A Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by *Pseudomonas aeruginosa*

Sponsor Protocol Number: D5470C00004

Study Identifier: EVADE (**E**ffort to Pre**v**ent Nosocomi**a**l Pneumonia caused by *P seu**d**omonas aeruginosa* in Mechanically V**e**ntilated Subjects)

Application Number: Redacted

Investigational Product: MEDI3902

Sponsor: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC, One MedImmune Way, Gaithersburg, Maryland, 20878, USA

Medical Monitor: Redacted

Coordinating Principal Investigator: Redacted

Contract Research Organization: Redacted

Protocol History, Date: Original Protocol, 16Oct2015
Amendment 1, 15Jul2016
Amendment 2, 22Dec2016
Amendment 3, 06Jun2018

PROTOCOL SYNOPSIS

TITLE

A Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by Pseudomonas aeruginosa

HYPOTHESES

Prophylactic use of MEDI3902 in mechanically ventilated subjects in the intensive care unit (ICU) who are colonised with *Pseudomonas aeruginosa (P aeruginosa)* in the lower respiratory tract will reduce the incidence of nosocomial pneumonia caused by *P aeruginosa* through 21 days postdose irrespective of mechanical ventilation status at time of diagnosis.

A single intravenous (IV) dose of MEDI3902 administered to mechanically ventilated subjects in the ICU will have an acceptable safety profile.

OBJECTIVES

Primary objectives

1. To evaluate the effect of MEDI3902 in reducing the incidence of nosocomial pneumonia caused by *P aeruginosa*
2. To evaluate the safety of a single IV dose of MEDI3902 in mechanically ventilated patients

Secondary objectives

1. To evaluate the serum pharmacokinetics (PK) of MEDI3902
2. To evaluate the serum antidrug antibody (ADA) responses to MEDI3902

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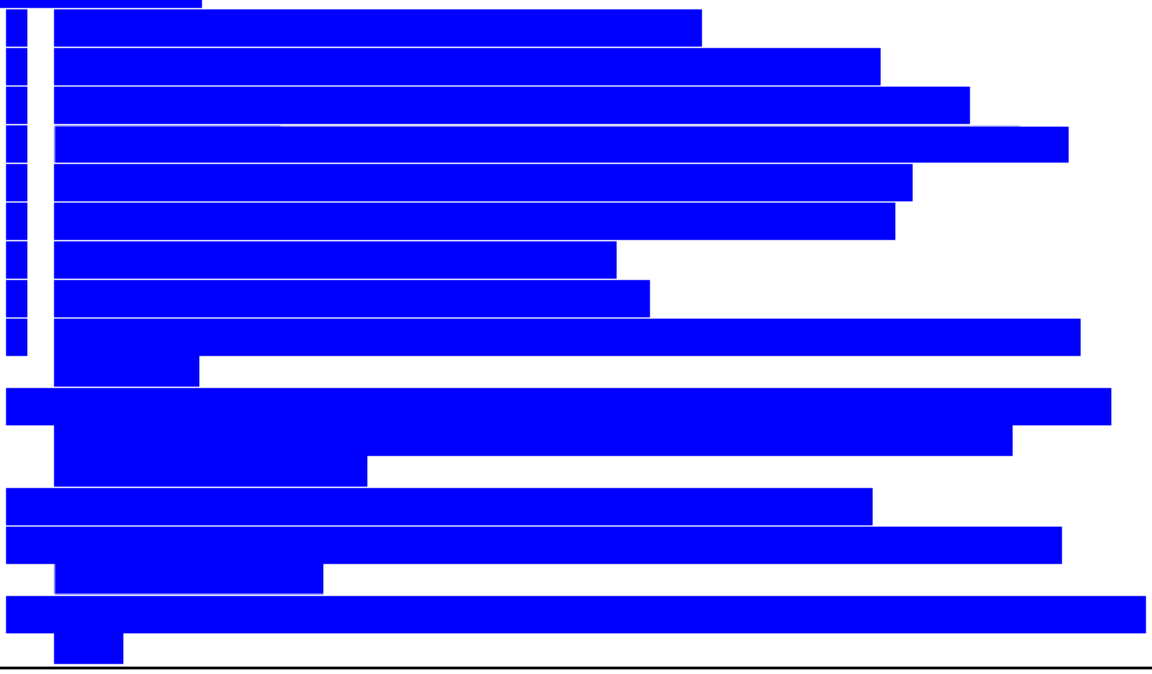

STUDY ENDPOINTS

Primary endpoints:

Efficacy

1. Incidence of nosocomial pneumonia caused by *P aeruginosa* through 21 days postdose

Safety

1. Treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs) and adverse events of special interest (AESIs) through 49 days postdose

Secondary endpoints:

1. MEDI3902 serum concentration and PK parameters through 49 days postdose
2. MEDI3902 ADA response in serum through 49 days postdose

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STUDY DESIGN

This is a Phase 2, randomised, double-blind, placebo-controlled, single-dose, dose-ranging, proof-of-concept study evaluating 2 dosage levels of MEDI3902 in mechanically ventilated patients in the ICU who are at high risk for *P aeruginosa* infections and who are currently free of *P aeruginosa*-related disease but are colonised with *P aeruginosa* in the lower respiratory tract. At study start, approximately 429 subjects were to be enrolled and dosed at approximately 120 sites primarily in Europe. Subjects were to be randomly assigned in a 1:1:1 ratio to receive a single IV dose of R R mg MEDI3902, Red mg MEDI3902, or placebo. However, based on data

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from a separate study in a similar population with another monoclonal antibody, data from a PK study in mice (see Section 3.2.1) and from simulation results using data from the Phase 1 study (Study D5470C00002), a single dose of Red mg MEDI3902 is not expected to maintain the new target level of Red µg/mL for 21 days. Therefore, enrolment in the Red mg MEDI3902 group will be discontinued. Approximately 286 subjects will be randomised in a 1:1 ratio to one of 2 treatment groups Red mg MEDI3902 or placebo (N = 143 for each treatment group).

A PK interim analysis will be performed after at least 10 subjects in each of the Red mg MEDI3902 and placebo groups are followed through 21 days postdose. The interim PK analysis will allow the determination of serum PK profile of MEDI3902 in mechanically ventilated subjects. Enrolment will continue in both the Red mg MEDI3902 and placebo groups while the PK interim analysis is conducted. If the mean serum concentration of MEDI3902 on Day 22 in the Red mg MEDI3902 dose group is lower than the target concentration of Red µg/mL, a dose adjustment to Red mg MEDI3902 will be considered. An independent DMC will be responsible for recommending dose adjustment.

In case of a dose adjustment from Red mg to Red mg MEDI3902, approximately 143 subjects will be randomised to receive the Red mg MEDI3902 dose to maintain 1:1 ratio with the placebo group. Subjects who have been enrolled and randomised in the Red mg and Red mg MEDI3902 groups will be followed until the end of the study period (Day 50).

Randomisation will be stratified by geographic region and by duration of antipseudomonal antibiotic treatment (no antibiotics use, duration of ≤ 72 hours, duration of > 72 hours) within the 96 hours prior to randomisation. Subjects will be followed through Day 50 (49 days postdose).

The study is being conducted through the Innovative Medicines Initiative Joint Undertaking (IMIJU, 2012), which is a pan-European public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. The Sponsor will execute this study in conjunction with Combatting Bacterial Resistance in Europe - Molecules against Gram Negative Infection (COMBACTE-MAGNET), which is a consortium of partners from the pharmaceutical industry and academia in the field of antibiotic-resistant bacteria, hospital-acquired pneumonia and ventilator-associated pneumonia.

TARGET SUBJECT POPULATION

Subjects in this study will be adult patients 18 years of age or older in the ICU, who require mechanical ventilation and who are currently free of *P aeruginosa*-related disease, but are colonised with *P aeruginosa* in the lower respiratory tract.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

At the study start, subjects were to be randomly assigned to receive a single dose of Red mg MEDI3902, Red mg MEDI3902, or placebo administered via IV infusion on Day 1. Subsequent to Amendment 2, subjects will be randomly assigned to receive a single dose of Red mg MEDI3902 (or in the case of dose adjustment, Red mg MEDI3902) or placebo administered via IV infusion on Day 1.

STATISTICAL ANALYSIS PLAN

Statistical analyses

The key efficacy analyses will be based on Red mg MEDI3902 and placebo subjects, given there is no dose adjustment after the PK interim analysis. Data will be provided in data listings sorted by treatment group and subject identification number. Tabular summaries will be presented by treatment group. Categorical data will be summarised by the number and percentage of subjects falling within each category. Continuous variables will be summarised by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. No multiplicity adjustments will be made to any of the analyses, because this is a Phase 2 study. Subjects who discontinue before Day 22 will be included in the primary efficacy (ie, Intent-to-treat [ITT]) population as described in the primary efficacy analysis section below. If a dose adjustment is made from Red mg MEDI3902 to Red mg MEDI3902 for this dose group, the key efficacy analyses will be based on Red mg MEDI3902 and placebo subjects. Subjects who received Red mg MEDI3902 will be summarized descriptively. Due to the decision to discontinue the lower dose, subjects who received Red mg MEDI3902 will also be summarized descriptively. Additional details of statistical analyses will be described in the statistical analysis plan.

Primary Analysis

The percent reduction of incidence of nosocomial pneumonia caused by *P aeruginosa* through 21 days postdose will be the primary efficacy endpoint. For subjects with multiple *P aeruginosa* pneumonia events, only the first occurrence will be used in the primary analysis. Subjects with mixed cultured results, which include *P aeruginosa*, will be counted towards the primary endpoint.

The primary analysis of the primary endpoint will be evaluated using the mITT Population. *P aeruginosa* pneumonia that occurs prior to discontinuation will contribute to the primary efficacy analysis. If no *P aeruginosa* pneumonia occurs prior to discontinuation, the subject will be considered as having no *P aeruginosa* pneumonia infection in the primary efficacy analysis. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary efficacy analysis, to estimate the relative risk of *P aeruginosa* pneumonia through 21 days postdose between the Red t mg MEDI3902 and placebo groups, using the term of treatment group as a covariate. The relative risk reduction, defined as 1 – Relative Risk (RR), and its corresponding 2-sided 90% CI will be estimated from the model. In addition, the 2-sided p-value testing the null hypothesis that the incidence of having *P aeruginosa* pneumonia between the Red t mg MEDI3902 and placebo groups are the same will also be obtained from the model. The significance testing will be performed against a 2-sided alpha level of 0.2.

The Poisson regression with robust variance analysis will be implemented using the SAS PROC GENMOD procedure with the REPEATED statement for subject ID and logarithm link. The estimated parameter $\hat{\beta}$ [ie, log ($\widehat{RR}$)], 2-sided 80% confidence interval for $\hat{\beta}$, and the 2-sided p-value will be provided from the SAS outputs. The estimated relative risk ($\widehat{RR}$) and corresponding confidence interval for the relative risk is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of relative risk reduction is given by [(1 – exp ($\hat{\beta}$)) * 100%]. The confidence interval for the percent of relative risk reduction is given by ([1 – exp (upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp (lower confidence limit for $\hat{\beta}$) * 100%]).

Sample Size/Power Calculation

Approximately 286 colonised subjects will be enrolled and randomised (1:1 ratio) to Red t mg MEDI3902 (or in the case of dose adjustment, Red t mg MEDI3902; n = 143) or placebo (n = 143).

Key assumptions used for sample size/power calculations: placebo group *P aeruginosa* pneumonia incidence 20%, relative reduction 50%, at least 80% power, 20% adjustment for attrition. Relative reduction of 50% was recommended to Sponsor as a clinically meaningful effect by experts in critical care, pulmonary medicine, and infectious diseases. In addition, 50% relative reduction was demonstrated in a study by Francois and colleagues (Francois et al, 2012) involving a monoclonal antibody to prevent *Pseudomonas* pneumonia in mechanically ventilated patients, supporting the biological feasibility of such an effect.

Power calculations are based on Poisson regression with robust variance comparing each MEDI3902 treatment group separately versus placebo, 2-sided, with $\alpha = 0.2$.

The sample size may be modified after approximately 50% of the subjects are enrolled and followed through 21 days postdose based on blinded assessment of the event rate and/or attrition rate in the overall population.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	Alkaline phosphatase
ALT	alanine transaminase
APACHE-II	Acute Physiology and Chronic Health Evaluation-II
AST	aspartate transaminase
AUC	area under concentration time curve
AUC_{∞}	area under the concentration-time curve from time zero to infinity
$AUC_{Day22\text{-}Day29}$	area under concentration time curve from day 22 to day 29
BAL	bronchoalveolar lavage
CCC	Clinical Coordinating Centre
C_{max}	mean observed maximum concentration
CPIS	Clinical Pulmonary Infection Score
CRP	C-reactive protein
DMC	data monitoring committee
EC_{90}	effective serum concentration associated with 90% survival
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-5L	EuroQol - 5 Dimensions - 5 Levels
FAAN	Food, Allergy and Anaphylaxis Network
FiO_2	fraction of inspired oxygen
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
HL	Hy's Law
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG1	immunoglobulin G1
IL	interleukin
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
LLOQ	lower limit of quantification

Abbreviation or Specialized Term	Definition
mAb	monoclonal antibody
mITT	modified intent-to-treat
MMP-9	matrix metalloproteinase 9
MPO	myeloperoxidase
NE	neutrophil elastase
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no observed adverse effect level
O_2	oxygen
OPK	opsonophagocytic killing
P aeruginosa	*Pseudomonas aeruginosa*
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetics
PSB	protected-specimen brush
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SID	subject identification
SOFA	Sequential Organ Failure Assessment
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNFα	tumour necrosis factor alpha
ULN	upper limit of normal
VAP	ventilator-associated pneumonia
Vd_{ss}	volume of distribution at steady state
WBC	white blood cell
w/v	weight/volume

1 INTRODUCTION

1.1 Disease Background

Pseudomonas aeruginosa (*P aeruginosa*) is an important nosocomial pathogen, and pneumonia is one of its most important manifestations. Mechanical ventilation is the most important risk factor for nosocomial pneumonia caused by *P aeruginosa*, with cumulative risk increasing with the duration of ventilation (Zahar et al, 2009). In one study, *P aeruginosa* accounted for 13% of cases of microbiologically confirmed pneumonia acquired in the intensive care unit (ICU) by patients who were not mechanically ventilated, and 24% of cases in those who were (Esperatti et al, 2010). In a review of global epidemiology data, *P aeruginosa* caused approximately 27% of ventilator-associated pneumonia (VAP; Jones, 2010). Respiratory tract colonisation with *P aeruginosa* is another important risk factor (Rehm and Kollef, 2014). Despite the existence of antipseudomonal antibiotics, pneumonia, particularly VAP, due to *P aeruginosa* remains associated with significant mortality and morbidity, increased ICU and hospital length of stay, and substantial economic burden. Although general strategies exist to decrease the incidence of pneumonia in mechanically ventilated patients, there are no systemic agents approved for the prevention of pneumonia caused by *P aeruginosa.*

1.2 MEDI3902 Background

MEDI3902 is briefly described below. Refer to the current Investigator's Brochure for details.

P aeruginosa possesses a number of virulence factors that play a role in the severity of disease, and MEDI3902 was developed to target two of these factors. Redacted

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1.4 Summary of Clinical Experience

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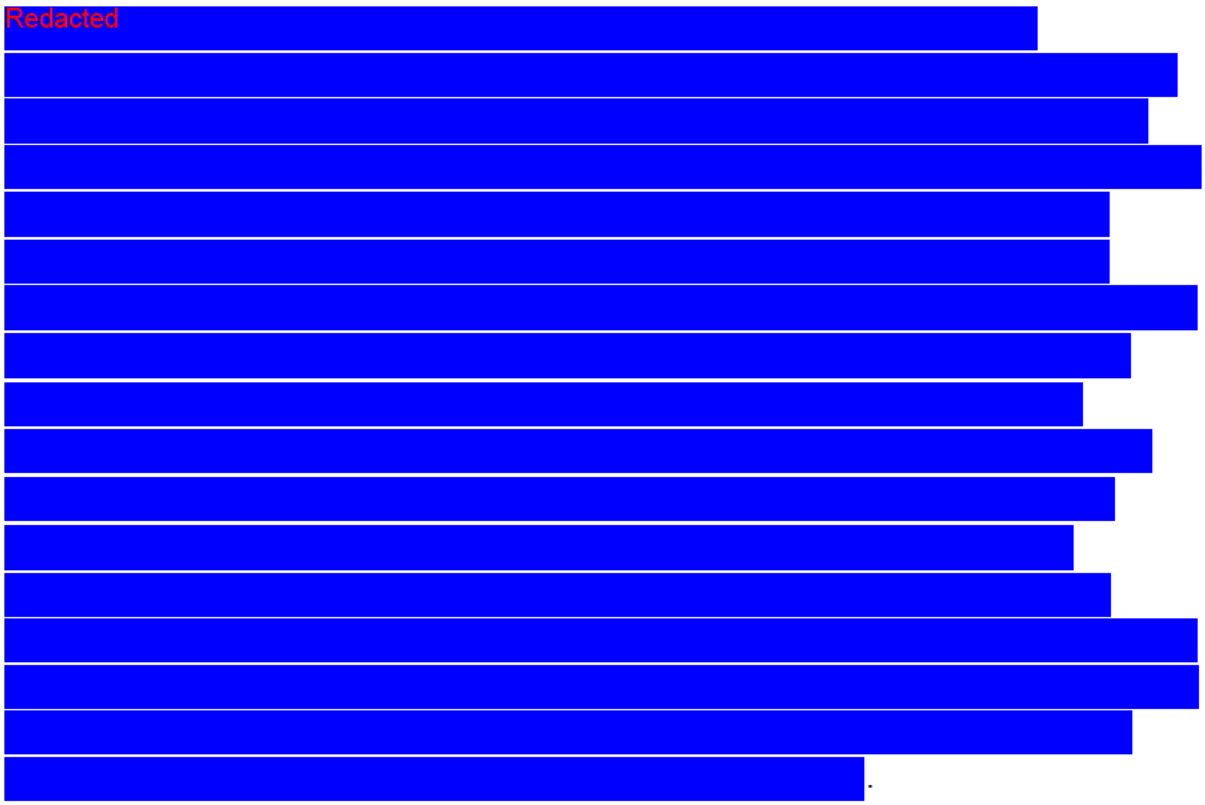

1.5 Rationale for Conducting the Study

Patients in the ICU are at risk for developing serious pneumonia infection and mechanical ventilation increases the risk for pneumonia in the ICU. *P aeruginosa* is a common cause of ICU pneumonia and multidrug resistance has complicated the management of *P aeruginosa* infection. Even when not antibiotic resistant, *P aeruginosa* is an important nosocomial pathogen associated with high morbidity and mortality (Kollef et al, 2014). With limited antimicrobial therapeutic options, consideration of new approaches, such as immunoprophylaxis for the prevention of *P aeruginosa* would address an important unmet need.

The efficacy of MEDI3902 for the prevention of lethal *P aeruginosa* pneumonia was demonstrated in animal models. Prophylactic use of MEDI3902 is anticipated to prevent *P aeruginosa*-related disease in at-risk patients in the ICU. It is being developed for the prevention of nosocomial pneumonia in high-risk patients who are likely to be mechanically ventilated with the expectation that they will require ventilation for ≥ 72 hours and who also have lower respiratory tract colonisation with *P aeruginosa*.

MEDI3902 was found to be generally safe in the initial Phase 1 study. Because there is no correlate of protection for *P aeruginosa* disease, the next development step is to evaluate if

the PK and PD profile translate into clinical efficacy and evaluate the safety profile in the target population.

The current study is designed to determine the efficacy, safety, and PK responses to MEDI3902 in adult subjects admitted to the ICU who require mechanical ventilation and who are also colonised with *P aeruginosa* in the lower respiratory tract. Results will also form the basis for subsequent studies in adult populations at high risk for *P aeruginosa* disease.

1.6 Research Hypotheses

Prophylactic use of MEDI3902 in mechanically ventilated subjects in the ICU who are colonised with *P aeruginosa* in the lower respiratory tract will reduce the incidence of nosocomial pneumonia caused by *P aeruginosa* through 21 days postdose irrespective of mechanical ventilation status at time of diagnosis.

A single IV dose of MEDI3902 administered to mechanically ventilated subjects in the ICU will have an acceptable safety profile.

2 OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

1. To evaluate the effect of MEDI3902 in reducing the incidence of nosocomial pneumonia caused by *P aeruginosa*
2. To evaluate the safety of a single IV dose of MEDI3902 in mechanically ventilated patients

2.1.2 Secondary Objectives

1. To evaluate the serum PK of MEDI3902
2. To evaluate the serum ADA responses to MEDI3902

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2.2 Study Endpoints

2.2.1 Primary Endpoint

Efficacy of MEDI3902:

1. Incidence of nosocomial pneumonia caused by *P aeruginosa* through 21 days postdose

Safety of MEDI3902:

1. Treatment-emergent AEs (TEAEs), treatment-emergent SAEs (TESAEs) and AESIs through 49 days postdose

2.2.2 Secondary Endpoints

1. MEDI3902 serum concentration and PK parameters through 49 days postdose
2. MEDI3902 ADA response in serum through 49 days postdose

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3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a Phase 2, randomised, double-blind, placebo-controlled, single-dose, dose-ranging, proof-of-concept study evaluating 2 dosage levels of MEDI3902 in mechanically ventilated patients in the ICU who are at high risk for *P aeruginosa* infections and who are currently free of *P aeruginosa*-related disease but are colonised with *P aeruginosa* in the lower respiratory tract. At study start, approximately 429 subjects were to be enrolled and dosed at approximately 120 sites primarily in Europe. Subjects were to be randomly assigned in a 1:1:1 ratio to receive a single IV dose of Redacted mg MEDI3902, Redacted mg MEDI3902, or placebo.

However, based on data from a separate study in a similar population with another monoclonal antibody, data from a PK study in mice (see Section 3.2.1) and from simulation results using data from the Phase 1 study (Study D5470C00002), a single dose of 500 mg MEDI3902 is not expected to maintain the target level of Redacted µg/mL for 21 days. Therefore, enrolment in the Redacted mg MEDI3902 group will be discontinued. Approximately 286 subjects will be randomised in a 1:1 ratio to one of 2 treatment groups, Redacted mg MEDI3902 or placebo (N = 143 for each treatment group).

A PK interim analysis will be performed after at least 10 subjects in each of the Redacted mg MEDI3902 and placebo groups are followed through 21 days postdose. The interim PK analysis will allow the determination of serum PK profile of MEDI3902 in mechanically ventilated subjects. Enrolment will continue in both the Redacted mg MEDI3902 and placebo groups while the PK interim analysis is conducted. If the mean serum concentration of MEDI3902 on Day 22 in the Redacted mg MEDI3902 dose group is lower than the target concentration of Redacted µg/mL, a dose adjustment to Redacted mg MEDI3902 will be considered. An independent DMC will be responsible for recommending dose adjustment.

In case of a dose adjustment from Redacted mg to Redacted mg MEDI3902, approximately 143 subjects will be randomised to receive the Redacted mg MEDI3902 dose to maintain 1:1 ratio with the placebo group. Subjects who have been enrolled and randomised in the Redacted mg and Redacted mg MEDI3902 groups will be followed until the end of the study period (Day 50).

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Redacted Subjects will be followed through Day 50 (49 days post investigational product administration Figure 3.1.1-1).

The study is being conducted through the Innovative Medicines Initiative Joint Undertaking (IMI JU, 2012), which is a pan-European public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. The Sponsor will execute this study in conjunction with Combatting Bacterial Resistance in Europe - Molecules against Gram Negative Infections (COMBACTE-MAGNET), which is a consortium of partners from the pharmaceutical industry and academia in the field of antibiotic-resistant bacteria, hospital-acquired pneumonia and ventilator-associated pneumonia.

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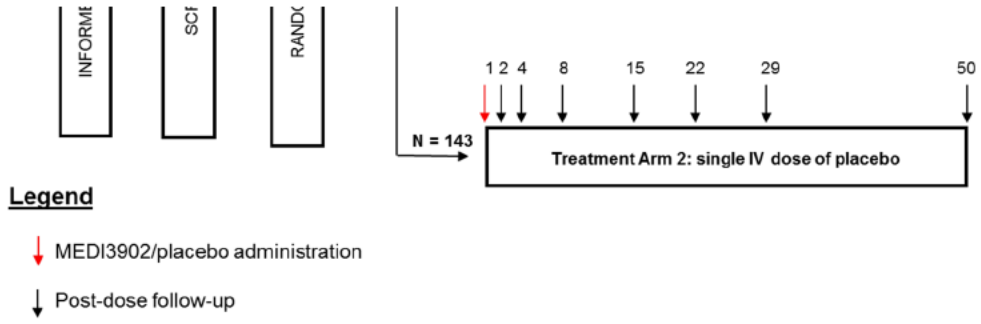


Figure 3.1.1-1 Study Flow Diagram

ADA = anti-drug antibody; IV = intravenous; N = number of subjects; PK = pharmacokinetics

a In case of a dose adjustment from Red mg to Red mg MEDI3902, approximately 143 subjects will be randomised to receive the 3000 mg MEDI3902 dose to maintain 1:1 ratio with the placebo group. Subjects who have been enrolled in the Red mg and Red mg MEDI3902 groups will be followed until the end of the study period (Day 50).

Note: This study flow diagram was revised based on the change in the study design and illustrates how approximately 286 subjects will be randomised in a 1:1 ratio to one of the two treatment groups: Red mg MEDI3902 (or Red mg in case of dose adjustment; N = 143) or placebo (N = 143). Efficacy will be assessed through 21 days postdose (Day 22); safety, PK and ADA will be assessed through 49 days postdose (Day 50). The sample size may be modified after approximately 50% of the subjects are enrolled and followed through 21 days postdose based on blinded assessment of the event rate and/or attrition rate in the overall population.

The endpoints to be measured in this study are described in Section 2.2.

3.1.2 Treatment Regimen

At study start, subjects were to be randomly assigned to receive a single dose of [redacted] mg MEDI3902, [redacted] mg MEDI3902, or placebo administered via IV infusion on Day 1. However, based on emerging data (see Section 3.1.1), subsequent to Amendment 2, subjects will be enrolled and randomly assigned (1:1 ratio) to receive a single IV infusion of [redacted] mg MEDI3902 (or in the case of dose adjustment, [redacted] mg MEDI3902) or placebo.

3.1.3 Management of Study Medication Related Toxicities

All subjects will be premedicated with antihistamine, for example, [redacted] mg diphenhydramine IV, clemastine [redacted] mg IV, or dexchlorpheniramine [redacted] mg IV (or another antihistamine preparation utilised in routine clinical practice for management of acute allergic reactions) within 15 to 30 minutes prior to start of IP administration. The data monitoring committee (DMC) will monitor the rate and severity of infusion or allergic reactions observed during the study. The DMC may authorise additional premedication of subjects with acetaminophen [redacted] mg orally and/or methylprednisolone [redacted] mg IV in combination with the antihistamine, or the antihistamine together with famotidine [redacted] mg orally with or without acetaminophen and/or methylprednisolone prior to start of investigational product infusion.

In the event of any infusion related reactions observed, the following options should be considered:

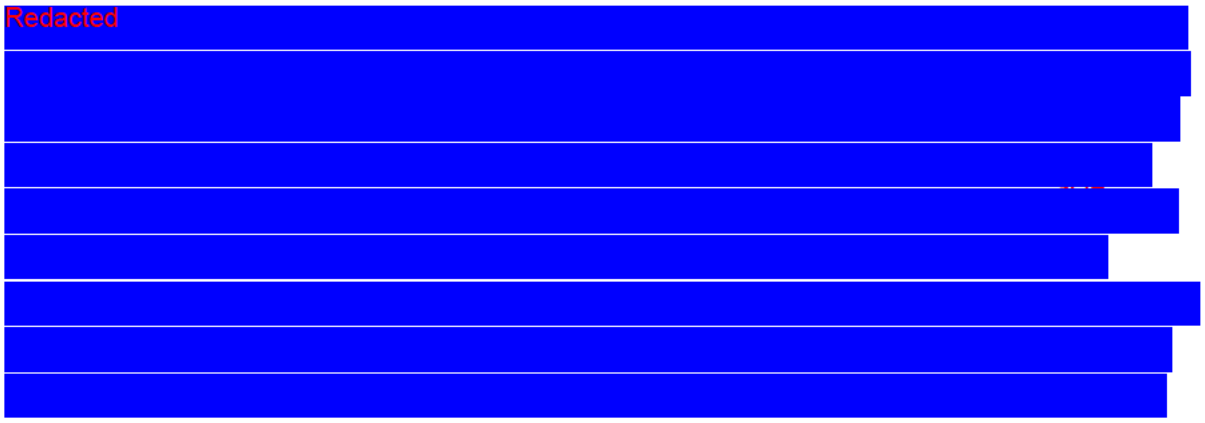
1. Administer antihistamine, for example, diphenhydramine [redacted] mg IV, clemastine [redacted] mg IV, or dexchlorpheniramine [redacted] mg IV, or another antihistamine preparation utilised in routine clinical practice for management of acute allergic reactions.
2. Administer methylprednisolone [redacted] mg IV
3. Stop the infusion, and reassess the signs and symptoms as well as the overall condition of the patient in about 30 to 60 minutes
    a. If the signs and symptoms abate, consider restarting the study drug at an infusion rate, approximately half of the baseline infusion rate
    b. If the signs and symptoms of infusion related reaction do not show resolution, or there is worsening of the symptoms or in subject's general condition, permanently discontinue the study drug, and consider additional symptomatic treatment, including but not limited to antihistamines, epinephrine, and or systemic corticosteroids

3.2 Study Design and Dose Rationale

3.2.1 Dose Rationale

The dosage levels to be evaluated in the Phase 2 study are based on data from the Phase 1 study (Study D5470C00002), PK/PD data from preclinical pharmacology studies, and a clinical report of median (range) time to VAP onset of 10 (3-16) days (Francois et al, 2012). Interim PK data analysis from the Phase 1 study showed that MEDI3902 exhibits linear PK. The target exposure level in the clinic was set at Redac µg/mL based on the effective serum concentration associated with 90% survival (EC_{90}) determined in a murine *P aeruginosa* pneumonia model (MedImmune Research Report ID3902-0011). Population PK simulation suggested that a single dose of Redacte mg MEDI3902 in humans was expected to maintain serum concentration above a target level of Reec µg/mL for 21 days in a majority of subjects (> 95%). Based on these data and PK simulation, a dose of Redacte mg was selected as the likely efficacious dose in Phase 2 subjects.

The serum exposure level of Redac µg/mL was calculated for the MEDI3902 progenitor mAb BiS4 against a highly pathogenic clinical isolate (5-fold the LD_{100}) of *P. aeruginosa* in a murine model. The results of the study identified the ED_{90} for mAb BiS4 to be Re.0 mg/kg (see the Investigator's Brochure for details of the study). Given that mAb BiS4 and MEDI3902 exhibited similar in vivo activity, Re.0 mg/kg was used as the ED_{90} for MEDI3902 against the same clinical isolate. However, a more recent study conducted to assess the protective activity of MEDI3902 against the same clinical isolate (1-fold the LD_{100}) demonstrated that the prophylactic delivery of MEDI3902 at Redacted mg/kg prevented lethality in the acute pneumonia model (see the Investigator's Brochure for details of the study). Since the Reda mg/kg dosage yielded >90% survival, a single-dose PK study of MEDI3902 at Redac mg/kg in normal healthy mice was conducted. Following the IP administration, a peak concentration of Reda µg/mL of MEDI3902 was observed at 8 hours post dose and the concentration decreased in a biexponential manner.



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3.2.2 Rationale for Study Population

The study population was selected to enrich for risk of nosocomial pneumonia caused by *P aeruginosa*. Both mechanical ventilation and colonisation are important risk factors for the development of nosocomial pneumonia caused by *P aeruginosa*. Additional enrichment factors may be applied based on epidemiologic data that are currently pending. Children are excluded until benefit has been observed in the adult population.

3.2.3 Rationale for Endpoints

The primary efficacy endpoint for this study is the incidence of nosocomial pneumonia caused by *P aeruginosa* through 21 days postdose (Day 22) after a single dose of MEDI3902 in mechanically ventilated subjects at risk for *P aeruginosa* nosocomial pneumonia. Twenty-one days was selected based on EC_{90} in the murine *P aeruginosa*-induced lethal pneumonia model. While it is anticipated that a number of mechanically ventilated subjects will continue to require mechanical ventilation throughout the 21-day postdose period, a substantial proportion of subjects may be weaned off the ventilator during this period. Since these subjects may develop nosocomial pneumonia caused by *P aeruginosa* after they no longer require mechanical ventilation, primary efficacy will be evaluated in subjects who were on mechanical ventilation at the time of enrolment, regardless of whether they remain on or are weaned off mechanical ventilation during the 21-day postdose period.

The primary safety endpoints will assess TEAEs, TESAEs and AESIs through 49 days postdose.

The secondary endpoints (MEDI3902 serum concentration, PK parameters, and ADA response to MEDI3902 through 49 days postdose) are designed to assess the presence of MEDI3902 in vivo.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 286 subjects will be enrolled and randomised (1:1 ratio) to receive Redacted mg MEDI3902 (N = 143) or placebo (N = 143). In case of a dose adjustment from Redacted mg to

[redacted] mg MEDI3902, approximately 143 subjects will be randomised to receive the [redacted] mg MEDI3902 dose to maintain 1:1 ratio with the placebo group. Subjects who have been enrolled in the [redacted] mg and [redacted] mg MEDI3902 groups will be followed until the end of the study period (Day 50).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male or female 18 years of age or older at the time of study entry
2. Written informed consent and any locally required authorisation obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations
3. Females of childbearing potential who are sexually active with a nonsterilised male partner must have evidence of not being pregnant upon enrolment and have a negative pregnancy test prior to administration of investigational product
    a. Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral oophorectomy, or complete hysterectomy) or those who are not premenarchal or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
4. Currently intubated and on mechanical ventilation in the ICU
5. Tracheal sample collected and positive by polymerase chain reaction (PCR) for *P aeruginosa* within 36 hours prior to randomisation
6. Expected to remain intubated and mechanically ventilated for ≥ 72 hours based on investigator estimate
7. No diagnosis of new-onset pneumonia within 72 hours prior to randomisation (subjects with evidence of resolved pneumonia will be eligible)
8. Expected to survive for > 2 weeks based on investigator judgment
9. Expected to participate in the study through 49 days postdose

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Acute confirmed or suspected pseudomonal disease at study enrolment and investigational product dosing (endotracheal colonisation is acceptable and required [see inclusion criterion 5])
2. CPIS of ≥ 6 based on contributing parameters measured within past 24 hours, prior to investigational product dosing (Appendix 4).
3. Active pulmonary disease that would impair the ability to diagnose pneumonia, such as active tuberculosis or fungal disease, obstructing lung cancer, large pleural effusion or empyema, cystic fibrosis, or acute respiratory distress syndrome with lung "white out"
4. Subjects who are tracheostomy-dependent prior to current hospital admission
5. Receipt of anti-*P aeruginosa* antibiotics (as listed below) for > 72 hours within 96 hours prior to randomisation or anticipated ongoing receipt of the anti-*P aeruginosa* antibiotics:
   - Systemic colistin
   - Aerosolized colistin
6. Burns > 40% body surface area
7. Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score ≥ 25 or SOFA score ≥ 12 at time of randomisation (Appendix 5 and Appendix 6). Vasopressors only used to improve cerebral perfusion pressure (eg, subarachnoid hemorrhage) should not be used in the calculation of the cardiovascular component of the SOFA score.
8. Receipt of any investigational drug therapy within 30 days prior to investigational product dosing
9. Previous receipt of a mAb
10. Subjects with human immunodeficiency virus (HIV) infection, who in the opinion of the investigator, do not have well-controlled HIV infection. Subjects with a history of HIV infection who have been on highly active antiretroviral therapy and asymptomatic from HIV infection for at least 6 months may be enrolled.
11. Lymphoma not in complete remission and on chemotherapy
12. Recipients of bone marrow, stem cell, or solid organ transplant who are not currently in complete remission
13. Receipt of chemotherapy or other immunosuppressive drugs including glucocorticoid therapy (prednisone 20 mg or equivalent, daily or every other day for 30 days) in the past 2 months
14. History of known hypersensitivity to any component of the investigational product
15. Pregnant or nursing female

4.1.4 Subject Enrolment and Randomisation

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained from the potential subject or their guardian/legal representative before any

study-specific procedures are performed. Those subjects who are unconscious or considered by the investigator clinically unable to consent at screening and who are entered into the study by the consent of a legally acceptable representative should provide their own written informed consent for continuing to participate in the study as soon as possible on recovery, as applicable, in accordance with local regulations (see Section 7.4 for description of informed consent process).

Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, interactive web response system [IWRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A Clinical Coordinating Centre (CCC) will be available to the study sites 24 hours/day, 365 days/year to evaluate subjects for study eligibility. The CCC will review the inclusion and exclusion criteria to determine if a subject meets the requirements for randomisation. Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomised or receive investigational product. See Section 4.6.1 for information on randomisation and assignment of treatment group.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomised), including the reason(s) for screening failure.

Subjects who have failed screening may be rescreened and will receive a new SID number. Subjects who are considered for rescreening beyond 7 days from the initial informed consent should be reconsented prior to being rescreened.

4.1.5 Withdrawal from the Study

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. AEs will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

All randomised subjects will receive a single dose of investigational product. An individual subject will not receive investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent
2. An AE that, in the opinion of the investigator or the sponsor, contraindicates dosing
3. Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation
4. A severe or potentially life-threatening serious systemic, allergic, or local reaction with onset after dosing has been initiated. If such a reaction is observed during investigational product infusion, the infusion would be immediately stopped, no further investigational product will be administered and the medical monitor must be contacted immediately.

Subjects who have not received investigational product, regardless of reason, will not be followed and collection of AEs will not be performed. Unless consent for follow-up is withdrawn, subjects discontinued after receiving a partial dose of investigational product will be followed for the full study period (through 49 days postdose) with all laboratory and clinical evaluations collected as defined in the protocol.

4.1.7 Replacement of Subjects

Once a subject has been randomised, the subject will not be replaced, including cases where subjects are randomised but not dosed or are randomised but do not complete any study evaluation.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor unless the subject specifically requests that the samples are destroyed.

Samples Obtained for Future Research

Samples obtained for future research will be labeled with a sample identification number linked to the SID number but will not be labeled with personal identifiers such as the

subject's name. If the subject withdraws consent for participating in the future research, the sponsor will locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 15 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

4.2 Schedule of Study Procedures

4.2.1 Enrolment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening visit. Assessments should be performed in the order shown in the table.

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	**Screening**
Visit Number	**V1**
Procedure / Study Day	**Up to 7 days prior to randomisation[a]**
Eligibility	
Written informed consent [b]	X
Assignment of SID number	X
Medical history, comorbidities, and risk factors	X
Physical examination	X
Weight, height	X

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	Screening
Visit Number	**V1**
Procedure / Study Day	**Up to 7 days prior to randomisation[a]**
Serum βhCG	X [c]
Verify eligibility criteria	**X**
Safety Assessments	
Vital signs	X
Serum chemistry	X [d]
Hematology	X [d]
Assessment of AEs/SAEs	X
Concomitant medications	X
Disease Assessments	
Evaluate for clinical symptoms/signs of pneumonia/serious *P aeruginosa* infection (eg, physical exam, vital signs, CPIS assessment, SOFA, APACHE-II, GCS, PaO_2/FiO_2 ratio, as clinically indicated)	X
Tracheal aspirate for *P aeruginosa* colonisation by PCR	X [e]
Chest x-ray	X
Tracheal aspirate for Gram stain and culture	X [f]

AE = adverse event; APACHE II = Acute Physiology and Chronic Health Evaluation II; βhCG = beta human chorionic gonadotropin; CPIS = Clinical Pulmonary Infection Score; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; PaO_2 = partial pressure of oxygen; PCR = polymerase chain reaction; *P aeruginosa* = *Pseudomonas aeruginosa*; SAE = serious adverse event; SID = subject identification; SOFA = Sequential Organ Failure Assessment; V = Visit.

a Rescreening of the same eligible subject is permitted if the subject was eligible but randomisation did not occur within 7 days of screening.

b Subjects enrolled in the study with consent obtained from a legally acceptable representative will provide their own informed consent as soon as they are capable during the active course of study participation.

c Female subjects of childbearing potential only; must be negative prior to randomisation.

d All screening laboratory tests will be performed within 7 days prior to randomisation. Abnormal results may be repeated at the investigator's discretion, preferably within 24-48 hours.

e Tracheal sample collected and positive by PCR for *P aeruginosa* within 36 hours prior to randomisation.

f Tracheal aspirate Gram stain and culture should be assessed on the sample obtained for determination of colonisation by PCR.

4.2.2 Randomised Treatment Period and Follow-up

Table 4.2.2-1 shows all procedures to be conducted during the treatment and follow-up periods for subjects who are not suspected of having a *P aeruginosa* infection. Table 4.2.2-2 shows procedures to be conducted for subjects who are suspected or confirmed of having a *P aeruginosa* infection.

Assessments should be performed in the order shown in the table. Whenever vital signs and blood draws are scheduled for the same nominal time, vital signs should be assessed first. The timing of the first two assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

Table 4.2.2-1 Schedule of Investigational Product Administration and Follow-up Study Procedures

Study Period	Investigational Product Dosing			Follow-up						
Visit Number	**V2**			**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Procedure / Study Day	**Day 1**			**Day 2**	**Day 4**	**Day 8 (± 2 days)**	**Day 15 (± 2 days)**	**Day 22 (± 2 days)**	**Day 29 (± 3 days)**	**Day 50 (± 4 days)**
	Predose[a]	**Dose**	**Postdose**							
Eligibility										
Medical history, comorbidities, and risk factors	X [b]									
Physical examination	X [b]									
Serum βhCG [c]	X									X
Verify eligibility criteria [d]	X									
Randomisation	X									
Premedication [e]		X								
Investigational Product Administration		X								
Efficacy Assessments										
Monitor for clinical symptoms/signs of pneumonia/ serious *P aeruginosa* infection (eg, physical exam, vital signs, oxygen status [f], CPIS , SOFA, as indicated)	X	X	X	Daily while in hospital [g]; in accordance with symptoms after hospital discharge For subjects with suspected or confirmed pneumonia, tracheobronchitis or bacteremia, see Table 4.2.2-2						
Microbiology										
Blood for culture	X									
Tracheal aspirate for Gram stain				X [h]	X [h]					
Tracheal aspirate for culture (intubated subjects only)				X [h]	X [h]					
Chest X-ray	X									

Table 4.2.2-1 Schedule of Investigational Product Administration and Follow-up Study Procedures

Study Period	Investigational Product Dosing			Follow-up						
Visit Number	V2			V3	V4	V5	V6	V7	V8	V9
Procedure / Study Day	Day 1			Day 2	Day 4	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 29 (± 3 days)	Day 50 (± 4 days)
	Predose[a]	Dose	Postdose							
Safety Assessments										
Vital signs [i]	X	X	X	X						
Serum chemistry	X [b]					X		X		
Hematology	X [b]					X		X		
AEs, SAEs, AESIs	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
PK/ADA/Other										
Serum PK	X [j]		X [j]	X [j]	X	X	X	X	X	X
Redacted	Re									
Serum ADA	X						X		X	X
Redacted										

Table 4.2.2-1 Schedule of Investigational Product Administration and Follow-up Study Procedures

Study Period	Investigational Product Dosing			Follow-up						
Visit Number	V2			V3	V4	V5	V6	V7	V8	V9
Procedure / Study Day	Day 1			Day 2	Day 4	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 29 (± 3 days)	Day 50 (± 4 days)
	Predose[a]	Dose	Postdose							
Redacted										

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; βhCG = beta human chorionic gonadotropin; CBC = complete blood count; CPIS = Clinical Pulmonary Infection Score; CRP = C-reactive protein; EQ-5D-5L = EuroQol - 5 Dimensions - 5 Levels; FiO_2 = fraction of inspired oxygen; Redacted; ICU = intensive care unit; IV = intravenous; O_2 = oxygen; PaO_2 = partial pressure of oxygen; PCR = polymerase chain reaction; PK = pharmacokinetics; *P aeruginosa* = *Pseudomonas aeruginosa*; SAE = serious adverse event; SOFA = Sequential Organ Failure Assessment.; WBC = white blood cell.

NOTE: Day 1 or Day 2 assessments scheduled to be performed postdose may not occur on the exact calendar day as specified in the assessment table, depending on the time of the start and completion of the infusion.

a Assessments conducted as part of screening within 24 hours prior to randomisation do not need to be repeated.

b Update screening medical history and physical examination (any new findings since screening); investigator to confirm and review baseline serum chemistry and hematology results

c Female subjects of childbearing potential who are sexually active with a nonsterilised male partner. Day 50 assessment is only performed for women who are no longer in the ICU.

d Contact Clinical Coordinating Centre to confirm the subject meets the requirements for randomisation.

e All subjects will be premedicated with antihistamine, for example, R mg diphenhydramine IV, clemastine R mg IV, or dexchlorpheniramine R mg IV (or another antihistamine preparation utilised in routine clinical practice for management of acute allergic reactions) within 15-30 minutes prior to start of IP infusion.

f Examples of oxygen status parameters are as follows: highest minute ventilation (L/min), highest FiO_2 (%), lowest PaO_2 results (for mechanically ventilated subjects); liters of oxygen (L/min), lowest O_2 saturation (%), FiO_2 (%; for nonmechanically ventilated subjects).

g For both the CPIS assessment and SOFA, the last available chest X-ray, serum chemistry, and/or CBC values obtained within 72 hours may be used in determining the score.

Table 4.2.2-1 Schedule of Investigational Product Administration and Follow-up Study Procedures

Study Period	Investigational Product Dosing			Follow-up						
Visit Number	V2			V3	V4	V5	V6	V7	V8	V9
Procedure / Study Day	Day 1			Day 2	Day 4	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 29 (± 3 days)	Day 50 (± 4 days)
	Predose[a]	Dose	Postdose							
R [redacted]										

i Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be obtained at screening, on the day of dosing prior to the start of infusion (2 recordings of blood pressure and pulse rate, 5 minutes apart), every 30 (± 5) minutes during investigational product infusion, at completion of infusion (± 5 minutes), every 30 (± 5) minutes after completion of infusion for 2 hours, and 24 hours (± 30 minutes) after completion of infusion.

j Blood samples for PK measurement will be collected immediately prior to investigational product dosing, at the end of infusion, 8 hours after the end of infusion, and at 24 hours after the end of infusion.

R [redacted]

l To be conducted if subject is extubated and able to complete the form. For subjects who remain intubated on Day 15, initial assessment to be conducted within 48 hours of extubation

Table 4.2.2-2 Schedule of Procedures for Subjects With Suspected or Confirmed Pneumonia, Tracheobronchitis or Bacteremia

Assessment [a]	Duration of Infection				
	Day 1 (Onset)	Day 2	Day 3	Day 4	Day 5 Through Resolution
Clinical Symptoms					
CPIS, SOFA, physical exam, vital signs	X	Daily through clinical resolution [b,c]			
Microbiology [d]					
Blood sample (culture) [e]					
All subjects	X	X	X		
Subjects positive for *P aeruginosa* bacteremia				Repeat every other day until blood culture negative for *P aeruginosa*	
Tracheal/bronchial aspirate [e]; intubated subjects only (Gram stain and culture)					
All subjects	X	X	X		
Subjects positive for *P aeruginosa* pneumonia or tracheobronchitis				As clinically indicated through clinical resolution [c]	
Expectorated sputum [e] (unless bronchoscopy performed for clinical management and BAL or PSB sample available); nonintubated subjects only (includes follow-up assessments through clinical resolution in subjects who were initially intubated at the onset of suspected infection, but were subsequently extubated prior to clinical resolution) (Gram stain and culture)					
All subjects	X	X	X		
Subjects positive for *P aeruginosa* pneumonia or tracheobronchitis				As clinically indicated through clinical resolution [c]	
Chest X-ray					
Subjects with suspected pneumonia or tracheobronchitis	X				
Subjects with confirmed pneumonia		As clinically indicated through clinical resolution [c]			
PK/ADA/Other					
Serum PK	X				
Redacted					
Serum ADA	X				

Table 4.2.2-2 Schedule of Procedures for Subjects With Suspected or Confirmed Pneumonia, Tracheobronchitis or Bacteremia

Assessment [a]	Duration of Infection				
	Day 1 (Onset)	Day 2	Day 3	Day 4	Day 5 Through Resolution
Blood for markers of inflammation (WBC with differential)					
All subjects	X				
Subjects positive for *P aeruginosa* pneumonia or bacteremia				X	X (Day of clinical resolution [c])
Serum for markers of inflammation (CRP and procalcitonin)					
All subjects	X				
Subjects positive for *P aeruginosa* pneumonia or bacteremia				X	X (Day of clinical resolution [c])
Redacted					
Redacted					
Redacted					
Redacted					
Redacted					
Redacted					
Redacted					
Redacted					
Redacted					
Redacted					
All subjects	X				

Table 4.2.2-2 Schedule of Procedures for Subjects With Suspected or Confirmed Pneumonia, Tracheobronchitis or Bacteremia

Assessment [a]	Duration of Infection				
	Day 1 (Onset)	Day 2	Day 3	Day 4	Day 5 Through Resolution
[redacted]					Redact
[redacted]					
[redacted]	[redacted]				
[redacted]				[redacted]	

ADA = anti-drug antibody; BAL = bronchoalveolar lavage; CBC = complete blood count; CPIS = Clinical Pulmonary Infection Score; CRP = C-reactive protein; [redacted] PCR = polymerase chain reaction; *P aeruginosa* = *Pseudomonas aeruginosa*; PK = pharmacokinetics; PSB = protected-specimen brush; SOFA = Sequential Organ Failure Assessment; WBC = white blood cell.

a Assessments conducted as part of a scheduled visit in Table 4.2.2-1 are not to be repeated. For subjects with onset of a suspected pneumonia or bacteremia or tracheobronchitis from Days 2 through 29, assessments will be collected at onset and through resolution of disease (even if resolution extends beyond Day 29).

b For both the CPIS assessment and SOFA, the last available chest X-ray, serum chemistry, and/or CBC values obtained within 72 hours may be used in determining the score.

c Clinical resolution is defined as all signs and symptoms of acute infection have subsided and the therapeutic antibiotic course has been completed.

d If pleural fluid aspirate or lung tissue is obtained as part of the subject's necessary clinical management, the sample should also be sent for Gram stain and culture.

e First blood sample and/or respiratory specimen are/is to be collected before start of new antibiotic therapy.

f [redacted].

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Clinical Signs and Symptoms

Subjects will be monitored for clinical signs and symptoms of pneumonia and other serious bacterial infections according to the assessments presented in Table 4.2.1-1 and Table 4.2.2-1 at screening, prior to administration of investigational product on Day 1, and from administration of investigational product through Day 29. For subjects with suspected or confirmed pneumonia, tracheobronchitis or bacteremia, clinical symptoms will continue to be monitored through clinical resolution (see Table 4.2.2-2). The CPIS assessment, APACHE-II, and SOFA are provided in Appendix 4, Appendix 5, and Appendix 6, respectively. Additionally, a conversion table for estimating partial pressure of oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) is provided in Appendix 7.

4.3.1.2 Microbiology

The schedule of follow-up procedures is shown in Table 4.2.2-1. Additional procedures for subjects who have suspected or confirmed pneumonia, tracheobronchitis or bacteremia are shown in Table 4.2.2-2 and are described below.

All subjects with onset of suspected or confirmed pneumonia, tracheobronchitis or bacteremia through Day 29 (irrespective of anatomical location) of the follow-up period, will have blood and respiratory specimens collected at onset (Day 1) of the suspected or confirmed infection. The first set of blood and respiratory specimens will be collected on Day 1 of infection before the start of any new antibiotic therapy and will continue on Days 2 and 3 of infection. Blood samples will be sent for culture and respiratory samples will be sent for Gram stain and culture.

Only subjects who are positive for *P aeruginosa* bacteremia, *P aeruginosa* pneumonia or *P aeruginosa* tracheobronchitis will have additional samples taken for microbiological assessment after Day 3 of infection. For subjects who are positive for *P aeruginosa* bacteremia, blood samples will continue to be collected every other day beginning at Day 4 of infection until blood culture is negative for *P aeruginosa*. For subjects who are positive for *P aeruginosa* pneumonia or *P aeruginosa* tracheobronchitis, respiratory samples will continue to be collected as clinically indicated until clinical resolution.

For respiratory specimens, tracheal aspirate will be collected if the subject is intubated. If the subject is not intubated at onset of suspected or confirmed pneumonia, tracheobronchitis or

bacteremia or is extubated thereafter, expectorated sputum samples will be collected (unless bronchoscopy was performed for clinical management and a bronchoalveolar lavage [BAL] or protected-specimen brush [PSB] sample is available).

If pleural fluid aspirate or lung tissue is obtained as part of the subject's necessary clinical management, the sample should also be sent for Gram stain and culture.

Qualitative respiratory culture results will be recorded by all study sites. Quantitative and semi-quantitative respiratory culture results will be recorded by study sites when available.

4.3.1.3 Radiography

A chest X-ray to assess for pneumonia will be conducted according to the schedule in Table 4.2.1-1 and Table 4.2.2-1 and evaluated by a qualified radiologist. A chest X-ray will be conducted in subjects at onset of suspected pneumonia or tracheobronchitis and as indicated through clinical resolution if pneumonia is confirmed (see Table 4.2.2-2). Chest X-rays performed as part of routine medical care can be used when available.

4.3.1.4 Definition of *P aeruginosa* Pneumonia

<u>*P aeruginosa* Pneumonia Criteria for Subjects Who Are Mechanically Ventilated</u>

A mechanically ventilated subject is intubated with an endotracheal or nasotracheal tube and receiving positive pressure ventilation support, or is not intubated with an endotracheal or nasotracheal tube, but requires ≥ 8 hours of positive pressure ventilation (eg, subjects with tracheostomy, continuous positive airway pressure, etc) within the past 24 hours.

Subjects should demonstrate the following new onset of symptoms/signs deemed not due to any overt noninfectious causes. All 3 criteria (ie, radiographic, clinical, AND microbiologic) must be met in order to meet the *P aeruginosa* pneumonia endpoint.

1. **Radiographic criteria:**
   a. New or worsening infiltrate consistent with pneumonia on chest x-ray obtained within 24 hours of the event (diagnosed by a qualified radiologist)

AND

2. **Clinical criteria:** At least **2** of the following minor or **1** major respiratory sign or symptom of new onset:

Minor criteria:

   a. Systemic signs of infection (one or more of the following): Abnormal temperature (oral or tympanic temperature > 38°C or a core temperature ≥ 38.3°C or hypothermia, defined as a core body temperature of < 35°C), and/or abnormal WBC count (WBC count > 10,000 cells/mm^3, WBC count < 4,500 cells/mm^3, or > 15% band neutrophils)
   b. Production of new purulent endotracheal secretions
   c. New physical examination findings consistent with pneumonia/pulmonary consolidation such as auscultatory findings (eg, rales, rhonchi, bronchial breath sounds) or dullness to percussion

Major criteria:

   a. Acute changes made in the ventilatory support system to enhance oxygenation, as determined by:
      i. PaO_2/FiO_2 ratio < 240 mm Hg maintained for at least 4 hours OR
      ii. A decrease in PaO_2/FiO_2 by ≥ 50 mm Hg maintained for at least 4 hours

AND

3. **Microbiologic confirmation** (obtained within 24 hours of onset of the event)**:** At least **1** of the following:
   a. Respiratory specimen positive for *P aeruginosa* by culture includes a specimen of respiratory secretion obtained by endotracheal aspiration or by bronchoscopy with BAL or PSB sampling in intubated subjects. In subjects who are not intubated but meet the protocol definition of mechanical ventilation, a specimen of expectorated sputum would be acceptable.
   b. Blood culture positive for *P aeruginosa* (and no apparent primary source of infection outside the lung)
   c. Pleural fluid aspirate or lung tissue culture positive for *P aeruginosa* during episode of pneumonia (only if obtained as part of the subject's necessary clinical management)

P aeruginosa **Pneumonia Criteria for Subjects Who Are No Longer Mechanically Ventilated**

A subject is not considered to be mechanically ventilated when an endotracheal or nasotracheal tube is not in place and the subject does not require positive ventilation support for at least 8 hours.

Subjects should demonstrate the following new onset of symptoms/signs deemed not due to any overt non-infectious causes. All 3 criteria (ie, radiographic, clinical, AND microbiologic) must be met in order to meet the *P aeruginosa* pneumonia endpoint.

1. **Radiographic criteria:**
   a. New or worsening infiltrate consistent with pneumonia on chest x-ray obtained within 24 hours of the event (diagnosed by qualified radiologist)

AND

2. **Clinical criteria:** At least **2** of the following minor or **1** major respiratory sign or symptom of new onset:

Minor criteria:

a. Systemic signs of infection (one or more of the following): Abnormal temperature (oral or tympanic temperature > 38°C or a core temperature ≥ 38.3°C or hypothermia, defined as a core body temperature of < 35°C), and/or abnormal WBC count (WBC count > 10,000 cells/mm^3, WBC count < 4,500 cells/mm^3, or > 15% band neutrophils)
b. A new onset of cough (or worsening of cough)
c. Production of purulent sputum
d. New physical examination findings consistent with pneumonia/pulmonary consolidation such as auscultatory findings (eg, rales, rhonchi, bronchial breath sounds), dullness to percussion, or pleuritic chest pain
e. Dyspnea, tachypnea (respiratory rate > 30 breaths/minute), or hypoxemia defined as:
   i. Oxygen (O_2) saturation < 90% or PaO_2 < 60 mm Hg on room air if lower than baseline, OR
   ii. A need to initiate or increase sustained (≥ 3 hours) supplemental O_2 to maintain pre-event baseline O_2 saturations

Major criteria:

a. A need to initiate non-invasive mechanical ventilation or re-initiate invasive mechanical ventilation because of respiratory failure or worsening of respiratory status

AND

3. **Microbiologic confirmation** (obtained within 72 hours of onset of the event)**:** At least **1** of the following:
   a. Respiratory specimen positive for *P aeruginosa* by culture. Includes either expectorated sputum or (only if obtained as part of the subject's necessary clinical management) a specimen of respiratory secretions obtained by bronchoscopy with BAL or PSB sampling
   b. Blood culture positive for *P aeruginosa* (and no other apparent primary source of infection outside the lung)
   c. Pleural fluid aspirate or lung tissue culture positive for *P aeruginosa* (only if obtained as part of the subject's necessary clinical management)

During study execution, a blinded independent endpoint adjudication committee will review the data for adjudication of efficacy endpoints.

In addition to the primary endpoint, the Phase 2 study includes key secondary and exploratory endpoints, which will be used to guide Phase 3 development for MEDI3902.

4.3.1.5 Definition of *P aeruginosa* tracheobronchitis in mechanically ventilated Subject

A subject will be considered for a tracheobronchitis event if he/she is intubated with an endotracheal or nasotracheal tube; or, if the subject has a tracheostomy tube in place and requires ≥ 8 hours of positive pressure ventilation.

Subjects should demonstrate the following new onset of symptoms/signs deemed not due to any overt noninfectious causes. All 3 criteria (ie, radiographic, clinical, AND microbiologic) must be met in order to meet the *P aeruginosa* tracheobronchitis endpoint.

1. **Radiographic criteria:**
   a. No new infiltrate or change from baseline consistent with pneumonia on chest x-ray obtained within 24 hours of the event (diagnosed by a qualified radiologist)

AND

2. **Clinical criteria:**
   a. Production of new purulent endotracheal secretions
   AND
   b. Temperature (oral or tympanic temperature) > 38°C or a core temperature ≥ 38.3°C

AND

3. **Microbiologic confirmation** (obtained within 24 hours of onset of the event)**:**
   a. Respiratory specimen positive for *P aeruginosa* by culture. Includes a specimen of respiratory secretions obtained by endotracheal/tracheostomy aspiration or (if performed as part of routine clinical care) by bronchoscopy with BAL or PSB sampling in intubated subjects

Redacted

4.3.3 Medical History and Physical Examination, Weight, and Vital Signs

Medical History, Physical Examination, and Weight

Medical history, comorbidities, and risk factors will be collected at screening. A targeted physical examination, including height and weight, will be conducted at screening. Any new

findings since screening for medical history and physical examination will be updated on Day 1 prior to administration of investigational product.

Vital Signs

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be obtained as indicated in Table 4.2.1-1, Table 4.2.2-1 and Table 4.2.2-2.

4.3.4 Clinical Laboratory Tests

Clinical laboratory safety tests including serum pregnancy tests will be performed in an accredited clinical laboratory. Abnormal laboratory results may be repeated at the investigator's discretion (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Table 4.2.1-1, Table 4.2.2-1, Table 4.2.2-2 for the schedule of tests):

Serum Chemistry

• Calcium	• Alanine transaminase (ALT)
• Chloride	• Gamma-glutamyl transpeptidase
• Potassium	• Bilirubin total
• Sodium	• Creatinine
• Bicarbonate	• Blood urea nitrogen
• Aspartate transaminase (AST)	• Alkaline phosphatase (ALP)

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology

• WBC count with differential	• Hemoglobin
• Hematocrit	• Platelet count
• Red blood cell (RBC) count	

Pregnancy Test (females of childbearing potential only)

- Serum beta human chorionic gonadotropin βhCG (at screening only prior to randomisation [if > 24 hours after screening] and on Day 50)

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

4.3.6 Anti-drug Antibody Evaluation and Methods

Blood samples will be collected to evaluate ADA responses to MEDI3902 in serum according to the schedule in Table 4.2.2-1. For subjects with a suspected serious *P aeruginosa* infection, blood samples will be collected for ADA evaluation on the day of onset of illness (see Table 4.2.2-2).

Evaluations for ADA will be performed using a set of electrochemiluminescent, solution-phase, bridging immunoassays. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and positive-negative cutoff points will be employed that were statistically determined from drug-naive validation samples. Samples confirmed positive for ADA may be characterised for neutralising antibody activity.

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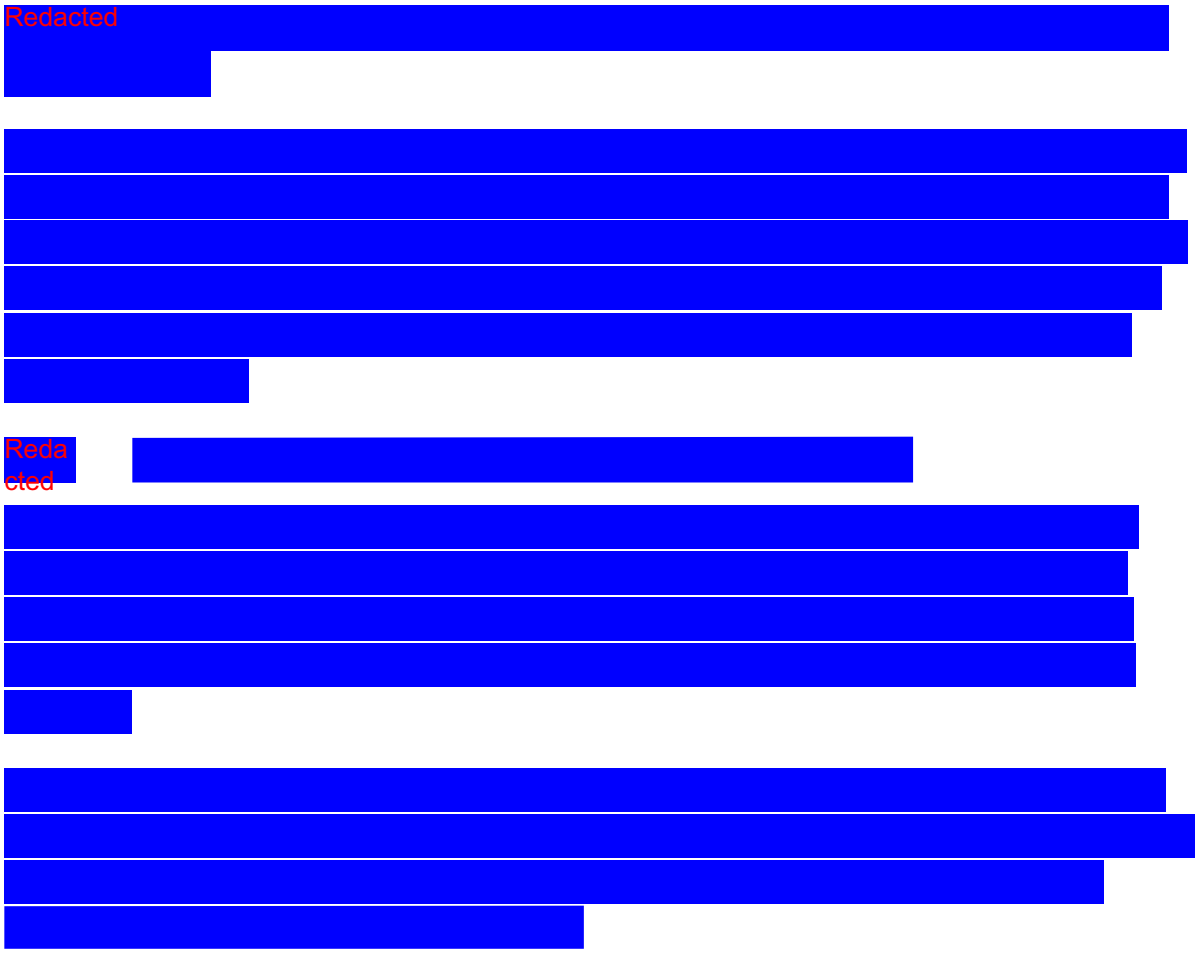

4.3.9 Estimate of Volume of Blood to be Collected

Investigators should ensure that the maximum volume of blood drawn per day meets their standard institutional guidelines and that samples are prioritised accordingly. The amount of blood to be taken from an individual subject is estimated on a per-day basis across all tests combined in Table 4.3.9-1. Many of the study specified blood tests and cultures may replace those that would be ordered with routine ICU medical management, therefore the table represents a conservative estimate of study-specific phlebotomy volume. Additional samples may be obtained for assessment of safety or as necessary for medical management; for example, clinically significant abnormal laboratory values are to be repeated, preferably within 24 to 48 hours.

Table 4.3.9-1 Estimated Blood Volume to be Collected by Visit

Visit Day	Estimated Blood Volume (mL)
Screening	10
Day 1 (Predose and postdose)	30
Day 2	12

Table 4.3.9-1 Estimated Blood Volume to be Collected by Visit

Visit Day	Estimated Blood Volume (mL)
Day 4	2
Day 8	30
Day 15	15
Day 22	20
Day 29	15
Day 50	10
Total Volume for Scheduled Assessments	**144 mL**
Subjects With Suspected or Confirmed Pneumonia, Tracheobronchitis or Bacteremia	
Day 1 of illness	30
Day 2 of illness	10
Day 3 of illness	10
Day 4 of illness	20
Day 5 of illness and every other day through clinical resolution (only for subjects positive for *P aeruginosa* bacteremia)	10
Day of clinical resolution	25

P aeruginosa = *Pseudomonas aeruginos*a

4.4 Study Suspension or Termination

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. Death in any subject in which the cause of death is assessed as related to investigational product
2. Anaphylaxis that is related to investigational product
3. Other events that, in the judgment of the sponsor or the principal investigator, are deemed serious enough to warrant immediate review by an independent DMC (see Section 4.8.10 for description of data review committees)
4. Subject enrolment is unsatisfactory
5. Noncompliance that might significantly jeopardise the validity or integrity of the study
6. Sponsor decision to terminate development

If the Sponsor determines that temporary suspension or termination of the study is required, the Sponsor will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, Sponsor will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board/Independent Ethics Committee (IRB/IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

The sponsor will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centres.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI3902	MedImmune	Redacted
Placebo	MedImmune	Redacted
Diluent for reconstitution of lyophilised investigational product.	To be provided by study sites	Redacted
Diluent for preparing clinical doses of investigational product	To be provided by study sites	Redacted

Investigational product (MEDI3902 and placebo) should be stored at 2ºC to 8ºC (36ºF to 46ºF). Prior to injection, MEDI3902 will be reconstituted with sterile water for injection. MEDI3902 or placebo will then be diluted in Re da % weight by volume (w/v) saline in an infusion bag and administered as an IV infusion.

Investigational product will be supplied to the site as open-labeled cartons, with each carton containing one vial. Each carton has a unique number that is printed on the outer carton label and the label of the vial within the carton.

Refer to Section 4.6.2 for information on blinding.

4.5.1.1 Investigational Product Dose Preparation

Investigational product should not be removed from storage at 2ºC to 8ºC (36ºF to 46ºF) until all other procedures required prior to subject dosing have been completed.

Investigational Product Inspection

Each vial selected for dose preparation should be inspected. MEDI3902 is supplied as a sterile lyophilised drug product with a post-reconstitution MEDI3902 concentration of R ed mg/mL.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to Section 4.5.1.4 for further instructions.

Dose Preparation Steps

Preparation of MEDI3902 or placebo and preparation of the infusion bag are to be performed by an unblinded investigational product manager using aseptic technique. Total in-use storage time from needle puncture of the first vial of MEDI3902 or placebo for investigational product preparation to start of administration should not exceed 4 hours at room temperature or 24 hours at 2ºC to 8ºC. If storage time exceeds these limits, a new dose must be prepared from new vials and the study monitor must be notified *immediately*. MEDI3902 and placebo do not contain preservatives, and any unused portion must be discarded.

Reconstitution Procedure for MEDI3902

Clean the rubber stopper of the investigational product vial with R ed % ethanol or equivalent and allow to air dry. Tilt the vial containing MEDI3902 and slowly add R e mL of sterile water for injection such that the liquid stream is directed along the wall of the vial and not directly upon the Redacted The solution must be swirled intermittently until all solids have been dissolved. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. At the end of reconstitution, invert the vial to dissolve any product that might be on the cap. Visually inspect to ensure that the entire content of the Redacted is reconstituted. The

reconstituted solution should appear clear to opalescent and colorless to slightly yellow. A thin layer of bubbles on the surface of the liquid is normal.

No reconstitution procedure is required for placebo.

The infusion bag dose preparation steps are as follows:

1. The investigational product vial rubber stopper should be cleaned with [redacted]% ethanol or equivalent and allowed to air dry. To avoid foaming, the vial should not be shaken.
2. Polyolefin, polyvinyl chloride, ethylene vinyl acetate, polyethylene or polypropylene infusion bags and polypropylene syringes should be used for dose preparation as no incompatibilities have been observed between MEDI3902 and these materials. Do not exceed the manufacturer specified maximum allowable needle sticks into the bag. The size of infusion bag required is specified in Table 4.5.1.1-1 and Table 4.5.1.1-2.
   a. To prepare doses in a prefilled infusion bag, a volume of [redacted]% (w/v) saline equivalent to the required investigational product dose volume must be withdrawn from the bag (Table 4.5.1.1-1). An equivalent volume of reconstituted MEDI3902 or placebo must be withdrawn from the vials using a 19-, 20-, or 21-gauge × 1.5-inch needle and added directly to the infusion bag.
   b. To prepare doses in an empty infusion bag, the required volume of investigational product (MEDI3902 or placebo) must be withdrawn from vials using a 19-, 20-, or 21-gauge × 1.5-inch needle and added directly to an empty sterile infusion bag, followed by addition of the required volume of [redacted]% (w/v) saline (Table 4.5.1.1-2).
3. Gently mix the contents of the infusion bag; do not shake the contents.
4. Label the infusion bag as specified in Section 4.5.3.

MEDI3902 is sensitive to light. Therefore, plastic IV bag colored sleeves of appropriate sizes should be used to ensure product quality is not compromised.

Table 4.5.1.1-1 Investigational Product Dose Preparation; Prefilled Infusion Bag

Treatment Group (Dose Level)	Number of Vials Required	Capacity of Infusion Bag (mL)	Investigational Product Dose Volume (mL)	Total Filled Bag Volume (mL)	Minimum Dose Administration Time (minutes)
[redacted] mg MEDI3902 or placebo	8	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] MEDI3902 or placebo	15	[redacted]	[redacted]	[redacted]	[redacted]

a The contents of 8 vials equates to [redacted], therefore following dose preparation [redacted]ml will remain unused in one of the vials

Table 4.5.1.1-2 Investigational Product Dose Preparation; Empty Infusion Bag

Treatment Group (Dose Level)	Number of Vials Required	Capacity of Infusion Bag (mL)	Investigational Product Dose Volume(mL)	0.9% (w/v) Saline Volume (mL)	Total Filled Bag Volume (mL)	Minimum Dose Administration Time (minutes)
Redacted MEDI3902 or placebo	8	Redacted	[redacted]	[redacted]	[redacted]	[redacted]
Redacted MEDI3902 or placebo	15	Red	[redacted]	[redacted]	[redacted]	[redacted]

a The contents of 8 vials equates to Redt, therefore following dose preparation Rml will remain unused in one of the vials

4.5.1.2 Treatment Administration

The day of dosing with investigational product is considered Day 1. All subjects must receive the entire Redac-mL volume (or Redac ml if a decision is made to adjust the dose from Redacted mg to Redacted mg MEDI3902) of investigational product (MEDI3902 or placebo) IV unless the infusion is discontinued due to an AE. MEDI3902 or placebo must be infused through a low protein binding Redacµm or Redacted µm filter using an IV infusion pump over a minimum duration time as mentioned in Table 4.5.1.1-1 and Table 4.5.1.1-2. *If the duration of the infusion exceeds 8 hours for the Redacted mg MEDI3902/placebo groups or 12 hours (in case of dose adjustment) for the Redacted mg MEDI3902/placebo groups, the medical monitor must be notified immediately. MEDI3902 or placebo must never be administered via IV push or bolus.*

During preparation of the investigational product infusion, the capacity of the tubing should be calculated in order to adjust the volume of investigational product solution needed to prime the IV tubing (see example below). This step is necessary because the same volume of saline will be needed at completion of the infusion to flush the IV tubing in order to deliver the complete volume of investigational product solution. Because the IV tubing contains investigational product solution, the flush must be infused using the same infusion rate as that used for the investigational product solution in the infusion bag.

Example:

If the IV tubing capacity is Reda mL, the IV tubing should be primed with Reda mL of investigational product solution from the investigational product infusion bag before initiating the investigational product infusion. Once the investigational product infusion bag

is empty, the IV tubing should be flushed with at least [redacted] mL of [redacted]% normal saline via infusion pump at the same rate as dosing.

The start time of the investigational product infusion will be the time the infusion of the investigational product solution from the infusion bag (with IV tubing already primed with investigational product solution) is started. The stop time of the infusion should be the time the IV tubing has been flushed to administer the residual investigational product solution.

4.5.1.3 Monitoring of Dose Administration

Subjects will be monitored with assessment of vital signs (temperature, respiration rate, heart rate, and blood pressure). Vital signs will be obtained on the day of dosing prior to the start of infusion (2 recordings of blood pressure and pulse rate, 5 minutes apart), every 30 (± 5) minutes during investigational product infusion, at completion of infusion (± 5 minutes), every 30 (± 5) minutes after completion of infusion for 2 hours, and 24 hours (± 30 minutes) after completion of infusion.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis.

4.5.1.4 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational products must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

[redacted]

4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The infusion bags will be labeled by an unblinded investigational product manager at the time of use according to site standard operating procedures and instructions provided by MedImmune. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

4.5.4 Storage

Store investigational product at 2°C to 8°C.

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to Sponsor. All unused investigational product will be returned to a Sponsor-authorised depot or disposed of upon authorisation by Sponsor.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IWRS will be used for randomisation to a treatment group and assignment of blinded investigational product kit number. A subject is considered randomised into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS assigns a treatment arm and blinded investigational product vial numbers will be assigned to

the subject. The IWRS will send confirmation of this information to the unblinded investigational product manager who dispenses the investigational product to the subject per the response system and records the appropriate information in the subject's medical records and investigational product accountability log.

Subjects will be randomised at a 1:1 ratio to receive either MEDI3902 Redacted mg (or in the case of dose adjustment, Redacted mg MEDI3902) or placebo. Randomisation will be stratified by geographic region and by duration of anti-*P aeruginosa* antibiotic treatment (see Appendix 10; no antibiotics use, duration of ≤ 72 hours, duration of > 72 hours) within the 96 hours prior to randomisation. Detailed instructions for the randomisation process will be provided in the IWRS manual.

Investigational product (MEDI3902 or placebo) infusion must be initiated the same day and within 6 hours after investigational product is assigned or within 4 hours of first vial puncture for investigational product preparation. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately. The duration between the start of investigational product infusion and the completion of infusion must not exceed 8 hours for the Redacted mg MEDI3902/placebo groups and 12 hours (in case of dose adjustment) for the Redacted mg MEDI3902/placebo groups. In the event of a delay, the medical monitor must be notified immediately. Details of the administration procedure are presented in Section 4.5.1.2.

4.6.2 Methods for Ensuring Blinding

This is a double-blind study in which MEDI3902 and placebo are visually indistinguishable. Neither the subject/legal representative nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Council for Harmonisation [ICH] E9). Investigational product will be handled by an unblinded investigational product manager at the site. The unblinded personnel will not reveal the treatment allocation to the sponsor or blinded site staff. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*. If the treatment allocation for a subject need to be known to treat an individual subject for an AE, the investigator must notify the sponsor *immediately*. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. The investigator is encouraged to attempt to contact the medical monitor, prior to unblinding the investigational product allocation for an individual subject, to discuss the medical emergency and the reason for wanting to unblind, as long as it does not jeopardise the safety of the individual subject. Instructions for unblinding an individual subject's investigational product allocation are contained in the IWRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

MedImmune retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

4.6.3.2 Unblinding for Interim Pharmacokinetic Analysis Purposes

One interim PK analysis is planned. Description of this analysis is provided in Section 4.8.11. To ensure the blinding of each subject's treatment assignment throughout the study, the interim analysis will be performed by a limited number of sponsor personnel who are not involved in the conduct of the study. The PK analysis will be performed by a MedImmune pharmacokineticist, who will present the PK interim analysis data to the DMC. The DMC will be responsible for recommending dose adjustment as outlined in Section 4.8.11. Site investigators and site monitors will remain blinded to the treatment assignment of individual subjects until the last subject completes the study and the database is locked. Sponsor personnel who will have access to the treatment assignments of individual subjects in order to prepare the PK dataset for the analysis will be identified in the unblinding plan. Further details will be included in the unblinding plan before the interim analysis is performed.

4.7 Restrictions During the Study and Concomitant Treatment

4.7.1 Contraception

Female subjects of child bearing potential (who are sexually active with a nonsterilised male partner) will be advised to avoid becoming pregnant by initiating and continuing at least

1 highly effective method of contraception for 49 days postdose; cessation of contraception after this point should be discussed with a qualified health care provider or a physician. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. The acceptable methods of contraception are described in Table 4.7.1-1.

Table 4.7.1-1 Highly Effective Methods of Contraception

Nonhormonal Methods	Hormonal Methods
• Vasectomised sexual partner • Tubal occlusion • IUD	• Levonorgestrel-releasing intrauterine system • Medroxyprogesterone injections • Etonogestrel implants • Normal and low-dose combined oral pills • Norelgestromin/EE transdermal system • Intravaginal device (eg, EE and etonogestrel) • Desogestrel

EE = ethnyl estradiol; IUD = intrauterine device

4.7.2 Concomitant Medication

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the electronic case report forms (eCRFs).

4.7.2.1 Permitted Concomitant Medications

All subjects will be premedicated with antihistamine, for example, Re da mg diphenhydramine IV, clemastine R e mg IV, or dexchlorpheniramine R e mg IV (or another antihistamine preparation utilised in routine clinical practice for management of acute allergic reactions). Additional suggested concomitant medications in the event of an infusion reaction are summarised in Section 3.1.3.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate therapeutic and supportive care. Specifically, subjects should receive full medical care during the study, including contraceptives, transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

4.7.2.2 Prohibited Concomitant Medications

Investigators are reminded to minimise concomitant medication use unless necessary for medical management. Any other experimental/investigational products are prohibited through 49 days postdose. The sponsor must be notified in the event that a subject was to receive an investigational product during the study.

4.8 Statistical Evaluation

4.8.1 General Considerations

The key efficacy analyses will be based on Reda mg MEDI3902 and placebo subjects, given there is no dose adjustment after interim PK analysis. Data will be provided in data listings sorted by treatment group and subject identification number (SID). Tabular summaries will be presented by treatment group. Categorical data will be summarised by the number and percentage of subjects in each category. Continuous variables will be summarised by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. No multiplicity adjustments will be made to any of the analyses because this is a Phase 2 study. Subjects who discontinue prior Day 22 will be included in the primary efficacy (ie, intent-to-treat [ITT]) population as described in the primary efficacy analysis section below. If a dose adjustment is made from Reda mg to Reda mg MEDI3902 for this dose group, the key efficacy analyses will be based on 3000 mg MEDI3902 and placebo subjects. Subjects who received Reda mg MEDI3902 will be summarized descriptively. Due to the decision to discontinue the lower dose arm, subjects who received Red acte mg MEDI3902 will also be summarized descriptively. Additional details of statistical analyses will be described in the statistical analysis plan (SAP).

Analysis Populations

The ITT Population is defined as all subjects who are randomised. Subjects will be analysed by the treatment group corresponding to their randomised treatment.

The mITT Population is defined as all subjects who are randomised into the study and who receive any amount of investigational product. Subjects will be analysed by the treatment group corresponding to their randomised treatment. All analyses, with the exception of safety, will be performed on the mITT Population.

The As-treated Population will include all subjects who are randomised into the study and who receive any amount of investigational product. Subjects will be analysed by the

treatment group corresponding to the treatment actually received. All safety analyses will be performed on the As-treated Population.

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

The percent reduction of incidence of nosocomial pneumonia caused by *P aeruginosa* through 21 days postdose will be the primary efficacy endpoint. For subjects with multiple *P aeruginosa* pneumonia events, only the first occurrence will be used in the primary analysis. Subjects with mixed cultured results, which include *P aeruginosa,* will be counted towards the primary endpoint.

The primary analysis of the primary endpoint will be evaluated using the mITT Population. *P aeruginosa* pneumonia that occurs prior to discontinuation will contribute to the primary efficacy analysis. If no *P aeruginosa* pneumonia occurs prior to discontinuation, the subject will be considered as having no *P aeruginosa* pneumonia infection in the primary efficacy analysis. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary efficacy analysis, to estimate the relative risk of *P aeruginosa* pneumonia through 21 days postdose between 1500 mg MEDI3902 and placebo groups, using the term of treatment group as a covariate. The relative risk reduction, defined as 1 – Relative Risk (RR), and its corresponding 2-sided 90% CI will be estimated from the model. In addition, the 2-sided p-value testing null the hypothesis that the incidence of having *P aeruginosa* pneumonia between MEDI3902 and placebo groups are the same will also be obtained from the model. The significance testing will be performed against a 2-sided alpha level of 0.2.

The Poisson regression with robust variance analysis will be implemented using the SAS PROC GENMOD procedure with the REPEATED statement for subject ID and logarithm link. The estimated parameter $\hat{\beta}$ [ie, log($\widehat{RR}$)], 2-sided 80% confidence interval for $\hat{\beta}$, and the 2-sided p-value will be provided from the SAS outputs. The estimated relative risk ($\widehat{RR}$) and corresponding confidence interval for the relative risk is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of relative risk reduction is given by [(1 – exp($\hat{\beta}$)) * 100%]. The confidence interval for the percent of relative risk reduction is given by ([1 – exp(upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp (lower confidence limit for $\hat{\beta}$) * 100%]).

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4.8.4 Safety

The safety of MEDI3902 will be analysed through 49 days postdose in the As-treated Population.

4.8.4.1 Analysis of Adverse Events

Safety of MEDI3902 will primarily be assessed and measured by the occurrence of all TEAEs and TESAEs.

- Occurrence of AEs through 49 days postdose
- Occurrence of SAEs through 49 days postdose
- Occurrence of AESIs to include targeted AEs of hepatic function abnormalities, hypersensitivity reactions (including anaphylaxis), infusion related reactions, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis) through 49 days postdose

Adverse events and SAEs will be summarised by Medical Dictionary for Regulatory Activities system organ class and preferred term, and by severity and relationship to investigational product.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Clinical laboratory measurements (ie, serum chemistry, and hematology) will be summarised from baseline through 21 days postdose.

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4.8.6 Pharmacokinetics

Individual MEDI3902 concentrations in serum will be tabulated for all subjects by treatment group along with descriptive statistics through 49 days postdose. Redacted Noncompartmental PK data analysis will be performed for MEDI3902 data obtained from treatment group with scheduled PK sample collection where data allows. Relevant descriptive statistics of noncompartmental PK parameters for MEDI3902 will be provided and may include AUC, C_{max}, clearance, and half-life and Vd_{ss}.

4.8.7 Anti-drug Antibody Response

The immunogenic potential of MEDI3902 will be assessed by summarising the number and percentage of subjects who develop detectable ADAs in serum through 49 days postdose. The impact of ADA on PK will be assessed if data allow. Safety data will also be assessed in subjects with ADA.

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4.8.10 Data Review Committees

Safety data will be reviewed regularly by the sponsor and an independent DMC. Efficacy data will be assessed by a blinded independent adjudication committee.

Data Monitoring Committee

An independent DMC will review safety data regularly and make recommendations regarding further study conduct. The DMC will also be responsible for recommending dose adjustment as outlined in Section 4.8.11. Further details will be provided in the DMC charter.

Adjudication Committee

A blinded independent endpoint adjudication committee will review clinical, radiographic, and microbiologic data for adjudication of efficacy endpoints and may request to review all data relevant to a potential case, including any radiographic and imaging studies performed for medical management of a subject, and any other clinical and/or microbiologic data as deemed relevant by the adjudication committee.

4.8.11 Interim Analysis

An interim PK data analysis will be performed after at least 10 subjects in each of the Redacted mg MEDI3902 and placebo groups are followed through 21 days postdose. The interim PK analysis will allow the determination of serum PK profile of MEDI3902 in mechanically ventilated subjects. Enrolment will continue in both the Redacted mg MEDI3902 and placebo groups while the PK interim analysis is conducted. An independent DMC will be responsible for recommending dose adjustment as outlined in the following criteria: If the mean serum concentration of MEDI3902 on Day 22 in the Redacted mg MEDI3902 dose group is lower than

the target concentration of Reda µg/mL, a dose adjustment to Redacted mg MEDI3902 will be considered.

4.8.12 Planned Analysis

A blinded sample size re-estimation will be performed after approximately 50% of subjects have been followed through 21 days postdose, as described in Section 4.8.2. A final analysis will be performed after all subjects have completed the study.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine RBC increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisations; or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this investigational product.

5.3.1 Hepatic Function Abnormality

Hepatic function abnormality meeting the definition of Hy's law is considered an AESI. See Section 5.4.3.1 for the definition and reporting of AESIs of hepatic function abnormality.

5.3.2 Hypersensitivity (Including Anaphylaxis) and Infusion related Reactions

Administration of polyclonal immunoglobulin preparations and mAbs have been associated with hypersensitivity (including anaphylaxis) and infusion related reactions that occur during or after dosing. A hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both, during infusion of investigational product (but does not meet the definition of anaphylaxis). Anaphylaxis is an acute onset, potentially fatal, systemic allergic reaction that is distinct from simple allergic reactions (eg, rash, pruritus) because of the simultaneous involvement of several organ systems (Sampson et al, 2006). An infusion related reaction is defined as any other reaction (other than hypersensitivity or anaphylaxis) occurring during infusion of investigational product or felt to be temporally related to the infusion.

Anaphylaxis and infusion related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion related reactions typically develop within

30 minutes to 2 hours after the initiation of first drug infusion. However, though less frequent, infusion related reactions can occur later on within first 24 hours from the start of infusion, and are less common following subsequent exposures. Infusion related reactions may manifest with single or multiple signs and symptoms. Most of them are mild in intensity, but severe and even fatal reactions have been reported. Unlike infusion related reaction, anaphylaxis is a rare event, usually occurring after subsequent exposure to antigen, and it is most commonly accompanied by severe systemic skin and/or mucosal reactions. A full definition of anaphylaxis is provided in Appendix 3.

Signs and symptoms of hypersensitivity (including anaphylaxis) and infusion related reactions include, but are not limited to, fever, chills, rigors, myalgia, weakness, flushing, sweating, headache, dizziness, lightheadedness, syncope, seizure, anxiety, nasal congestion, rhinitis, sneezing, oropharyngeal or laryngeal edema, bronchospasm, dyspnea, tachypnea, cyanosis, respiratory arrest, tachycardia, hypotension, arrhythmia, chest pain, ischemia or infarction, cardiac arrest, flushing, erythema, pruritus, urticaria, angioedema, maculopapular rash, nausea, vomiting, cramping, and diarrhea (Kang and Saif, 2007).

Infusion of biological products is commonly associated with infusion related reactions. Anaphylaxis and infusion related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion related reactions are commonly observed during or shortly after the first time exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to investigational product, and consider the above mentioned facts prior to making a final diagnosis. For the investigator's convenience and in order to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food, Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Appendix 3.

5.3.3 Immune Complex Disease

Immune complex disease can manifest in the form of a number of conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. Drug-induced immune complex (type III) hypersensitivity reactions can occur when host immune system generates antibodies to drug resulting in soluble circulating antigen-antibody complexes formation and their deposition in blood vessels. Subsequently this initiates tissue damaging inflammatory reactions mediated by complement and/or leukocytes and mast cells.

The pathology and clinical manifestations are dependent on the tissues/organs involved, with vascular, skin and renal tissues being common sites of injury. Common examples of immune complex hypersensitivity reactions are serum sickness (systemic) and Arthus reactions (local). The clinical manifestations of serum sickness include skin rash, fever, malaise and polyarthralgias or polyarthritis. Symptoms typically develop 1 to 2 weeks after first exposure to antigen and usually resolve in several weeks after withdrawal of the causative agent. Serum sickness needs to be differentiated from other 'serum-sickness-like' reactions that have a similar clinical presentation (eg, viral infections, anti-seizure drugs), but are believed to have different pathogenic mechanisms. Both serum sickness and serum sickness-like reactions have been reported with mAbs (eg, rituximab, infliximab). Clinical presentation and time to onset should be taken into account for the diagnosis and differentiation of these reactions. Diagnosis of these suspected reactions is best confirmed via biopsy of the affected tissues.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor see Section 5.4 for the definition of SAEs and Appendix 2 for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

5.4.1 Time Period for Collection of Adverse Events

AEs will be collected from time of signature of informed consent through 49 days postdose according to the schedule in Table 4.2.1-1 and Table 4.2.2-1.

All SAEs and AESIs will be recorded from the time of informed consent through 49 days postdose according to the schedule in Table 4.2.1-1 and Table 4.2.2-1. Assessment for these events after 49 days postdose will be conducted by telephone contact.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the

eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.4.3 Recording of Adverse Events of Special Interest

Adverse events of special interest (AESI) will be collected from the period immediately following investigational product administration through 49 days postdose according to the schedule in Table 4.2.2-1.

5.4.3.1 Hepatic Function Abnormality

Events of hepatic function abnormality, as defined in Section 5.3.1, should be recorded according to the definitions of AE and SAE (Section 5.1 and Section 5.2 respectively)

- If the underlying diagnosis for hepatic function abnormality is known (including progression of pre-existing disease), the diagnosis should be recorded as an AE or SAE per 5.4 or Section 5.5 respectively.
- If the underlying diagnosis for the hepatic function abnormality remains unknown, the term “hepatic function abnormal” should be used to report the AE or SAE per Section 5.4 or Section 5.5, respectively.

Medications used to treat these events should be recorded.

5.4.3.2 Hypersensitivity (including Anaphylaxis) and Infusion related Reactions

Events of hypersensitivity (including anaphylaxis) and infusion related reactions (as defined in Section 5.3.2 and Appendix 3) should be recorded according to the definitions of AE and SAE (Section 5.1 and 5.2 respectively). Medications used to treat these events should be recorded.

5.4.3.3 Immune Complex Disease

Events associated with immune complex disease (eg, vasculitis, endocarditis, neuritis, and glomerulonephritis), as defined in Section 5.3.3, should be recorded according to the definitions of AE and SAE (Section 5.1 and Section 5.2 respectively). Medications used to treat these events should be recorded.

5.5 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate Sponsor representative(s) within one day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to the Sponsor Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform the designated Sponsor representative(s).

If the EDC system is not available, then the Investigator or other study site personnel reports an SAE to the appropriate Sponsor representative by telephone. The Sponsor representative will advise the Investigator/study site personnel how to proceed.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose for this study is defined as administration of investigational product in excess of Redacted mg MEDI3902, the highest dose tested in the Phase 1 FTIH study (Redacted).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose of study drug occurs in the course of this study, then the Investigator or other site personnel inform appropriate sponsor representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the Investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses, reporting must occur within 30 days.

5.6.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of this study, then the Investigator or other site personnel informs the appropriate sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor representative works with the Investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site within 1 calendar day (life-threatening events) or 5 calendar days for all other SAEs (see Section 5.2), and within 30 days for all other pregnancies.

The same timelines apply when pregnancy outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.6.3 Hepatic Function Abnormality

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3x upper limit of normal (ULN) together with total bilirubin $\geq$ 2xULN may need to be reported as SAEs. Please refer to Appendix 9 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

If a case of Hy's law occurs in the course of this study, the Investigator or other site personnel must inform appropriate sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

5.6.4 Adverse Events of Special Interest

5.6.4.1 Anaphylaxis and Serious Allergic Reactions (Including Hypersensitivity) and Infusion related Reaction

If a case of anaphylaxis and serious allergic reactions (including hypersensitivity) and infusion related reaction occurs in the course of this study, the Investigator or other site personnel must inform appropriate sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

5.6.4.2 Immune Complex Disease

If a case of immune complex disease occurs in the course of this study, the Investigator or other site personnel must inform appropriate sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilised.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative or designee will have regular contacts with the study site, including visits to:

- Provide information and support to the investigators

- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

A Clinical Study Agreement must be in place with the Principal Investigator before any study-related procedures take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit/assessment (including telephone contact), regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.5).

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

6.4 Data Management

Data management will be performed by Redacted LLC according to the Data Management Plan.

A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the principal investigator of the applicable site. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

7.2 Subject Data Protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to Sponsor before enrolment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

Sponsor or designee should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

Sponsor or designee will handle the distribution of any of these documents to the national regulatory authorities.

Sponsor or designee will provide Regulatory Authorities, IRB/IEC and Principal Investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

Each Principal Investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. Sponsor or designee will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.4 Informed Consent

In a situation where a subject is unable to provide consent, informed consent will be obtained by using one of the following possible options, which must comply with the applicable country's local laws and ethics committees regulating the enrolment of incapacitated adults into clinical trials: Verbal consent from a legally appointed individual via telephone, confirmed by signed consent form sent by fax or email (at least 2 people from the study site are required, one to administer the informed consent and the second as a witness). When consent is obtained by fax or email, an original signature must be obtained at the earliest opportunity.

In extreme and urgent circumstances when immediate action is required, an independent physician, who is a qualified medical doctor with at least one year of experience in intensive care medicine, may sign the independent physician statement to authorize subject enrolment into the study, if the local laws, regulations and ethics committees approve this process. The presumed will of the subject will be determined by the physician and documented based on his/her knowledge of the study subject.

The study subject must be presented with the informed consent as soon as it is possible and reasonable, and informed consent obtained for continued study participation. The legally authorized representative may act as an agent on the subject's behalf once they are available to provide informed consent.

The above process must be expedited to ensure that securing consent from an authorized representative does not lead to delays that may result in increased risk to the subject. Furthermore, at no time will medical treatment be delayed to secure authorised informed consent for study participation.

The Principal Investigator(s) at each centre will:

- Ensure each subject's authorised representative is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject's authorised representative is notified that they are free to discontinue from the study at any time
- Ensure that each subject's authorised representative is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject's authorised representative provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC
- Ensure that subjects who are unconscious or considered by the investigator clinically unable to consent at screening and who are entered into the study by the consent of a legally acceptable representative provide their own written informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with local regulations.

7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and Sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

Sponsor will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB/IEC see Section 7.3.

If a protocol amendment requires a change to a site's ICF, Sponsor and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

7.6 Audits and Inspections

Authorised representatives of Sponsor, a regulatory authority, or an IRB/IEC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact Sponsor immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO PROTOCOL

9.1 Protocol Amendment 1, 15Jul2016

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are summarized below:

1. Protocol Synopsis, Section 2.2.1 (Primary Endpoint), Section 3.2.3 (Rationale for Endpoints), Table 4.2.2-1 (Schedule of Investigational Product Administration and Follow-up Study Procedures), Section 5.4 (New Onset of Chronic Diseases) and Section 5.4.1 (Time Period for Collection of Adverse Events): NOCDs as a safety assessment has been removed. Since AEs, SAEs and AESIs are being assessed at each study visit through the end of study (Day 50), any potential NOCDs will be recorded as AEs, SAEs, or AESIs, making it unnecessary to capture NOCDs separately.

2. Table 4.2.2-1 (Schedule of Investigational Product Administration and Follow-up Study Procedures): Under Microbiology, blood for culture assessments on Days 2 and 4 were removed.
3. Table 4.2.2-1 (Schedule of Investigational Product Administration and Follow-up Study Procedures), Table 4.2.2-2 (Schedule of Procedures for Subjects with Suspected or Confirmed Pneumonia or Bacteremia), Section 4.3.7 Redacted
4. Table 4.2.2-1 (Schedule of Investigational Product Administration and Follow-up Study Procedures): Under PK/ADA/Other, Redacted .
5. Table 4.2.2-2 (Schedule of Procedures for Subjects with Suspected or Confirmed Pneumonia or Bacteremia): Under Microbiology, tracheal or bronchial aspirate may be collected (in intubated subjects only) for Gram stain and culture.
6. Section 4.3.1.2 (Microbiology): Clarified that qualitative respiratory culture results will be recorded by all study sites and that quantitative and semi-quantitative respiratory culture results will be recorded by study sites when available.
7. Section 4.3.1.3 (Radiography): Clarified that chest X-rays performed as part of routine medical care can be used when available.
8. Section 4.3.1.4 (Definition of *P aeruginosa* Pneumonia): Under *P aeruginosa* Pneumonia Criteria for Subjects Who Are Mechanically Ventilated, clarified that respiratory specimen positive for *P aeruginosa* by culture also includes expectorated sputum. Under *P aeruginosa* Pneumonia Criteria for Subjects Who Are No Longer Mechanically Ventilated, clarified that a subject is not considered to be mechanically ventilated when an endotracheal or nasotracheal tube is not in place and the subject does not require positive ventilation support for at least 8 hours
9. Table 4.3.9-1 (Estimated Blood Volume to be Collected by Visit) has been updated reflecting the change in blood collection on Day 2 and Day 4 in Table 4.2.2-1. On Day 4, 2 mL of blood is collected for serum PK analysis. On Day 2, 12 mL of blood is collected for serum PK analysis and for serum Redacted . The estimated blood volume for Day 15 and Day 29 has been increased to 15 mL. The estimated volume of blood to be collected on day of clinical resolution has been increased to 25 mL.
10. Section 4.8.2 (Sample Size and Power Calculations) Redacted Redacted .
11. Section 4.8.3.2 (Additional Analyses of the Primary Endpoint): Approximated the antibiotic usage time after randomization from hours to days. Clarified that for subjects with *P aeruginosa* pneumonia, the microbiology culture results will be summarized descriptively for both quantitative and semi-quantitative results, when available.
12. Section 4.8.11 (Planned Analysis): Clarified that no interim analyses are planned during the study.

9.2 Protocol Amendment 2, 22Dec2016

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Major changes to the protocol are summarised below:

1. Updated synopsis to be consistent with the protocol body.
1. Clarified that IWRS will be used as a method for assigning subjects to treatment groups throughout the protocol.
2. Section 3.1.1 (Overview): Modified text to include the rationale for discontinuing enrolment in the Redacted mg MEDI3902 group. In addition, modified text to reflect the number of subjects who will be enrolled and randomised into the study.
3. Section 3.1.1 (Overview) and Section 4.6.1 (Methods for Assigning Treatment Groups): Removed the restriction of 75% in either stratum.
4. Figure 3.1.1-1 (Study Flow Diagram): Updated the study flow diagram to reflect the change to the study design.
5. Section 3.1.2 (Treatment Regimen): Modified text to reflect the new treatment regimen.
6. Section 3.2.1 (Dose Rationale): Added results from PK study in mice to justify the discontinuation of the Redacted mg MEDI3902 group.
7. Section 4.1.1 (Number of Subjects) and Section 4.8.2 (Sample Size and Power Calculations): Modified the text stating that in case of a dose adjustment from Redacted mg to Redacted mg MEDI3902, approximately 143 subjects will be randomised to receive the Redacted mg MEDI3902 dose to maintain 1:1 ratio with the placebo group. Subjects who have been enrolled and randomised in the Redacted mg and Redacted mg MEDI3902 groups will be followed until the end of the study period (Day 50).
8. Section 4.1.3 (Exclusion Criteria): Modified exclusion criterion 5 to exclude enrolment of subjects who received anti-*P. aeruginosa* antibiotics for > 72 hours (instead of > 48 hours) within 96 hours (instead of 72 hours) prior to randomization. Similarly, Section 3.1.1 (Overview) and Section 4.6.1 (Methods for Assigning Treatment Groups) were modified to state that randomisation will be stratified by geographic region and by whether subjects received anti-*P aeruginosa* antibiotic treatment for > 72 hours within 96 hours of randomisation.
9. Section 4.1.3 (Exclusion Criteria) and Appendix 6 (Sequential Organ Failure Assessment): Modified exclusion criterion 7 to increase the SOFA score to ≥ 12 (instead of ≥ 9) and added that vasopressors used to improve cerebral perfusion pressure should not be used in the calculation of the cardiovascular component of the SOFA score. The same has been added as a footnote in Appendix 6.
10. Table 4.2.2-2 and Section 4.3.1.2 (Microbiology): Modified text to state that the tracheal/bronchial aspirate (for Gram stain and culture) and expectorated sputum (Gram stain and culture) will be collected on Day 1 of onset of illness, Day 2, Day 3 and from Day 4 as clinically indicated until clinical resolution.
11. Section 4.5.1.1 (Investigational Product Dose Preparation), Table 4.5.1.1-1 (Investigational Product Dose Preparation; Prefilled Infusion Bag) and Table 4.5.1.1-2 (Investigational Product Dose Preparation; Empty Infusion Bag): Modified text that

described the reconstitution procedure, dose preparation for MEDI3902 and duration of infusion.

12. Section 4.6.3.2 (Unblinding for Interim Pharmacokinetic Analysis Purposes): Added the section describing the unblinding plan and the personnel who will remain blinded.
13. Section 4.8 (Statistical Evaluation – General Considerations): Added that if a dose adjustment is made from Redacted mg MEDI3902 to Redacted mg MEDI3902 for this dose group, the key efficacy analyses will be based on Redacted mg MEDI3902 and placebo subjects and that the subjects who received Redacted mg or Redacted mg MEDI3902 will be summarized descriptively.
14. Section 4.8.11 (Interim Analysis): Added the section that describes the PK interim analysis.
15. Section 5.6.1 (Overdose): Modified the definition of overdose as per the highest dose tested in the Phase 1 FTIH study (Redacted

9.3 Protocol Amendment 3, 06Jun2018

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. Major changes to the protocol are summarised below:

1. Updated synopsis to be consistent with the protocol body.
2. Section 2.1.2 (Secondary Objectives): Removed the secondary objective #3. Removal of this objective was based on feedback received from regulators.
3. Section 2.2.2 (Secondary Endpoints): Removed the secondary endpoints #3 and #4 (corresponding to the secondary objective #3) that was removed from Section 2.1.2. The description of these endpoints in Section 3.2.3(Rationale for Endpoints) was also removed.
4. Redacted
5. Section 3.1.1 (Overview) and Section 4.6.1 (Methods for Assigning Treatment Groups): Modified text to reflect change in terms of stratification by receipt of anti- *P aeruginosa* antibiotic treatment (no antibiotics use, duration of ≤ 72 hours, duration of > 72 hours) within 96 hours prior to randomisation.
6. Section 4.1.3 (Exclusion Criteria): Modified exclusion criteria #5 to state that only receipt of systemic colistin and aerosolized colistin anti-*P aeruginosa* antibiotics for > 72 hours within 96 hours prior to randomisation or anticipated ongoing receipt of the aforementioned anti-*P aeruginosa* antibiotics are exclusionary. This modification will potentially allow for more subjects to be enrolled in the study.
7. Table 4.2.2-1 (Randomised Treatment Period and Follow-up): Removed Redacted rom routine schedule of events at Day 1, pre-dose and Day 8 as sites are capturing same values in hematology CRF.
8. Table 4.2.2-2 (Schedule of Procedures for Subjects With Suspected or Confirmed Pneumonia, Tracheobronchitis or Bacteremia): Added tracheobronchitis as suspected outcome, prompting Day 1 onset visit assessments.
9. Section 4.3.1.5 (Definition of *P aeruginosa* tracheobronchitis in Mechanically Ventilated Subjects): Clarified the definition of tracheobronchitis

10. Section 4.5.1.2 (Treatment Administration): Clarified that if the duration of the infusion exceeds 8 hours for the Reda mg MEDI3902/placebo groups and 12 hours (in case of dose adjustment) for the Reda mg MEDI3902/placebo groups, the medical monitor must be notified immediately.
11. Section 4.8 (Statistical Evaluation) and Section 4.8.3 (Efficacy): Changed primary efficacy population to mITT rather than ITT to account for the subjects who were randomised and not dosed. Removed secondary efficacy endpoint analyses. Added clarification to primary efficacy analysis.
12. Appendix 10 (List of Study-specified Anti-*P aeruginosa* Antibiotics for Stratification): Added Appendix 10 with list of study-specified anti-*P aeruginosa* antibiotics for stratification.

Appendix 1 Signatures

Sponsor Signature(s)

A Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by *Pseudomonas aeruginosa*

Redacted

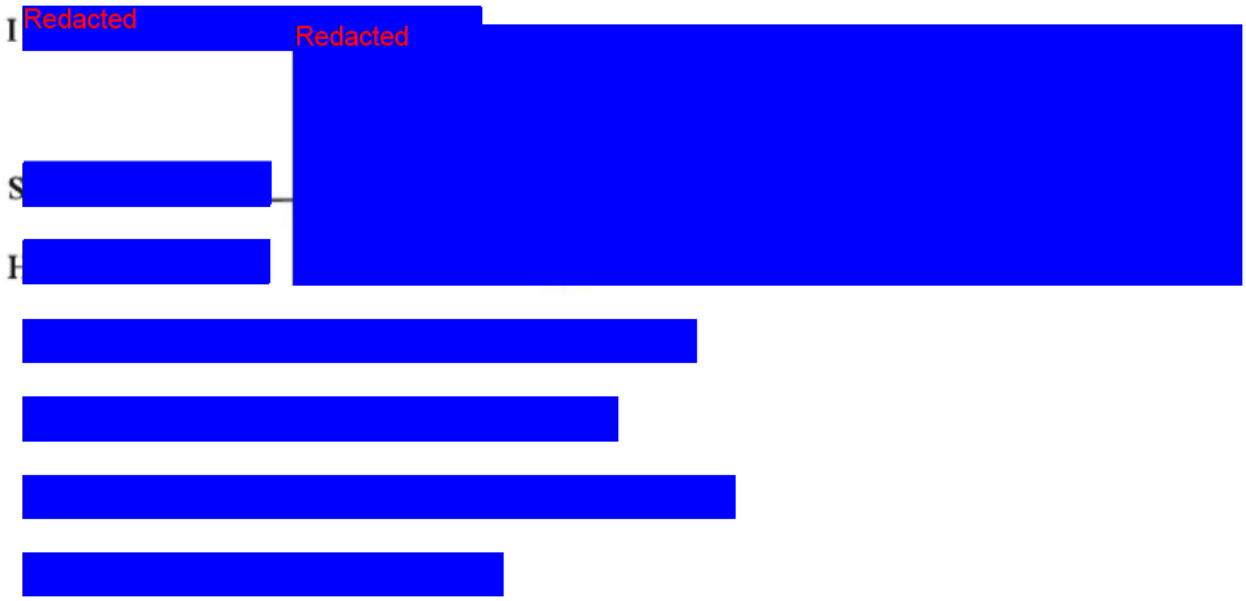
Signature and date: Redacted 11-JUNE-2018

Redacted Redacted Therapeutic Area Head

78, USA

Signature of European Federation of Pharmaceutical Industries and Associations (EFPIA) Lead

A Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by *Pseudomonas aeruginosa*



Signature of Coordinating Principal Investigator

A Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by *Pseudomonas aeruginosa*

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Redacted

Redacted

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from MedImmune or AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

Signature of Principal Investigator

A Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by *Pseudomonas aeruginosa*

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I understand that the protocol may not be modified without written approval of the sponsor.

All changes to the protocol must be submitted to the applicable regulatory authority and IEC, and must be approved by the IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Centre Number (if available) _____

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Appendix 2 Additional Safety Guidance

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes non-TESAEs (ie, SAEs that occur prior to the administration of investigational product) as well as TESAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

Appendix 3 National Institute of Allergy and Infectious Diseases and Food, Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117:391-7.

NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognise 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalised hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalised hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Appendix 4 Clinical Pulmonary Infection Score

Simplified version of the CPIS.

Component	Value	Points
Temperature °C	≥36.5 and ≤38.4	0
	≥38.5 and ≤38.9	1
	≥39.0 and ≤36.0	2
Blood leukocytes per mm^3	≥4000 and ≤11,000	0
	<4000 or >11,000	1
Tracheal secretions	Few	0
	Moderate	1
	Large	2
	Purulent	+1
Oxygenation Pao_2/Fio_2, mm Hg	>240 or presence of ARDS	0
	≤240 and absence of ARDS	2
Chest radiograph	No infiltrate	0
	Patchy or diffuse infiltrate	1
	Localized infiltrate	2

ARDS, acute respiratory distress syndrome.
Total points for CPIS varied from 1 to 10 points.

Source: Luna et al, 2003.

Appendix 5 Acute Physiology and Chronic Health Evaluation-II

Physiologic Variable	High Abnormal Range						Low Abnormal Range		
	+4	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
1. Temperature core/rectal (°C) [a]	≥ 41	39-40.9		38.5-38.9	36.0-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9
2. Mean arterial pressure (mmHg)	≥ 160	130-159	110-129		70-109		50-69		≤ 49
3. Heart rate (ventricular response)	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
4. Respiratory rate (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
5. Oxygenation A-aDO_2 or PaO_2 (mmHg) If $FiO_2 \geq 0.5$: record A-aDO_2	≥ 500	350-499	200-349		< 200				
If $FiO_2 < 0.5$: record only PaO_2					> 70	61-70		55-60	< 55
6. Arterial pH If no ABGs record serum HCO_3 below	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
7. Serum sodium	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110
8. Serum potassium	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
9. Serum creatinine (mg/dL) Double points for acute renal failure	≥ 3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
10. Hematocrit (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
11. White blood count (k/mm^3)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
12. GCS (Score = 15 minus actual GCS)	15-GCS=								
A Total Acute Physiology Score (APS)	Sum of the 12 individual variable points								
* Serum HCO_3 (venous-mmol/L) Not preferred, use if no ABGs	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	< 15

Glasgow Coma Scale (Circle appropriate response)		**B Age Points**		**C Chronic Health Points**		**APACHE-II Score** (Sum of A+B+C)
Eyes open	**Verbal - nonintubated**	Age	Points		If any of the 5 CHE categories is answered yes	
4 - spontaneously	5 - oriented	≤ 44	0		give +5 points for non-operative or emergency	**A** APS points
3 - to speech	4 - confused	45-54	2		postoperative subject and give +2 points if	**+B** Age points
2 - to pain	3 - inappropriate words	55-64	3		elective postoperative subject	**+C** Chronic Health Points
1 - no response	2 - incomprehensible sounds	65-74	5			
	1 - no response	≥ 75	6	Liver	Cirrhosis with PHT or encephalopathy	**=Total APACHE-II**
Motor response				CV	Class IV angina or at rest or with minimal	
6 - to verbal command	**Verbal - intubated**	**Age points**			self-care activities	
5 - localizes to pain	5 - seems able to talk			Pulmonary	Chronic hypoxemia or hypercapnia or	
4 - withdraws to pain	3 - questionable ability to talk				polycytaemia of PHT > 40 mmHg	
3 - flexion to pain	1 - generally unresponsive			Kidney	Chronic peritoneal or hemodialysis	
2 - extension to pain				Immune	Immune compromised host	
1 - no response					**Chronic Health Points**	

ABG = arterial blood gas; APACHE-II = Acute Physiology and Chronic Health Evaluation-II APS = Acute Physiology Score; CHE = Chronic Health Evaluation; FiO2 = fraction of inspired oxygen GCS = Glasgow Coma Scale; HCO_3 = bicarbonate; PaO_2 = partial pressure of oxygen; PHT = portal hypertension.

a A core temperature (rectal, esophageal, central venous catheter monitor urinary bladder thermistor) must be used when available. If a core temperature is not available for that subject, use non-core temperature with the following adjustments: (i) axillary temperature reading, add 1.0°C; (ii) oral temperature reading, add 0.5°C.

Appendix 6 Sequential Organ Failure Assessment

Sequential Organ Failure (SOFA) Score
European Society of Intensive Care Medicine (ESICM), 1994

SOFA score evaluate status of the following organ systems separately:

1. Respiration
2. Coagulation
3. Liver
4. Cardiovascular
5. Central Nervous System
6. Renal

Organ System	Measurement	SOFA Score				
		0	1	2	3	4
Respiration	PaO_2/FiO_2, mmHg	Normal	<400	<300	<200	<100
Coagulation	Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver	Bilirubin, mg/dL	Normal	1.2 -1.9	2.0-5.9	6.0-11.9	≥12.0
Cardiovascular	Hypotension	Normal	MAP <70 mHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine >5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine >15 or epinephrine > 0.1 or norepinephrine > 0.1
Central Nervous System	Glasgow Coma Score	Normal	13 -14	10-12	6-9	<6
Renal	Creatinine, mg/dL or Urine output	Normal	1.2 -1.9	2.0-3.4	3.5-4.9 <500 mL/day	≥5.0 <200 mL/day

* adrenergic agents administered for at least 1 hour (doses given are in mcg/kg/min)

Source: Vincent et al, 1996.

Note: Vasopressors only used to improve cerebral perfusion pressure (eg, subarachnoid hemorrhage) will not be entered in the calculation of the cardiovascular component of the SOFA score.

Appendix 7 Conversion Tables for Estimating PaO_2 and FiO_2

Estimating the PaO_2 from a given SpO_2	
SpO_2 (%)	PaO_2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

Estimating FiO_2 from Oxygen Flow Rate	
Nasal Canula	
100% O_2 Flow Rate (L/min)	FiO_2 (%)
1	24
2	28
3	32
4	36
5	40
6	44
Oxygen Mask	
100% O_2 Flow Rate (L/min)	FiO_2 (%)
5-6	40
6-7	50
7-8	60
9	90
10	99+
Oxygen Mask with Reservoir Bag	
100% O_2 Flow Rate (L/min)	FiO_2 (%)
6	60
7	70
8	80

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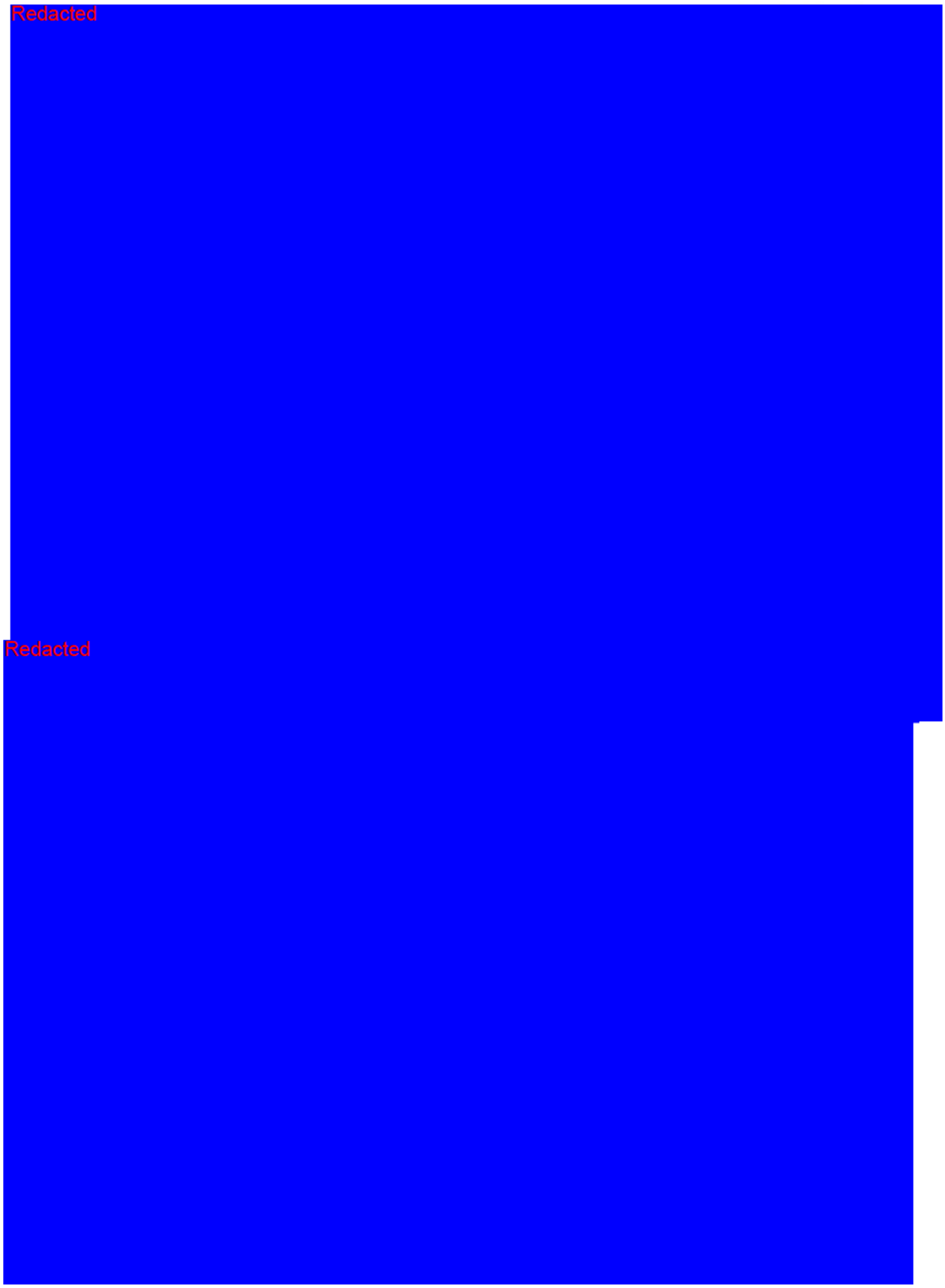
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Appendix 9 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of potential hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to sponsor study representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the sponsor study representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor study representative
- Determine whether the patient meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the study representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the sponsor study representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the Hy's law lab kit should be used.
- Complete the Liver CRF Modules as information becomes available
- If at any time (in consultation with the Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of potential hy's law cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Medical Monitor will contact the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Clinical Medical Monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review


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References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf