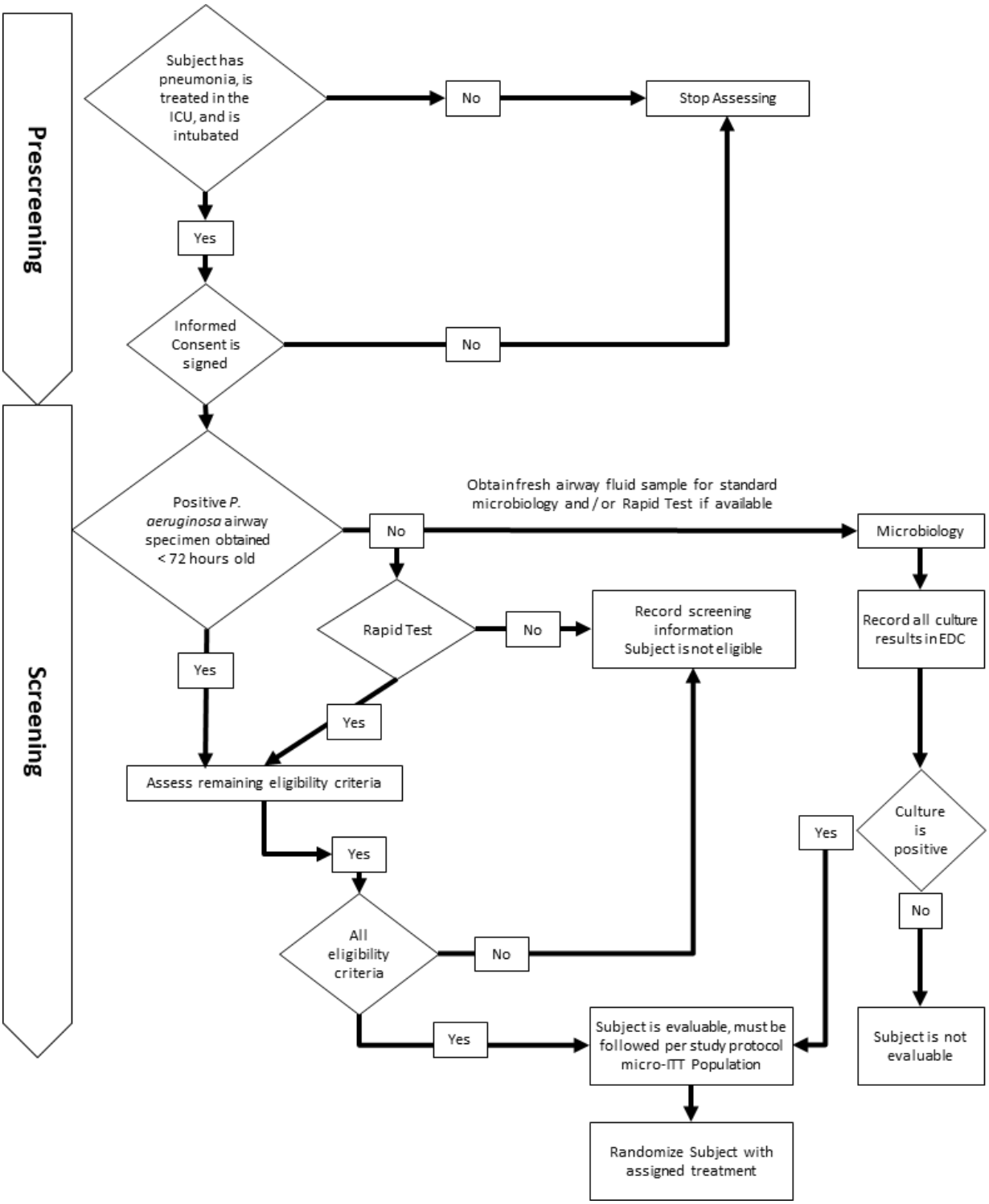
b. VAP
Pneumonia (as defined below) occurring in a patient mechanically ventilated for at least 48 hours.

c. Healthcare-associated bacterial pneumonia (HCABP)
Pneumonia occurring in a patient who was in a hospital or a similar institution (e.g., long-term care facility) more than 7 days and less than 90 days prior to developing pneumonia

d. Community-acquired bacterial pneumonia (CABP)
Pneumonia occurring outside of any of the conditions described in points a, b and c.

- For any subject who has a positive culture for *P. aeruginosa,* promptly assess all remaining eligibility criteria.

Figure 6-2: Screening and Randomization Process



6.3 Baseline and Randomization (Day -1, prior to treatment)

- Confirm eligibility and collect corresponding source documents.

- Medical and surgical history
- Concomitant medications
    - To include current antibiotic therapy, its duration and whether or not effective against the *P. aeruginosa* assumed to be responsible of the pneumonia.
- History of current condition (case history)
    - Reason for admission
    - Date and time of diagnosis of pneumonia, including the supporting evidence (see Section **4.1**).
- Pregnancy testing if woman of child bearing potential (urine or serum)
- Severity status, including date and time. "Severe" is defined as $PaO_2/FiO_2 \leq 200$.
- Physical exam
- Vital signs
- 12-lead electrocardiography (ECG)
- Laboratory tests. For details, please refer to the Section **8.9** for a list of the required tests, and to the Laboratory Manual for the corresponding procedures.
    - Standard safety tests
    - Baseline ADA sample
    - Future biomarker samples (where applicable)
- Compute baseline scores (APACHE II, SOFA) and collect source data as instructed. Please refer to Section **14** (Appendix B) and to the EDC / IWRS manual.
- Obtain respiratory data:
    - Mechanical ventilation parameters
    - Changes in PaO_2/FiO_2 (e.g. by arterial blood gases) OR changes in non-invasive measures of oxygenation (e.g. by pulse oximetry)
    - Use of supplemental oxygen
- As soon as *P. aeruginosa* is confirmed on a valid airway specimen, all eligibility criteria are met, and baseline assessments are completed, the subject should be randomized and treated at once. Please refer to section **5.3** and the EDC / IWRS Manual for details.

6.4 Treatment (Day 0, Time 0)

- Pre-dose (baseline) PK sample prior to dose administration.
- Treatment administration. Please refer to Section **5.5** for details.
- PK sample at end of infusion (i.e., 2 hours after treatment initiation) and the other Day 0 PK samples as required depending upon participation in the Full or Sparse PK sub-studies.

- Adverse Events. Monitor for 24 hours from treatment initiation for signs or symptoms including procedure-related complications, such as injection-site pain, swelling, bruising, or redness, infusion reactions, such as fever, chills, or diaphoresis, anaphylactoid reactions (e.g. urticaria, angioedema), anaphylaxis, and cardiovascular instability.
- Concomitant Medications
- Vital signs prior to treatment (time 0) and at 1, 2, 4, 12 and 24 hours after treatment initiation.
- Safety laboratory tests
- For subjects participating in the **FULL PK** sub-study, additional PK samples at 4, 12, and 24 hours after treatment initiation. For subjects participating in the **SPARSE PK** sub-study, 1 sample at 4h, 12h or 24h after treatment initiation (inclusive). Time of sampling to be recorded.
- Compute SOFA score 12 hours following treatment initiation and collect source data on the corresponding worksheet.
- Obtain respiratory data 12 hours post treatment initiation:
    - Mechanical ventilation parameters
    - Changes in PaO_2/FiO_2 (e.g. by arterial blood gases) possible OR changes in non-invasive measures of oxygenation (e.g. by pulse oximetry)
    - Use of supplemental oxygen

6.5 Daily follow-up for efficacy and safety (Day 1 to 28)

These assessments are required daily for as long as the index pneumonia has not been deemed resolved by the investigator.

- Clinical status including Clinical Cure of pneumonia
    - Note date and time of extubation and obtain a last airway specimen prior to extubation.
    - If Clinical Cure, record/collect full documentation of assessment, including a chest X-ray if performed as part of SOC.
    - As soon as *P. aeruginosa* is confirmed on a valid airway specimen, all eligibility criteria are met, and baseline assessments are completed, the subject should be randomized and treated at once.
    - Document Clinical Cure, persistence or re-infection/new infection of index pneumonia
    - Clinical Cure status to be analyzed on Day 7, 14, 21, 28.
- Respiratory health:
        – Mechanical ventilation parameters

  - PaO_2/FiO_2 ratio (e.g. by arterial blood gases), OR changes in non-invasive measures of oxygenation (e.g. by pulse oximetry)
  - Use of supplemental oxygen

- SOFA scores on Day 4, 7, 14, 21, 28 for the duration of stay in the ICU and/or while intubated and mechanically ventilated.
- Adverse events
- Concomitant Medications
- Safety laboratory tests as available from medically indicated assessments. Key parameters of interest include white blood cells, neutrophils and CRP. Additional parameters should be recorded in the EDC system if available.
- Microbiology:
  - **Airway specimens are to be obtained:**
    - **At any time when as medically indicated**
    - **At the least, a valid airway specimen (BAL, mini-BAL or ETA) is to be obtained just prior to extubation. Ideally, an ETA specimen would be preferred for the airway culture. If BAL or mini-BAL, make sure that either BUN or urea is collected at or about the same time as sampling.**
    - **An aliquot (i.e. half of the specimen) is to be reserved for assessing bioavailability (refer to microbiology lab manual for instructions).**
    - **If not obtained on Day 7, 14, and 21, the nearest specimen collected will be used to assess microbiological outcome.**
  - Obtain airway specimens (by BAL, mini-BAL, or protected ETA) for quantitative/semi-quantitative culture by the local microbiology laboratory. Other sampling methods, including sputum, are acceptable after extubation.
  - The local microbiology laboratory will perform culture including identification of genus and species, quantitative/semi-quantitative culture and susceptibility testing as outlined in the microbiology laboratory manual.
  - The local microbiology laboratory will obtain isolates of unique organisms from airway specimen cultures and send them to the central laboratory. The central microbiology laboratory will perform confirmation of organism identification, susceptibility testing and serotyping on target organisms as outlined in the microbiology laboratory manual.
  - Record microbiological assessments from the local laboratory in the EDC system, including:
    - Assessment of the quality of the sample
    - Organism identification (genus and species)
    - Quantification

  - Any organisms identified
  - The corresponding antibiotic susceptibility profile for each pathogen as determined by the local microbiology laboratory
  - An assessment of microbiological outcome
- Chest X-Rays at any time as medically indicated.

6.6 Day 4, 7, 14, and 21: Required full assessments

- All daily assessments as detailed above are required whether the subject is in the ICU or has been transferred out of the ICU.
- Perform full assessment of the clinical status of pneumonia
- Document Clinical Cure, persistence or re-infection/new infection of index pneumonia using the daily assessments described above.
- Microbiology:
  - **Airway specimens are to be obtained:**
    - **At any time when as medically indicated**
    - **At the least, a valid airway specimen (BAL, mini-BAL or ETA) is to be obtained just prior to extubation. Ideally, an ETA specimen would be preferred for the airway culture. If BAL or mini-BAL, make sure that either BUN or urea is collected at or about the same time of sampling.**
    - **An aliquot (i.e. half of this specimen) is to be reserved for assessing bioavailability (refer to microbiology lab manual for instructions).**
    - **If not obtained on Day 4, 7, 14, and 21, the nearest specimen collected will be used to assess microbiological outcome.**
  - Obtain airway specimens for local and central laboratory assessment (by BAL, mini-BAL, or protected endotracheal tube aspiration) for standard microbial culture (quantitative, semi-quantitative). Other sampling methods, including sputum, are acceptable after extubation.
  - Obtain isolates for assessment by the central laboratory.
  - Record microbiological assessments from the local laboratory in the EDC system, including:
    - Assessment of the quality of the sample
    - Organism identification (genus and species)
    - Quantification
    - Any organisms identified,
    - The corresponding antibiotic susceptibility profile for each pathogen as determined by the local microbiology laboratory

  - An assessment of microbiological outcome

- Physical exam
- Vital signs
- Adverse Events
- Concomitant Medications
- Respiratory health:
  - Mechanical ventilation parameters
  - 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)
  - Use of supplemental oxygen
- Laboratory tests.
  - Standard safety tests (required on these days regardless of medical need)
  - For subjects participating in the **FULL PK** sub-study, PK samples at Day 4, Day 7, Day 14, and Day 21. For subjects participating in the **SPARSE PK** sub-study, 1 sample at any of the following visits: Day 4, 7, 14 or 21. Instructions for scheduling such sampling will be provided on a per-subject basis.
  - Future biomarker samples (where applicable)
- Chest X-Rays at any time as medically indicated

6.7 End of study (Day 28) or Early Termination

- Perform full assessment of the status of pneumonia
- Document final clinical outcome of the index pneumonia
- Airway specimens are to be obtained:
  - **At any time when as medically indicated**
  - **At the least, a valid airway specimen (BAL, mini-BAL or ETA) is to be obtained <u>just prior to extubation</u>. Ideally, an ETA specimen would be preferred for the airway culture. If BAL or mini-BAL, make sure that either BUN or urea is collected at or about the same time as sampling.**
  - **An aliquot (i.e. half of the specimen) is to be reserved for assessing bioavailability (refer to microbiology lab manual for instructions).**
  - **If not obtained on Day 28, the nearest specimen collected will be used to assess microbiological outcome.**
- Obtain airway specimens for local and central laboratory assessment (by BAL, mini-BAL, or protected endotracheal tube aspiration) for standard microbial culture (quantitative, semi-quantitative). Other sampling methods, including sputum, are acceptable after extubation.

- Obtain isolates for assessment by the central laboratory.
- Record microbiological assessments from the local laboratory in the EDC system, including:
  - Assessment of the quality of the sample
  - Organism identification (genus and species)
  - Quantification
  - Any organisms identified
  - The corresponding antibiotic susceptibility profile for each pathogen as determined by the local microbiology laboratory
  - An assessment of microbiological outcome

- Respiratory health:
  - Mechanical ventilation parameters
  - 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)
  - Use of supplemental oxygen
- Physical exam
- Vital signs
- Chest X-Rays at any time when as medically indicated
- All-cause mortality
- Adverse Events
- Concomitant Medications
- Laboratory tests
  - Standard safety tests (required on these days regardless of medical need)
  - For subjects participating in the **FULL PK** sub-study, PK sample is to be obtained on Day 28. For subjects participating in the **SPARSE PK** sub-study, a PK sample is to be obtained on Day 28 if it has not been collected previously at any of the following visits: Day 4, 7, 14, or 21.
  - ADA sample
  - Future biomarker sample, where applicable.
- Ensure that outcomes of all recorded adverse events are known, final and recorded.
- If early termination, reason(s) for early study termination and date thereof. Death is a possible reason for early termination.
- Date of discharge from the ICU (when applicable)
- Date of discharge from the hospital (when applicable)

7 EFFICACY ASSESSMENTS

7.1 Primary Clinical Efficacy Parameter

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 (**Table 7-1**) and will be applied post-hoc by an independent adjudication committee.

Table 7-1 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 #3 (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:
     - Fever > 38°C or hypothermia (< 35°C) attributable to the primary bacterial pneumonia
     - 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

7.2 Secondary Clinical Efficacy Parameters

1. Proportion of patients with Clinical Cure at Day 28
2. Proportion of patients with Clinical Cure at Day 14
3. All-cause mortality
4. Pneumonia-related mortality
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 PaO2/FiO2, using arterial blood gases and/or pulse oximetry measurements.
7. Mean change from baseline in overall clinical status measured by:
   a. 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 in place

7.3 Microbiological Endpoints

1. Microbiological outcome of the index *P. aeruginosa* pneumonia based on the data provided by the local microbiology laboratory and central microbiology laboratory.
2. 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.

An antibiotic susceptibility profile will be obtained locally in order to confirm the effectiveness of the concomitant antibiotic regimen prior to enrollment and thereafter, as medically indicated.

Quantitative and semi-quantitative cultures will be performed locally prior to treatment (baseline), as medically indicated, just prior to extubation, and at Day 28 (if not extubated prior to Day 28).

Organism identification and antibiotic susceptibility profiles will be confirmed by the central microbiology laboratory for the purpose of confirming the infecting pathogen(s), and the adequacy of the concomitant antibiotic regimen.

Serotyping will be performed by the central microbiology laboratory.

7.4 Pharmacokinetic Measurements

Blood samples for determination of Aerucin® concentration will be collected at specified times from all subjects. A sub-set of 16 subjects will contribute to a Full PK sub-study. All other subjects will contribute to a Sparse PK sub-study.

At each sampling time, a primary and a back-up sample of 3 mL each will be obtained. The detailed handling, storing and shipping procedures are detailed in the Laboratory Manual.

7.4.1 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.

7.4.2 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 approach will be used to characterize the PK of Aerucin® for the SPARSE PK population.

8 SAFETY ASSESSMENTS

8.1 Safety Parameters

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

8.2 Contraceptive Requirements and Pregnancy Testing

Females of child bearing potential must agree to use at least 2 effective methods of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, barrier methods, abstinence) or male partner sterilization alone for the duration of the study and for at least 120 days after dosing. Males with female partners of reproductive potential must agree to practice abstinence or to use a condom (male) plus an additional barrier method (female partner) of contraception for the duration of the study and for at least 120 days after dosing.

WOCBP must have a negative pregnancy test result at Screening (serum or urine) to meet the eligibility criteria for enrollment. Women who are post-menopausal as evidenced by the absence of menstruation for at least 1 year prior to Screening Visit are eligible; the date of the last menstruation is to be recorded in the study file unless postmenopausal status is obvious due to age.

8.3 Adverse Events

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

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of randomization until 28 days after last dose. Subjects should be instructed to report any adverse event that they experience to the Investigator. Beginning at Day 0, Investigators should make an assessment for adverse events at each visit and record the adverse event on the appropriate eCRF using the EDC system.

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

Any medical condition already present prior to Day 0 should be recorded as a pre-existing condition in the Medical History, and not be reported as an adverse event. However, should the medical condition or signs or symptoms present at baseline change in severity or seriousness at

any time after randomization or during the study, an adverse event should be reported (worsening of pre-existing condition).

Clinically significant abnormal laboratory or other examination (e.g. electrocardiogram) findings independent from the underlying medical condition that are detected during the study or are present at prior to Day 0 and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

Worsening of the index infection due to insufficient therapeutic effect of study drug is captured as an efficacy measure (i.e., clinical failure) and in general will not be considered an AE. However, if the worsening of the index infection meets seriousness criteria (see Section **8.3**), the event will be deemed an SAE.

8.3.1 Adverse (Drug) Reaction

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

8.3.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For Aerucin®, the reference safety information is included in 7.1 of the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.3.3 Assessment of Adverse Events by the Investigator

Unless an adverse event is considered serious and meets SAE criteria, progression or worsening of the index infection due to insufficient effect of study drug should not be deemed an AE or deemed related to study drug.

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of "yes" or "no".

Assessment of Severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment:

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

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

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

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

The following factors should also be considered:

- The temporal sequence from study drug administration: The event should occur during or after the study drug is administered. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug: Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug: The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.4 Serious Adverse Events

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

- Death,
- A life-threatening adverse event,
    - NOTE: An adverse event or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
    - NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a serious adverse event (SAE) under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected

complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect,
- An important medical event.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.5 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

Serious adverse events will be reported in compliance with country-specific regulatory requirements relating to safety reporting to the regulatory authority IRB/EC and investigators.

All SAEs occurring from randomization until 28 days following the last administration of study drug must be reported to the Contact Research Organization (CRO) Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Aridis Pharmaceuticals Inc.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, CRO Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to CRO Safety at medpace-safetynotification@medpace.com or call the CRO SAE hotline (phone number listed below), and fax/email the completed paper SAE form to CRO (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Clinical Safety

SAE hotline – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-579-5196
Email: medpace-safetynotification@medpace.com

SAE hotline – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
Email: medpace-safetynotification@medpace.com

Follow-Up Reports

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

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

8.6 Pregnancy Reporting

If a study subject becomes pregnant during the study or within 28 days of discontinuing study drug, the Investigator should report the pregnancy to Clinical Safety within 24 hours of being notified. Clinical Safety will then forward the Exposure in Utero form to the Investigator for completion.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.7 Expedited Reporting

The Sponsor, or CRO (on behalf of the Sponsor), will report all relevant information about initial suspected unexpected serious adverse reactions (SUSAR) that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and to the Central Ethics Committees, and in any case no later than 7 days after knowledge by the Sponsor or CRO of such a case, and relevant follow-up information will subsequently be communicated within an additional 8 days.

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

The Sponsor and the CRO (on behalf of the Sponsor) will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators if country requirements are different than the above.

The Sponsor will also inform all investigators as required.

Expedited reporting of suspected unexpected serious adverse reactions related to non-investigational medical products (NIMPs) will not be necessary. Listings of cases related to NIMPs will be included in the Development Safety Update Report.

8.8 Follow-up Phone Calls

For subjects who decide to discontinue assessments prior to Day 28, a study exit safety follow-up phone call will be conducted on Day 28 (+7 days) to assess survival, Clinical Cure, and adverse events.

For subjects deemed clinically cured and discharged from the hospital, subjects are encouraged to return to the clinic to receive study procedures for the remaining key visit days until Day 28. If not able to visit the clinic on key visit days, a follow-up phone call will be conducted on key visit days (Day 4, 7, 14, 21 and 28) until Day 28.

8.9 Clinical Safety Laboratory Evaluations

8.9.1 Standard safety laboratory tests

Laboratory results obtained in the course of standard medical care should be used to provide the information required below whenever available. All these 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, creatinine, serum 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)

8.9.2 Immunogenicity (ADA)

- The corresponding sample will be collected, stored and shipped per instructions (see laboratory manual).
- Samples will be obtained at screening/baseline and Day 28.
- Assays will be performed by a central laboratory.

- A primary and a back-up sample of 1.5 mL each of serum will be collected and stored at -20º C.

8.9.3 Future biomarker samples will be collected, where applicable.

- The corresponding sample will be collected, stored and shipped per instructions (see laboratory manual).
- Samples will be obtained at Day 4, 7, 14, 21, and 28.
- Assays will be performed at a central laboratory.

8.10 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 eCRF. The same method of measuring a patient's body temperature should be used throughout the study.

8.10.1 Baseline, Treatment, and Daily in-ICU

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.

8.11 Electrocardiograms

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.

8.12 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.

8.13 Chest X-rays

Minimum of one Chest X-rays or a sequence of at least 2 Chest X-rays showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia to diagnose a pneumonia needs to be taken during screening. Chest X-rays may be taken at any time during the course of the study if medically necessary. All clinically relevant Chest X-rays may be uploaded to SureClinical.

8.14 Airway specimen

Airway specimens will be collected by only acceptable methods such as BAL, mini-BAL, or protected endotracheal tube aspiration or by sputum after extubation as outlined in the

microbiology laboratory manual. Additionally, please refer to the manual for detailed handling, storing and shipping procedures.

9 STATISTICS

9.1 Analytical Populations

9.1.1 Safety Population (Safety)

All subjects who have received the investigational therapy.

9.1.2 Modified Intent-to Treat Population (mITT)

All subjects who have been randomized and treated with any amount of study drug, regardless of microbiological documentation.

9.1.3 Microbiological Intent-to-Treat Population (micro-ITT)

All mITT 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.

9.1.4 Per-protocol Population (PP)

All micro-ITT subjects who completed the study without any major protocol deviation.

9.2 Sample Size and Statement of Power

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, 154 subjects (77 per group) will be randomized.

9.3 Statistical Methods

Continuous data will be summarized by means, standard deviations, median, min, and max. Categorical data will be summarized by frequency and percentages.

The primary endpoint of Clinical Cure rate at Day 21 will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test. The CMH test will be stratified by baseline randomization strata. Time to Clinical Cure will be analyzed using a stratified log rank test. Other continuous endpoints will be analyzed using an Analysis of Covariance (ANCOVA), with treatment as a main effect, site, and baseline strata as covariates. Treatment by site interaction will be evaluated separately. Secondary endpoints will be analyzed using a sequential procedure in predefined order. Categorical variables will be analyzed using a stratified CMH test.

The primary comparisons for all endpoints will be between the 20 mg/kg dose group and placebo and will be done at 0.05 level of significance. The details of the planned analyses will be provided in the Statistical Analysis Plan.

9.3.1 Demographics, Baseline Characteristics, and Disposition

Demographics and baseline characteristics will be summarized by treatment group and overall. Disposition will be summarized by treatment group, and various outcomes (completed or discontinued the study, and reasons for discontinuations, etc.).

9.3.2 Safety analysis

Safety evaluations will include treatment emergent adverse events, vital signs, physical exam, and laboratory values. Safety will be summarized by treatment group. All treatment emergent adverse events, and serious adverse events, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Relationship to treatment, as well as severity will also be summarized. Changes in vital signs and physical exam will be summarized by group. Changes in laboratory values, as well as shifts (normal-> abnormal) will be summarized by treatment group.

9.3.3 Pharmacokinetic analyses

Two types of pharmacokinetic analyses will be performed to assess the PK hypothesis that the PK profile of Aerucin® in the target patient population is similar to the profile observed in healthy human volunteers (HV). The first pharmacokinetic analysis will consist of a population PK (compartmental modeling) approach using the combined concentration data collected in the PK sub-study and the sparse concentration data, pooled with the available PK data from healthy volunteers (Study ARC-11-01). A compartmental population PK model will be developed and the effects of select intrinsic and extrinsic factors, including but not limited to patient status (e.g., HV versus patient with pneumonia), high or low bacterial load, and cause of admission [trauma or non-trauma]) on the PK of Aerucin® will be evaluated via covariate analysis. The population PK model will be described by the estimation of mean structural model parameters, the magnitude of IIV in these parameters, and the magnitude of RV.

The second pharmacokinetic analysis to be performed will be a non-compartmental analysis of the extensively sampled concentration-time data collected in the PK sub-study. The pharmacokinetic parameters to be derived from the individual concentration-time profiles will include: the maximum observed plasma concentration (C_{max}), the time of occurrence of C_{max} (t_{max}), the area under the plasma concentration-time curve from time 0 to Day 28 (AUC_{0-28}), the terminal elimination rate constant (λz), and, if data permits, the terminal half-life ($t_{1/2}$). Parameter estimates will be summarized and tabulated by individual and overall. Graphs of plasma concentration versus time profiles will be generated for each subject and graphs of mean ± SD profiles will be generated to compare patient and HV data.

9.3.4 Interim Analysis

No interim analysis is planned.

9.3.5 Missing data

Assessing microbiological outcome at Day 7, 14, 21 (Primary Efficacy endpoint), and 28 will be done using the nearest microbiological data available prior to that day (last observation carried forward, LOCF).

Missing data for secondary efficacy endpoints will be analyzed using the LOCF approach.

For the purpose of sensitivity analysis, missing data will be imputed using baseline observation carried forward (BOCF) and observed case.

9.4 Data Monitoring Committee (DMC)

An independent DMC will be reviewing on a regular basis the safety information collected to-date. The corresponding procedures will be defined in a charter. DMC meetings will include a blinded session, when personnel in charge of the study will provide background information to facilitate review, and an open session, closed to all but DMC members, during which access to unblinded reports and/or subject-specific data will be allowed.

In addition, all SAEs deemed related will be communicated to the DMC, as defined in the charter, for immediate review.

The Medical Monitor will call for a meeting of the DMC whenever safety concerns of immediate significance may arise, such as abnormal frequency of non-serious events or unrelated events.

9.5 Adjudication Committee

An Independent Adjudication Committee will assess clinical outcomes post hoc, microbiological outcome, adequacy of antibiotic therapy at baseline for use in statistical analyses. Clinical outcome will be adjudicated consistent with the newly defined criteria (Table 7-1).

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

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

10.1.2 Computer Systems

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

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress in a timely manner, keeping in mind that the EDC system is programmed to assist study personnel in complying with protocol requirements on a daily basis. This concerns both screening (pre-baseline) and post-randomization study data.

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

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

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

The eCRFs must be reviewed and electronically signed by the Investigator prior to locking and unblinding the database for analysis.

10.2 Record Keeping

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

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

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

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enroll a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Investigators must comply with all applicable IRB/IEC and local requirements in the reporting of protocol deviations.

11.2 Institutional Review Board/Independent Ethics Committee

11.2.1 United States of America

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

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

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.2.2 Europe and other non-US countries

It is the responsibility of the Sponsor or its designee (i.e., CRO) to obtain the approval of the responsible ethics committees according to the national regulations.

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

11.3 Informed Consent

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

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject or the subjects legal representative (if applicable) before any

study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

11.3.1 Russia

For subjects who are unable to read and sign either version of the informed consent (i.e., shortened or complete version), decisions regarding the subject's enrollment will be made by the CIP.

11.4 Subject Card

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

11.5 Study Monitoring Requirements

In the USA: It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

In the European Union: It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki (Seoul 2008) and that valid data are entered into the eCRFs.

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

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

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

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal

representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

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

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

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

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication.

This is a multicenter study. Therefore, the primary publication will be made under the oversight of the Steering Committee, or when designated, the Publication Committee. Individual study sites or groups of study sites will not be allowed to publish their individual results prior to the core publication being made. It is intended to publish the core result of this study within 12 months of the database being locked and unblinded. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e., initiation of study centers) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the investigators by the CRO or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/EC and, where appropriate, Competent Regulatory Authority approval prior to implementation, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days and in the countries outside of the United States according to the national regulation.

12.2 Study Termination

The study can be terminated at any time for any reason by the Sponsor.

In addition, the study may be terminated for safety reasons upon recommendation by the DMC and review by the Steering Committee. Per its charter, the DMC will, at the conclusion of each of its meeting, make any of the following recommendations:

- Continue the study without modification
- Continue the study with modifications
- Continue the study pending additional information
- Suspend the study pending additional information; or
- Stop the study due to safety concerns

12.3 Address List

12.3.1 Sponsor

Aridis Pharmaceuticals, Inc.
5941 Optical Court
San Jose, CA 95138
Phone: 408-385-1742
Fax: 408-960-3822

12.3.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
Telephone: 513-579-9911
Fax: 513-579-0444

12.3.3 Drug Safety

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Fax: +1-866-336-5320 or +1-513-579-0444

Email: Medpace-safetynotification@medpace.com

12.3.4 Biological Specimens

Clinical Laboratory
Medpace Reference Labs
5365 Medpace Way
Cincinnati, OH 45227
Telephone: +1-800-749-1737 or +1-513-366-3270
Fax: +1-800-705-2177 or +1-513-366-3273

Microbiological Laboratory
International Health Management Associates, Inc. (IHMA)
2122 Palmer Drive
Schaumburg, IL 60173-3817
Tel: +1-847-303-5003
Fax: +1-312-637-3121
Website: www.ihmainc.com

13 APPENDIX A: CLINICAL LABORATORY ANALYTICS

Safety laboratory tests are described in Section **8.9**. All safety laboratory tests will be performed by the site's local laboratory.

Required special laboratory tests include PK and ADA. Additional laboratory tests may be performed during the study or thereafter using bio banked samples. All special laboratory tests will be performed by a central laboratory.

Sampling methods, including those related to special laboratory evaluation, PK and immunogenicity (ADA) samples is provided in the Laboratory Manual.

14 APPENDIX B: OTHER TRIAL SPECIFIC PROCEDURES

14.1 APACHE II Score

The score computed by the study site according to standard practice will be entered in the EDC system. The corresponding worksheet, including all the data that were used to compute the recorded score, will be stored as source data in the site study files.

14.2 SOFA Score

The score computed by the study site according to standard practice will be entered in the EDC system. The corresponding worksheet, including all the data that were used to compute the recorded score, will be stored as source data in the site study files.

14.3 Microbiological basis for randomization and treatment

Any patients with pneumonia who are intubated (or have a tracheostomy) in whom evidence that *P. aeruginosa* is the infective pathogen can be randomized and treated. Such evidence can be provided by several means, either based on available cultures or on rapid testing methods. Patients with culture results of more than one pathogen can be included, if *P. aeruginosa* is regarded a key pneumonia causing pathogen.

14.3.1 Culture

Acceptable sampling methods are BAL, mini-BAL and ETA (ETA sample with < 10 squamous epithelial cells and > 25 polymorphonuclear cells per low power field). Acceptable airway specimens must have been obtained less than 72 hours prior to randomization.

Any method of identification of P. *aeruginosa* is acceptable, including standard microbial culture (quantitative, semi-quantitative), mass spectrometry or PCR.

If randomization and treatment is based on such evidence, a new sample must be obtained prior to treatment for standard microbial culture by the local microbiology laboratories. The culture at the local microbiology lab should include identification of genus and species, quantitative, semi-quantitative culture and susceptibility testing.

14.3.2 Rapid testing

Rapid testing is accepted as acceptable evidence of infection by *P. aeruginosa* whenever no other acceptable evidence is available. In such cases, a fresh airway specimen must be obtained by BAL, mini-BAL or ETA. The same specimen must be used for standard microbial cultures (quantitative, semi-quantitative)by the local and central laboratories. Rapid diagnostic testing will not be used for other purpose than screening and randomization in this study. In particular, they will not be used to assess microbiological outcomes.

Acceptable rapid diagnostic testing discussed hereunder are IUO / RUO. Other methods available at the site may be used (e.g., mass spectrometry, PCR, etc.).

14.3.2.1 Rapid testing using the IUO FilmArray LRTI Panel[i]

The BioFire Diagnostics, LLC (a BioMérieux company)'s IUO FilmArray lower respirometry tract infection (LRTI) panel can be used to determine whether *P. aeruginosa* is present in the sample obtained at baseline for the purpose of screening and randomizing patients who meet eligibility criteria. The corresponding methods are provided in the Laboratory Manual.

Briefly, the IUO FilmArray (FA) LRTI panel allows for identifying the etiological agent(s) of LRT infections. This is a multiplexed device, allowing the simultaneous detection of multiple bacteria, including *P. aeruginosa*, viruses and fungi. Semi-quantitative results can be obtained for bacteria (reported positive if detected at levels of 10e3.5 copies/mL or above). Although any relevant sample can be used, including sputum, only BAL, mini-BAL and ETA samples are allowed at baseline and prior to extubation to ensure the quality of standard microbial cultures and to avoid any ambiguity that would preclude determining the etiological agent or assessing bacterial load with confidence.

The procedure entails injecting an adequate airway specimen and rehydration medium to the IUO LRTI pouch, and then inserting the pouch in the FilmArray instrument. Time to results is about 1 hour.

14.3.2.2 Rapid testing using the GeneXpert RUO PA Cartridge[ii]

The CE marked Cepheid GeneXpert PA Assay, performed on the GeneXpert® Instrument Systems, is a qualitative in vitro test designed for the detection of *Pseudomonas aeruginosa* Gram negative bacteria.

The GeneXpert (GX) Instrument Systems automate and integrate sample preparation, nucleic acid purification and amplification, and detection of the target sequences in simple or complex samples using real-time PCR assays. The systems consist of an instrument, personal computer, and preloaded software for performing tests and viewing the results. The systems require the use of single-use disposable cartridges that hold the PCR reagents and host the PCR process. Because the cartridges are self-contained, cross- contamination between samples is minimized. For a full description of the system, see the GeneXpert Dx System Operator Manual or the GeneXpert Infinity System Operator Manual.

The primers and probes in the GeneXpert PA Assay detect proprietary sequences for the detection of *Pseudomonas aeruginosa*.

Endotracheal aspirates (ETA) may be used with the GeneXpert PA assay kit. For ETA samples, a swab is dipped into the sample, then material on the swab is eluted by breaking the swab into the Sample Reagent vial, followed by vortexing. The disposable transfer pipette provided in the GeneXpert PA kit is used to transfer the eluate to the Sample Chamber of the cartridge (Figure 2). All reagents required for sample preparation and real time PCR analysis are preloaded in the cartridge. Bacterial cells in the eluate are mixed with the sample preparation control and treatment

[i] FilmArray is a registered trademark of BioFire Diagnostics, LLC (a BioMérieux company).

[ii] GeneXpert is a registered trademark of Cepheid.

reagents, cells are captured on a filter and lysed by sonication. The released DNA is eluted, mixed with dry PCR reagents, and the solution is transferred to the reaction tube for real- time PCR and detection. Time to result is approximately 50 minutes.

14.4 Quantitative/semi-quantitative microbiology

Quantitative airway specimen cultures will be performed at baseline and follow up by the local microbiological laboratory as outlined in the microbiology laboratory manual. The necessary materials will be provided. Whenever possible the local microbiology laboratory is to report quantitative microbiology outcomes when available. Semi-quantitative methods for BAL, mini-BAL, ETA specimens will be acceptable if they represent the methodologies typically performed at the local reference laboratory centers and quantitative methods are not available.

15 APPENDIX C: CONVERSION TABLE FOR FiO_2

The conversion table [9] below applies to determining FiO_2 when supplemental oxygen is administered, and the subject is not mechanically ventilated. Oxygen flow is for 100% oxygen.

Oxygen flow (L/min)	FiO_2 (%)
Nasal cannula	
1	24
2	28
3	32
4	36
5	40
6	44
Oxygen mask	
5-6	40
6-7	50
7.8	60
9	90
10	99+
Mask with reservoir bag	
6	60
7	70
8	80

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