

NCT02296320

A Phase 2 Randomised, Double-blind, Placebo-controlled, Single-dose, Dose-ranging Study of the Efficacy and Safety of MEDI4893, a Human Monoclonal Antibody Against *Staphylococcus aureus* Alpha Toxin in Mechanically Ventilated Adult Subjects

Sponsor Protocol Number: CD-ID-MEDI4893-1139

Study Identifier: SAATELLITE - MEDI4893, a Human Monoclonal Antibody Against *Staphylococcus aureus* Alpha Toxin in Mechanically Ventilated Adult Subjects

Application Number: [REDACTED]

Investigational Product: MEDI4893

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Contract Research Organisation: [REDACTED]

Protocol History, Date

- Original Protocol, 07May2014
- Amendment 1, 07Aug2014
- Amendment 2, 04Jun2015
- Administrative Change 1, 26Jun2015
- Amendment 3, 14Aug2015

Amendment 4, 20Oct2016

Amendment 5, 15Mar2018

PROTOCOL SYNOPSIS

<p>TITLE</p> <p>A Phase 2 Randomised, Double-blind, Placebo-controlled, Single-dose, Dose-ranging Study of the Efficacy and Safety of MEDI4893, a Human Monoclonal Antibody Against <i>Staphylococcus aureus</i> Alpha Toxin in Mechanically Ventilated Adult Subjects</p>
<p>HYPOTHESES</p> <p>Primary Hypotheses</p> <ul style="list-style-type: none">• The primary efficacy hypothesis of this Phase 2 study is that prophylactic use of MEDI4893 in mechanically ventilated subjects in the intensive care unit (ICU) who are colonised with <i>S aureus</i> in the lower respiratory tract will reduce the incidence of <i>S aureus</i> pneumonia through 30 days post dose irrespective of mechanical ventilation status at time of diagnosis.• The primary safety hypothesis is that a single intravenous (IV) dose of MEDI4893 (dose range [REDACTED] mg) administered to mechanically ventilated subjects in the ICU will have an acceptable safety profile. <p>Secondary Hypothesis</p> <ul style="list-style-type: none">• Prophylactic use of MEDI4893 in mechanically ventilated subjects in the ICU who are colonised with <i>S aureus</i> in the lower respiratory tract will reduce the incidence of <i>S aureus</i> pneumonia (i) while mechanical ventilation is required, and (ii) after mechanical ventilation is no longer required.
<p>OBJECTIVES</p> <p><u>Primary Objectives</u></p> <ul style="list-style-type: none">• To evaluate the effect of MEDI4893 in reducing the incidence of <i>S aureus</i> pneumonia• To evaluate the safety of a single IV dose of MEDI4893 <p><u>Secondary Objectives</u></p> <ul style="list-style-type: none">• To evaluate the serum pharmacokinetics (PK) of MEDI4893• To evaluate the serum anti-drug antibody (ADA) responses to MEDI4893 <p><u>Exploratory Objectives</u></p> <ul style="list-style-type: none">• [REDACTED]
<p>STUDY ENDPOINTS</p> <p><u>Primary Endpoints</u></p> <ul style="list-style-type: none">• Efficacy of MEDI4893<ul style="list-style-type: none">◦ Incidence of <i>S aureus</i> pneumonia through 30 days post dose• Safety of MEDI4893<ul style="list-style-type: none">◦ Treatment-emergent adverse events (TEAEs) through 30 days and 90 days post dose◦ Treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and new onset chronic diseases (NOCDs) through 190 days post dose <p><u>Secondary Endpoints</u></p>

placebo. A PK interim analysis occurred after at least 10 subjects from each treatment group were dosed and followed through 30 days post dose to assess the serum PK profile of MEDI4893 in mechanically ventilated subjects in this study compared with the PK profile in healthy adult subjects dosed in the Phase 1 study (Study CD-ID-MEDI4893-1133). An independent data monitoring committee (DMC) was responsible for recommending dose adjustment or potential study termination as outlined in the following criteria: If the [REDACTED] mg MEDI4893 dose serum concentrations on Day 31 were lower than the MEDI4893 serum target level of [REDACTED] µg/mL in ≥ 2 subjects, a dose adjustment to [REDACTED] mg MEDI4893 was to be made; if the [REDACTED] mg MEDI4893 dose serum concentrations were lower than the target level of [REDACTED] µg/mL in ≥ 2 subjects, further enrolment was to be re-evaluated. After the DMC reviewed the interim analysis data (serum PK profiles of [REDACTED] and [REDACTED] mg MEDI4893), the DMC recommended that enrolment in the [REDACTED] mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [REDACTED] mg MEDI4893 and placebo groups instead of making a dose adjustment to [REDACTED] mg MEDI4893. As of 15 March 2018 approximately 206 subjects will be randomized in a 1:1 ratio to one of 2 treatment groups, [REDACTED] mg MEDI4893 or placebo (N = 103 for each treatment group). Randomisation will be stratified by country and then by whether or not subjects received anti-*S aureus* systemic antibiotic (treatment for ≤ 48 hours) within the 72 hours prior to randomisation. As the study is blinded, it is estimated that approximately 15 subjects may have already been enrolled and randomised in the [REDACTED] mg dose, prior to the decision of discontinuing this [REDACTED] arm, making the total number of study subjects to be approximately 221.

Additionally, the interim PK data analysis indicated that the serum exposure of MEDI4893 following a single dose of [REDACTED] or [REDACTED] mg in ICU patients was lower compared to the serum exposure in healthy adults in the Phase 1 study. Based on population PK modeling and simulation, MEDI4893 half-life in ICU patients with mechanical ventilation was estimated to be [REDACTED] days, shorter than the half-life in healthy adults in the Phase 1 study (80-112 days). On the basis of this observation, following investigational product administration on Day 1, subjects will be followed through Day 191 as part of Protocol Amendment 4, as compared to Day 361 previously.

This 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 (EFPIA), theme Combatting Antimicrobial Resistance in Europe (COMBACTE) (New Drugs for Bad Bugs [ND4BB] Subtopic 1C). MedImmune will execute this study in conjunction with the COMBACTE consortium of leading academic, clinical, and microbiological researchers in the field of antibiotic-resistant bacteria and ventilator-associated and ICU pneumonia.

TARGET SUBJECT POPULATION

Subjects in this study will be male or female adults, 18 years of age or older, requiring mechanical ventilation in the ICU, who are currently free of *S aureus*-related disease but are colonised with *S aureus* in the lower respiratory tract.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Subjects will be randomly assigned to receive a single dose of [REDACTED] mg MEDI4893, [REDACTED] mg MEDI4893, or placebo administered via IV infusion on Day 1.

STATISTICAL ANALYSIS PLAN

Data will be provided in data listings sorted by treatment group and subject identification number. 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. A Poisson regression model with robust variance will be used as the primary efficacy analysis, to compare the incidence of *S aureus* pneumonia through 30 days post dose between placebo and the MEDI4893 groups, including treatment group and dichotomous prior anti-*S aureus* systemic antibiotic use as covariates. If the number of subjects in either of the prior anti-*S aureus* systemic antibiotic use stratum is too small and/or convergence cannot be achieved, this covariate may not be included in the model. In addition, the 2-sided p-value and corresponding 2-sided 90% confidence interval (CI) around the observed relative risk will be provided from the model.

No multiplicity adjustments will be made to any of the analyses. Subjects who discontinue prior to the 30-day post-dose follow-up will be included in the primary efficacy (ie, Intent-to-treat) population as described in the primary efficacy analysis section below. Further, *S aureus* pneumonia that occurs prior to discontinuation will contribute to the primary efficacy analysis. If no *S aureus* pneumonia occurs prior to discontinuation, the subject will be considered as having no *S aureus* pneumonia infection in the primary efficacy analysis. Different

approaches to handle missing data (ie, early discontinuation and no *S aureus* pneumonia prior to discontinuation) may be considered for sensitivity analyses.

Interim Analyses

One interim analysis was planned. The interim analysis occurred after at least 10 subjects from each treatment group were followed through 30 days post dose to compare the serum PK profile of MEDI4893 in mechanically ventilated subjects in this study with healthy adult subjects dosed in the Phase 1 study (Study CD-ID-MEDI4893-1133). An independent DMC was responsible for recommending dose adjustment or potential study termination as outlined in the following criteria: If the [REDACTED] mg MEDI4893 dose serum concentrations on Day 31 were lower than the MEDI4893 serum target level of [REDACTED] µg/mL in ≥ 2 subjects, a dose adjustment to [REDACTED] mg MEDI4893 was to be made; if the [REDACTED] mg MEDI4893 dose serum concentrations were lower than the MEDI4893 target level of [REDACTED] µg/mL in ≥ 2 subjects, further enrolment was to be re-evaluated. After the DMC reviewed the PK interim analysis data (serum PK profiles of [REDACTED] and [REDACTED] mg MEDI4893), the DMC recommended that enrolment in the [REDACTED] mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [REDACTED] mg MEDI4893 and placebo groups instead of making a dose adjustment to [REDACTED] mg MEDI4893.

Primary Analysis

Two formal analyses (Stage 1 and Stage 2) are planned. The Stage 1 analysis will be conducted after the last subject has completed follow-up through 30 days post dose and will be the primary analysis for efficacy, for which the study is powered. During the Stage 1 analysis, all efficacy (ie, primary, secondary, and exploratory efficacy endpoints), serum PK, ADA, and safety data collected through 30 days post dose for the last subject enrolled will be analysed. The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study (ie, approximately 190 days post dose). During the Stage 2 analysis, safety, serum PK, and ADA through 90 days post dose will be analyzed. In addition, the [REDACTED] safety through study completion will be analysed.

Sample Size/Power Calculation



Approximately 206 subjects will be enrolled and randomised in a 1:1 ratio to one of 2 treatment groups: [REDACTED] mg MEDI4893 (N = 103) or placebo (N = 103). As the study is blinded, it is estimated that approximately 15 subjects may have already been enrolled and randomised in the [REDACTED] mg MEDI4893 dose, prior to the decision of discontinuing this lower dose arm, making the total number of study subjects to be approximately 221.

[REDACTED] As such, a study with a sample size of 92 per arm will allow a 70% power at 2-sided significance level of $\alpha = 0.1$ to detect a relative risk reduction 50% comparing [REDACTED] mg MEDI4893 versus placebo. A Poisson regression with robust variance (Zou, 2004) is employed in the calculation. N = 221 is derived when considering 10% attrition and adding an estimated 15 subjects in the [REDACTED] mg dose.

[REDACTED] In addition, 50% relative reduction was demonstrated in a study by François and colleagues (François et al, 2012) involving a monoclonal antibody to prevent *Pseudomonas pneumonia* in mechanically-ventilated patients, supporting the biological feasibility of such an effect.

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LIST OF ABBREVIATIONS

Abbreviation or Specialised Term	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
APACHE	Acute Physiology and Chronic Health Evaluation
AST	aspartate transaminase
AT	alpha toxin
BAL	bronchoalveolar lavage
BUN	blood urea nitrogen
CCC	Clinical Coordinating Centre
CI	confidence interval
CL	serum clearance
COMBACTE	Combatting Antimicrobial Resistance in Europe
CPAP	continuous positive airway pressure
CPIS	Clinical Pulmonary Infection Score
CRP	C-reactive protein
CT	computed tomography
DEHP	di(2-ethylhexyl)phthalate
DMC	Data Monitoring Committee
EC ₉₀	effective serum concentration associated with 90% survival
eCRF	electronic case report form
EFPIA	European Federation of Pharmaceutical Industries and Associations
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FAAN	Food Allergy and Anaphylaxis Network
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FTIH	first-time-in-human (study)
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GGT	gamma glutamyl transferase
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
HFP	high-power field
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgG1κ	immunoglobulin G1 kappa
IMI JU	Innovative Medicines Initiative Joint Undertaking
IL	Interleukin

Abbreviation or Specialised Term	Definition
ITT	Intent-to-treat
IV	Intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LC10	non-YTE version of MEDI4893
mAb	monoclonal antibody
MMP-9	matrix metalloproteinase 9
MPO	Myeloperoxidase
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NIAID	National Institute of Allergy and Infectious Diseases
ND4BB	New Drugs for Bad Bugs
NE	neutrophil elastase
NOCD	new onset chronic disease
PD	pharmacodynamics
PK	Pharmacokinetics
PSB	protected-specimen brush
PVC	polyvinyl chloride
RBC	red blood cell
<i>S aureus</i>	<i>Staphylococcus aureus</i>
SAE	serious adverse event
SID	subject identification
SOFA	Sequential Organ Failure Assessment
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TK	Toxicokinetic
TNF α	tumor necrosis factor alpha
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell
YTE	M252Y/S254T/T256E

1 INTRODUCTION

1.1 Disease Background

***Staphylococcus aureus* Infection**

Bacterial pneumonia occurring within the hospitalised or intensive care unit (ICU) population is a clinically significant and serious disease that contributes significantly to morbidity and mortality. This constitutes the second leading type of nosocomial infection and the leading cause of death from nosocomial infection in the United States of America (USA; [Spellberg and Talbot, 2010](#)). *Staphylococcus aureus* is the primary cause of nosocomial pneumonia. A recent study of European ICUs reported that 23% of mechanically ventilated ICU patients developed pneumonia caused by *S aureus*, with over half caused by methicillin-resistant *Staphylococcus aureus* (MRSA) ([Esperatti et al, 2010](#)). A study of morbidity and mortality associated with *S aureus* pneumonia in ICUs across Europe and Latin America found a mean duration for mechanical ventilation of 15.9 days (range 11 to 30.3 days), mean ICU mortality of 21.6% (range 10% to 60%), and mean Acute Physiology and Chronic Health Evaluation (APACHE) score of 18.6 (range 15.2 to 22) for patients with *S aureus* pneumonia ([Rello et al, 2013](#)).

S aureus pneumonia among mechanically ventilated intubated ICU patients is associated with significant healthcare-associated costs. Restrepo and colleagues ([Restrepo et al, 2010](#)) reported median incremental hospital costs of *S aureus* pneumonia compared to non-pneumonia controls to be \$101,660 when examined between 2002 and 2006. A recent analysis of a USA claims database of privately insured patients admitted to an ICU between 2006 and 2012 suggests that *S aureus* pneumonia was associated with a mean excess or incremental cost of approximately \$100,000 compared to the control intubated ICU patients (unpublished data).

Further complicating the morbidity and mortality described above, available therapy for treating *S aureus* pneumonia cases is often limited due to antibiotic-resistant strains or the patient's intolerance to treatment. Even with the introduction of new antibiotics against *S aureus*, continuing emergence of resistance requires new approaches to address the existing, and potentially expanding, unmet medical need for preventing *S aureus* disease.

Two major variables associated with an increased risk of *S aureus* pneumonia are respiratory colonisation with *S aureus* and the prolonged need for mechanical ventilation with endotracheal intubation (> 48 hours). The rate of *S aureus* pneumonia among intubated patients colonised with *S aureus* has been reported to be up to 35% ([Sirvent et al, 2000](#);

[Ewig et al, 1999](#)). A recent study by Mullins and colleagues ([Mullins et al, 2013](#)) reported a 62.2% *S aureus* pneumonia rate among mechanically ventilated intubated patients colonised with MRSA.

During infection, *S aureus* releases a number of toxins, and *S aureus* alpha toxin (AT) is the most prevalent virulence factor causing tissue invasion and necrosis ([Wilke and Bubeck Wardenburg, 2010](#)). The pivotal role of AT in *S aureus* pathogenesis is supported by animal models (dermonecrosis, pneumonia, sepsis, endocarditis, and mastitis) ([Bramley et al, 1989](#); [Bayer et al, 1997](#); [Bubeck Wardenburg et al, 2008](#); [Kobayashi et al, 2011](#); [Powers et al, 2012](#)) and by observational studies in humans in which the presence of anti-AT antibodies during severe infections was associated with improved outcome ([Adhikari et al, 2012](#); [Jacobsson et al, 2010](#); [Ruotsalainen et al, 2008](#)).

Antibiotics are the only intervention available for treating *S aureus* diseases. Despite the introduction of new antibiotics against *S aureus*, emergence of resistance requires new approaches for combatting *S aureus* diseases. While prevention of healthcare-associated infections caused by *S aureus* is an important public health goal, no vaccines or passive immunisation therapies are available. Prevention currently focuses on infection control practices and limited prophylactic use of antibiotics (eg, presurgery). Topical decolonisation regimens have been proposed for *S aureus* carriers, given that nasal carriage is a risk factor for hospital-acquired infection ([Muñoz et al, 2008](#); [Bode et al, 2010](#)). However, decolonisation efforts have not been consistently effective and are not universally implemented ([Kluytmans et al, 1996](#); [Perl et al, 2002](#); [Kalmeijer et al, 2002](#)).

1.2 MEDI4893 Background

MEDI4893 is briefly described below. Refer to the current Investigator’s Brochure for details.

MEDI4893 is being developed for the prevention of nosocomial pneumonia caused by *S aureus*.

[REDACTED]

1.3 Summary of Nonclinical Experience

[Redacted text block]

[Redacted text block]

[Redacted text block]

1.4 Summary of Clinical Experience

[Redacted text block]

[REDACTED]

[REDACTED]

1.5 Rationale for Conducting the Study

Patients in the ICU are at a high risk for developing serious *S aureus* infection, such as pneumonia, bacteremia, bone and joint infection, meningitis, and endocarditis. Mechanical ventilation increases the risk for pneumonia in the ICU, with *S aureus* being one of the most common causes of ICU pneumonia. The emergence of *S aureus* strains resistant to methicillin (MRSA) and glycopeptides (glycopeptide-intermediately resistant *S aureus* and glycopeptide-resistant *S aureus*) complicates the management of *S aureus* infection by limiting the antimicrobial therapeutic options, which highlights the need to consider new approaches, such as immunoprophylaxis. One approach to immunoprophylaxis is the use of a mAb that targets the AT of *S aureus*, a toxin that can induce substantial tissue and organ damage. Preemptive targeting of AT may prevent both serious antibiotic-susceptible *S aureus* and serious antibiotic-resistant *S aureus* disease in at-risk patients.

MEDI4893 was found to be generally safe in the initial Phase 1 study with an extended antibody half-life and the ability to neutralise AT. Because there is no correlate of protection for *S aureus* 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 MEDI4893 in adult subjects admitted to the ICU who require mechanical ventilation and who are also colonised with *S aureus* in the lower respiratory tract. Results will also form the basis for subsequent studies in adult populations at high risk for *S aureus* infections.

1.6 Research Hypotheses

1.6.1 Primary Hypotheses

The primary efficacy hypothesis of this Phase 2 study is that prophylactic use of MEDI4893 in mechanically ventilated subjects in the ICU who are colonised with *S aureus* in the lower respiratory tract will reduce the incidence of *S aureus* pneumonia through 30 days post dose irrespective of mechanical ventilation status at time of diagnosis.

The primary safety hypothesis is that a single IV dose of MEDI4893 (dose range [REDACTED] to [REDACTED] mg) administered to mechanically ventilated subjects in the ICU will have an acceptable safety profile.

2 OBJECTIVES

2.1 Objectives

2.1.1 Primary Objectives

1. To evaluate the effect of MEDI4893 in reducing the incidence of *S aureus* pneumonia
2. To evaluate the safety of a single IV dose of MEDI4893

2.1.2 Secondary Objectives

1. To evaluate the serum PK of MEDI4893
2. To evaluate the serum ADA responses to MEDI4893

2.1.3 Exploratory Objectives

[REDACTED]

[REDACTED]

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 study evaluating 2 dosage levels in mechanically ventilated subjects in the ICU at high risk for *S aureus* infections who are currently free of *S aureus*-related disease but are colonised with *S aureus* in the lower respiratory tract. At study start, approximately 462 subjects were to be enrolled from 60 to 80 centers primarily in Europe. Subjects were to be randomly assigned in a 1:1:1 ratio to receive a single IV dose of [REDACTED] mg MEDI4893, [REDACTED] mg MEDI4893, or placebo.

One interim analysis was planned. The interim analysis occurred after at least 10 subjects from each treatment group were followed through 30 days post dose to assess the serum PK profile of MEDI4893 in mechanically ventilated subjects in this study compared with the PK profile in healthy adult subjects dosed in the Phase 1 study (Study CD-ID-MEDI4893-1133). An independent data monitoring committee (DMC) was responsible for recommending dose adjustment or potential study termination as outlined in the following criteria: If the [REDACTED] mg MEDI4893 dose serum concentrations on Day 31 were lower than the MEDI4893 serum target level of [REDACTED] $\mu\text{g/mL}$ in ≥ 2 subjects, a dose adjustment to [REDACTED] mg MEDI4893 was to be made; if the [REDACTED] mg MEDI4893 dose serum concentrations were lower than the target level of [REDACTED] $\mu\text{g/mL}$ in ≥ 2 subjects, further enrolment was to be re-evaluated. After the DMC reviewed the interim analysis data (serum PK profiles of [REDACTED] and [REDACTED] mg MEDI4893), the DMC recommended that enrolment in the [REDACTED] mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [REDACTED] mg MEDI4893 and placebo groups instead of making a dose adjustment to [REDACTED] mg MEDI4893; resulting in a sample size of 270 subjects (randomised in a 1:1 ratio to either [REDACTED] mg MEDI4893 or placebo). Effective 15 March 2018, approximately 206 subjects will be randomized in a 1:1 ratio to one of 2 treatment groups, [REDACTED] mg MEDI4893 or placebo (N = 103 for each treatment group). Randomisation will be stratified by country and then by whether or not subjects received anti-*S aureus* systemic antibiotic (treatment for ≤ 48 hours) within the 72 hours prior to randomisation. Following investigational product administration on Day 1, subjects will be followed through Day 191. As the study is blinded, it is estimated that approximately 15 subjects may have already been enrolled and randomised in the [REDACTED] mg dose, prior to the decision of discontinuing [REDACTED], making the total number of study subjects to be approximately 221.

Additionally, on the basis of the interim PK data analysis (see Section 1.4 for details), following the investigational product administration on Day 1, subjects will be followed through Day 191 as part of Protocol Amendment 4, as compared to Day 361 previously.

Two formal analyses (Stage 1 and Stage 2) are planned. The Stage 1 analysis will be conducted after the last subject has completed follow-up through 30 days post dose and will be the primary analysis for efficacy, for which the study is powered. During the Stage 1 analysis, all efficacy (ie, primary, secondary, and exploratory efficacy endpoints), serum PK, ADA, and safety data collected through 30 days post dose for the last subject enrolled will be analysed. The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study (ie, approximately 190 days post dose). During the Stage 2 analysis, safety, serum PK, and ADA through 90 days post dose will be analyzed. [REDACTED]

A high-level flow diagram for this study is shown in [Figure 3.1.1-1](#). The endpoints to be measured in this study are described in [Section 2.2](#).

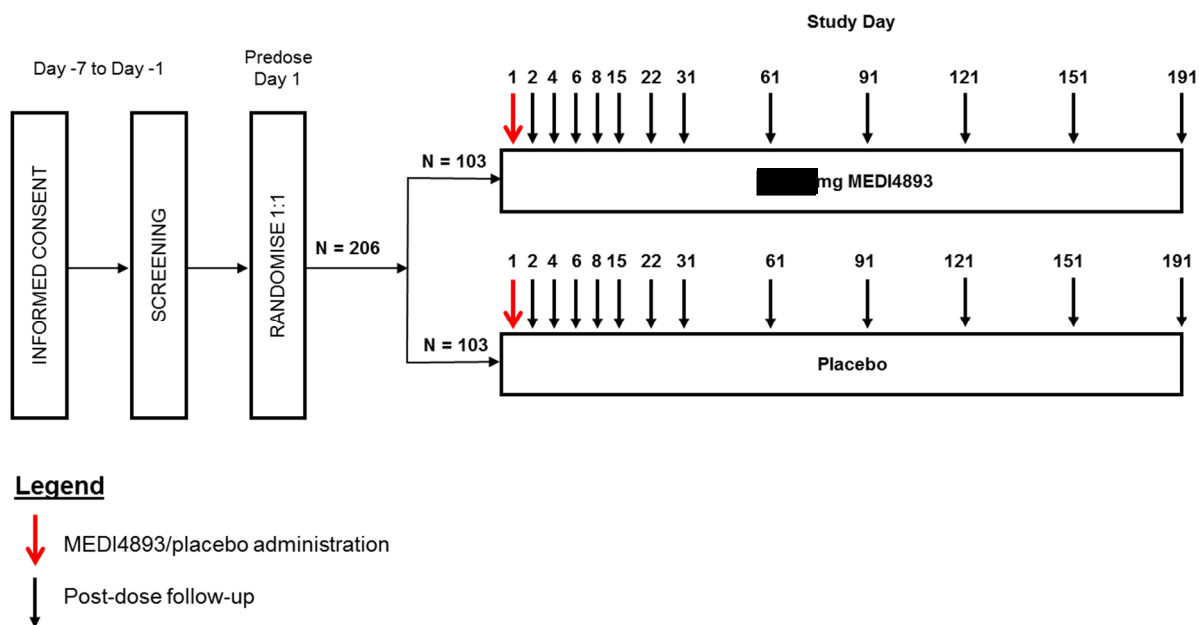


Figure 3.1.1-1 Study Flow Diagram

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

Note: This study flow diagram was revised based on the first interim analysis and illustrates how approximately 206 subjects will be randomised in a 1:1 ratio to one of 2 treatment groups: [redacted] mg MEDI4893 (N = 103) or placebo (N = 103). As the study is blinded, it is estimated that approximately 15 subjects may have already been enrolled and randomised in the [redacted] mg dose, prior to the decision of discontinuing [redacted], making the total number of study subjects to be approximately 221. Stage 1 analysis for efficacy, safety, serum PK, and ADA will be assessed through 30 days post dose (Day 31); Stage 2 analysis for long-term safety follow-up will be assessed through 190 days post dose (Day 191).

This 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 (EFPIA), theme Combatting Antimicrobial Resistance in Europe (COMBACTE) (New Drugs for Bad Bugs [ND4BB] Subtopic 1C). MedImmune will execute this study in conjunction with the COMBACTE consortium of leading academic, clinical, and microbiological researchers in the field of antibiotic-resistant bacteria and ventilator-associated and ICU pneumonia.

3.1.2 Treatment Regimen

Effective 15 March 2018, approximately 206 subjects will be enrolled and randomly assigned (1:1 ratio) to receive a single IV infusion of [REDACTED] mg MEDI4893 (N = 103), or placebo (N = 103) on Day 1. Subjects who have been enrolled and randomized into the [REDACTED] mg MEDI4893 group will continue to be followed through the end of study.

3.2 Study Design and Dose Rationale

3.2.1 Rationale for Study Design

This study is designed to determine if prophylactic administration of MEDI4893 reduces the incidence of *S aureus* pneumonia when added to standard-of-care therapy. The study is randomised, double-blinded, and placebo-controlled. Blinding and random assignment of treatment are standard elements that limit the occurrence of intentional or unintentional bias arising from knowledge of treatment assignment. There is no established medicinal product with proven prophylactic value in this indication with which to compare MEDI4893; therefore, placebo will be used in the control arm to maintain the blinded assessment of therapeutic effect and adverse events (AEs). All subjects will receive standard-of-care. The use of placebo will not replace or result in the withholding of a currently proven intervention during the study period.

3.2.2 Dose Rationale

Two single doses of MEDI4893, [REDACTED] mg and [REDACTED] mg, have been selected to be evaluated in the Phase 2 study based on the PK/PD data from preclinical pharmacology studies and PK data from the clinical Phase 1 study (Study CD-ID-MEDI4893-1133). [REDACTED]

[REDACTED]

As described in Section 3.1.1, an interim analysis occurred after at least 10 subjects from each treatment group were followed through 30 days post dose to compare the serum PK profile of MEDI4893 in mechanically ventilated subjects in this study with healthy adult subjects dosed in the Phase 1 study (Study CD-ID-MEDI4893-1133). An independent DMC was responsible for recommending dose adjustment or potential study termination as outlined in the following criteria: If the [REDACTED] mg MEDI4893 dose serum concentrations on Day 31 were lower than the MEDI4893 serum target level of [REDACTED] µg/mL in ≥ 2 subjects, a dose adjustment to [REDACTED] mg MEDI4893 was to be made; if the [REDACTED] mg MEDI4893 dose serum concentrations were lower than the target level of [REDACTED] µg/mL in ≥ 2 subjects, further enrolment was to be re-evaluated. After the DMC reviewed the interim analysis data (serum PK profiles of [REDACTED] and [REDACTED] mg MEDI4893), the DMC recommended that enrolment in the [REDACTED] mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [REDACTED] mg MEDI4893 and placebo groups instead of making a dose adjustment to [REDACTED] mg MEDI4893. Approximately 206 subjects will be randomised in a 1:1 ratio to one of 2 treatment groups: [REDACTED] mg MEDI4893 (N = 103) or placebo (N = 103).

3.2.3 Rationale for Study Population

Subjects in this study will be ICU patients on mechanical ventilation at the time of enrolment who are colonised with *S aureus* in the lower respiratory tract but without a diagnosis of acute pneumonia or *S aureus* infection. While data are limited on a comprehensive understanding of all variables that contribute to the risk of *S aureus* pneumonia, respiratory colonisation with *S aureus* and the prolonged need for mechanical ventilation with endotracheal intubation (> 48 hours) are widely recognised as 2 major contributing factors. The rate of *S aureus* pneumonia among intubated patients colonised with *S aureus* has been reported to be up to 35% ([Sirvent et al, 2000](#); [Ewig et al, 1999](#)), and up to 62.2% among mechanically ventilated intubated patients colonised with MRSA ([Mullins et al, 2013](#)).

Since the objective of the study is to prevent nosocomial pneumonia in mechanically ventilated high-risk patients, patients will be excluded if they have pre-existing confirmed or suspected *S aureus* infections, have an underlying condition that would impede a diagnosis of pneumonia, are not expected to have a reasonable probability to survive through the study evaluation period, or have received potentially effective systemic antibiotic therapy for *S aureus* for > 48 hours within 72 hours prior to dosing.

These enrolment criteria are expected to result in a population representative of patients encountered in clinical practice with a high risk of developing *S aureus* pneumonia, and will minimise confounding factors for the characterisation of efficacy of MEDI4893 in preventing pneumonia in mechanically ventilated patients.

3.2.4 Rationale for Endpoints

The primary efficacy endpoint for this study is the incidence of *S aureus* pneumonia through 30 days after a single dose of MEDI4893 in mechanically ventilated subjects at risk for *S aureus* pneumonia. It is anticipated that while a substantial number of mechanically ventilated subjects will continue to require mechanical ventilation throughout the 30-day post-dose period, a number of subjects will be weaned off the ventilator during this period. Since these subjects may develop *S aureus* pneumonia 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 30-day post-dose period.

The primary safety endpoint will assess AEs and serious adverse events (SAEs) temporally associated with MEDI4893 dosing through 30 days post dose as well as 90 days post dose. Given the extended half-life of MEDI4893, longer-term safety evaluation will assess SAEs, AESIs, and NOCDs through 190 days post dose (approximately 4 half-lives).

Secondary endpoints of MEDI4893 serum concentration and PK parameters, and ADA response to MEDI4893 are designed to assess the presence of MEDI4893 in vivo.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 206 subjects will be randomised to one of 2 treatment groups: [REDACTED] mg MEDI4893 (N = 103) or placebo (N = 103). As the study is blinded, it is estimated that approximately 15 subjects may have already been enrolled and randomised in the [REDACTED] mg dose, prior to the decision of discontinuing [REDACTED], making the total number of study subjects to be approximately 221.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Age 18 years or older at the time of study entry
2. Written informed consent and any locally required authorisation (eg, European Union [EU] Data Privacy Directive in the EU) 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.
 - Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral oophorectomy or complete hysterectomy), premenarchal, or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
4. Tracheal or bronchial sample positive by polymerase chain reaction (PCR) for *S aureus* within 36 hours prior to randomisation. Note: the 36-hour window will be determined by the time of sample collection.
5. Currently intubated, on mechanical ventilation in the ICU
6. Expected to remain intubated and mechanically ventilated for ≥ 3 days 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 for 190 days post dose

4.1.3 Exclusion Criteria

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

1. Acute confirmed or suspected Staphylococcal disease at study enrolment and investigational product dosing (endotracheal colonisation is acceptable and required [see Section 4.1.2, Inclusion Criterion 4])
2. CPIS of ≥ 6 based on contributing parameters measured within past 24 hours, prior to investigational product dosing (CPIS assessment is provided in [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 currently have been on mechanical ventilation for > 2 weeks **AND** are known to be colonised with *S aureus* in lower respiratory tract for > 2 weeks
5. Subjects who are tracheostomy-dependent prior to current hospital admission
6. Receipt of anti-*S aureus* systemic antibiotics for > 48 hours within 72 hours prior to randomisation that are considered active against the *S aureus* strain with which the subject is colonised, or anticipated ongoing receipt of anti-*S aureus* systemic antibiotics
7. Burns $> 40\%$ body surface area
8. APACHE-II score ≥ 25 (if Glasgow Coma Scale [GCS] score is > 5) or ≥ 30 (if GCS score is ≤ 5), or SOFA score ≥ 9 at time of randomisation (APACHE-II and SOFA are provided in [Appendix 5](#) and [Appendix 6](#), respectively). 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.

9. Receipt of any investigational drug therapy within 30 days prior to investigational product dosing
10. Previous receipt of a mAb
11. 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.
12. Lymphoma not in complete remission and on chemotherapy
13. Recipients of bone marrow, stem cell, or solid organ transplant who are not currently in complete remission
14. Receipt of chemotherapy or other immunosuppressive drugs including glucocorticoid therapy (prednisone 20 mg or equivalent, daily or every other day for 30 days) in past 2 months
15. History of allergic disease or reactions likely to be exacerbated by any component of the investigational product
16. Not able to complete follow-up for at least 30 days post dose based on investigator judgment
17. 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, an interactive voice/interactive web response system [IVRS/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. 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. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

In the event that a subject notifies the investigator ahead of a scheduled visit that he/she would not be able to participate in the study beyond the upcoming study visit, all attempts must be made to collect assessments included as part of the Day 91 visit (if the decision is made prior to Day 91) and the end-of-study visit (Day 191). Once the subject withdraws consent, no additional study assessments will be performed.

Lost to Follow-up

Subjects will be considered lost to follow-up only if no contact has been established through the time of the subject's last protocol-specified visit/assessment (as defined in Section 6.3).

Subjects refusing to abide by the study requirements or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up."

Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol. For subjects who are unable to attend a study visit in person for unforeseen reasons beyond their control, the investigator must utilise all means to perform whatever assessments possible, eg, assessing safety by telephone. If contact is lost after hospital discharge and not re-established until after Day 91, the Medical Monitor will determine whether any Day 91 or other missed assessments should be completed.

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. Unless consent for follow-up is withdrawn, subjects discontinued after receiving at least a partial dose of investigational product will be followed for the full study period with all laboratory and clinical evaluations collected as defined in the protocol (see Section 6.3).

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.

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 25 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 during the screening period. Assessments should be performed in the order shown in the table.

Table 4.2.1-1 Schedule of Screening Procedures

Assessment	Screening (up to 7 days prior to randomisation)
Written informed consent ^a	X
Assignment of SID number	X
Medical history	X
Physical examination	X
Height	X
Weight	X
Serum β hCG ^b	X ^c
Disease Assessment	

Table 4.2.1-1 Schedule of Screening Procedures

Assessment	Screening (up to 7 days prior to randomisation)
Evaluate for clinical symptoms of pneumonia/serious <i>S aureus</i> infection (physical exam, vital signs, CPIS assessment, SOFA, APACHE-II, GCS, PaO ₂ /FiO ₂ ratio, as clinically indicated)	X
Chest X-ray	X
Safety Assessments	
Vital signs	X
Serum chemistry	X ^c
Hematology	X ^c
Urinalysis	X ^c
AEs and SAEs	X
Concomitant medications	X
Tracheal or bronchial aspirate for <i>S aureus</i> colonisation by PCR	X ^d
Tracheal/bronchial aspirate for Gram stain	X ^e
Tracheal/bronchial aspirate for culture	X ^e
Verify eligibility criteria	X

AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; βhCG = beta human chorionic gonadotropin; CPIS = Clinical Pulmonary Infection Score; GCS = Glasgow Coma Scale; *S aureus* = *Staphylococcus aureus*; PCR = polymerase chain reaction; SAE = serious adverse event; SID = subject identification; SOFA = Sequential Organ Failure Assessment.

^a 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.

^b Female subjects of child-bearing potential only; must be negative prior to randomisation.

^c 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.

^d Tracheal or bronchial aspirate for *S aureus* colonisation by PCR should be obtained within 36 hours prior to randomisation.

^e Tracheal or bronchial aspirate Gram stain and culture should be assessed on the sample obtained for determination of colonization by PCR.

4.2.2 Treatment and Follow-up Periods

Table 4.2.2-1 shows all procedures to be conducted on the day of investigational product administration (Day 1) and during the post-dose follow-up period. Table 4.2.2-2 shows procedures for subjects with suspected serious *S aureus* infection from onset through resolution of illness. Assessments should be performed in the order shown in the tables.

Table 4.2.2-1 Schedule of Treatment and Post-dose Follow-up Procedures

Assessment	Day (Assessment Window)														
	1			2	4	6	8 ±1	15 ±1	22 ±1	31 +3	61 ±5	91 ±5	121 ±10	151 ±10	191 ±10
	Pre-dose ^a	Dose	Post-dose	Post-dose Follow-up											
Eligibility															
Medical history	X ^b														
Physical examination	X ^b														
Serum βhCG ^c	X											X			
Verify eligibility criteria ^d	X														
Randomisation	X														
Investigational Product Administration		X													
Efficacy Assessments															
Monitor for clinical symptoms/signs of pneumonia/ serious <i>S aureus</i> infection (physical exam, vital signs, oxygen status ^e , CPIS, SOFA, as indicated)	X	X	X	Daily while in hospital; in accordance with symptoms after hospital discharge For subjects with suspected pneumonia or bacteremia see Table 4.2.2-2											
Microbiology															
Blood for culture	X														
Chest X-ray	X														
Safety Assessments															
Vital signs ^f	X	X	X	X											
Serum chemistry	X ^b						X			X					
Hematology	X ^b						X			X					
Urinalysis	X ^b									X					
SAEs, AESIs, and NOCDs	X	X	X	X	X	X	X	X	X	X	X	X	X ^g	X ^g	X ^g

Table 4.2.2-1 Schedule of Treatment and Post-dose Follow-up Procedures

Assessment	Day (Assessment Window)														
	1			2	4	6	8 ±1	15 ±1	22 ±1	31 +3	61 ±5	91 ±5	121 ±10	151 ±10	191 ±10
	Pre-dose ^a	Dose	Post-dose	Post-dose Follow-up											

Abs = antibodies; ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; AT = alpha toxin; βhCG = beta human chorionic gonadotropin; CBC = complete blood count; CPIS = Clinical Pulmonary Infection Score; [REDACTED] G; min = minutes; NOCD = new onset chronic disease; PCR = polymerase chain reaction; PK = pharmacokinetics; *S aureus* = *Staphylococcus aureus*; SAE = serious adverse event; SOFA = Sequential Organ Failure Assessment.

^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); baseline serum chemistry, hematology, and urinalysis reviewed and found to be within normal limits by site investigator.

^c Female subjects of child-bearing potential only.

^d Contact Clinical Coordinating Centre to confirm the subject meets the requirements for randomisation within the next 6 hours.

^e Examples of oxygen status parameters are as follows: highest minute ventilation (L/min), highest FiO₂ (%), lowest PaO₂ results (for mechanically ventilated subjects); liters of oxygen (L/min), lowest O₂ saturation (%), FiO₂ (%) (for non-mechanically ventilated subjects).

^f Vital signs will be obtained before investigational product dosing; 2 predose blood pressure and heart rate readings should be obtained 5 minutes apart. Vital signs will also be obtained every 30 minutes (± 5 minutes) during investigational product infusion, at completion of the infusion (± 5 minutes), every 30 minutes (± 5 minutes) for 2 hours after investigational product dosing, and again 24 hours post dose.

^g Assessments after Day 91 through end of study may be conducted by telephone contact.

^h 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 24 hours after the end of infusion.

ⁱ [REDACTED]

^j [REDACTED]

Table 4.2.2-2 Schedule of Procedures for Subjects With Suspected or Confirmed Pneumonia 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 <i>S aureus</i> bacteremia				Repeat every other day until blood culture negative for <i>S aureus</i>	
Tracheal/bronchial aspirate; intubated subjects only (Gram stain and culture) ^e					
All subjects	X	X	X		
Subjects positive for <i>S aureus</i> pneumonia				Daily through clinical resolution ^c	
Expectorated sputum (unless bronchoscopy performed for clinical management and BAL or PSB sample available); non-intubated subjects only (Gram stain and culture) ^e					
All subjects	X	X	X		
Subjects positive for <i>S aureus</i> pneumonia				Daily through clinical resolution ^c	
Chest X-ray					
Subjects with suspected pneumonia	X				
Subjects with confirmed pneumonia		As clinically indicated through resolution			
PK/ADA/Other ^f					
Serum PK	X				
[REDACTED]					
Serum ADA	X				
[REDACTED]					
[REDACTED]					

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

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

ADA = anti-drug antibody; BAL = bronchoalveolar lavage; CBC = complete blood count; CPIS = Clinical Pulmonary Infection Score; PK = pharmacokinetic; PSB = protected-specimen brush; *S aureus* = *Staphylococcus aureus*; 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 from Days 2 through 31, assessments will be collected at onset and through resolution of disease (even if resolution extends beyond Day 31).
- ^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 to be collected before start of new antibiotic therapy.
- ^f PK/ADA/Other need to be collected as indicated unless a scheduled sample was already obtained on the same date.

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Clinical Symptoms

Subjects will be monitored for clinical symptoms of pneumonia and other serious *S aureus* infection 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 91. For subjects with a suspected pneumonia or bacteremia, clinical symptoms will continue to be monitored through resolution of illness (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 PaO₂ and FiO₂ is provided in [Appendix 7](#).

4.3.1.2 Microbiology

Blood and tracheal aspirate samples will be collected for microbiological assessment of pneumonia and other serious *S aureus* infection during screening and prior to administration of investigational product on Day 1 (see [Table 4.2.1-1](#) and [Table 4.2.2-1](#)).

For subjects with onset of a suspected pneumonia or bacteremia from Days 2 through 91, blood and respiratory specimens will be collected at onset and through resolution of disease (even if resolution extends beyond Day 91) according to the schedule in [Table 4.2.2-2](#). The first set of blood and respiratory specimens will be collected before the start of any new antibiotic therapy. Blood samples will be collected daily for the first 3 days of disease and then only for subjects who are positive for *S aureus* bacteremia every other day until resolution. While the subject is intubated, tracheal/bronchial aspirates will be collected for the first 3 days of disease and then daily until resolution only for subjects who are positive for *S aureus* pneumonia. If the subject is not intubated, expectorated sputum (unless bronchoscopy was performed for clinical management and bronchoalveolar lavage [BAL] or protected-specimen brush [PSB] sample is available) will be collected for the first 3 days of disease and then only for subjects who are positive for *S aureus* pneumonia daily until resolution.

Blood and tracheal aspirates will be tested for methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA using standard clinical microbiological methods.

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. For subjects with pneumonia, a chest X-ray will be conducted at onset of pneumonia and as clinically indicated through resolution of illness (see [Table 4.2.2-2](#)).

4.3.1.4 Definition of *S aureus* Pneumonia

1. ***S aureus* Pneumonia Criteria for Subjects Who are Mechanically Ventilated at the Time of Diagnosis**

(Subject will be considered mechanically ventilated if:

- Subject is intubated with an endotracheal or nasotracheal tube and receiving positive pressure ventilation support, or
- Subject 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 [CPAP], etc) within the past 24 hours)

Subject 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 *S aureus* pneumonia endpoint.

a. Radiographic criteria:

- New or worsening infiltrate consistent with pneumonia on chest X-ray obtained within 24 hours of the event (diagnosed by a qualified radiologist)

AND

b. Clinical criteria:

At least 2 of the following minor or 1 major respiratory signs or symptoms, of new onset:

- Minor criteria:
 - Systemic signs of infection (one or more of the following): Abnormal temperature (oral or tympanic temperature $> 38^{\circ}\text{C}$ or a core temperature $\geq 38.3^{\circ}\text{C}$ or hypothermia, defined as a core body temperature of $< 35^{\circ}\text{C}$), and/or abnormal WBC (WBC count $> 10,000$ cells/ mm^3 , WBC count < 4500 cells/ mm^3 , or $> 15\%$ band neutrophils)
 - Production of purulent endotracheal secretions
 - Physical examination findings consistent with pneumonia/pulmonary consolidation (eg, rales, rhonchi, bronchial breath sounds), dullness to percussion

- Major criteria
 - Acute changes made in the ventilatory support system to enhance oxygenation, as determined by:
 - PaO₂/FiO₂ ratio < 240 mmHg maintained for at least 4 hours, or
 - A decrease in PaO₂/FiO₂ by ≥ 50 mmHg maintained for at least 4 hours

AND

c. Microbiologic confirmation:

At least 1 of the following (obtained within 24 hours of onset of the event):

- Respiratory specimen is positive for *S aureus* by culture. Includes a specimen of respiratory secretions 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.
- Blood culture positive for *S aureus* (and no apparent primary source of infection outside the lung)
- Pleural fluid aspirate or lung tissue culture positive for *S aureus* during episode of pneumonia (only if obtained as part of the subject's necessary clinical management)

2. S aureus Pneumonia Criteria for Subjects Who are Not Mechanically Ventilated at the Time of Diagnosis

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.

Subject 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 *S aureus* pneumonia endpoint.

a. Radiographic criteria:

- New or worsening infiltrate consistent with pneumonia on chest X-ray obtained within 24 hours of the event (diagnosed by qualified radiologist)

AND

b. Clinical criteria:

At least 2 of the following minor or 1 major respiratory signs or symptoms:

- Minor criteria:

- Systemic signs of infection: 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 (WBC count > 10,000 cells/mm³, WBC count < 4500 cells/mm³, or > 15% band neutrophils)
- A new onset of cough (or worsening of cough)
- Production of purulent sputum
- 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
- Dyspnea, tachypnea (respiratory rate > 30 breaths/minute), or hypoxemia defined as:
 - O₂ saturation < 90% or PaO₂ < 60 mmHg on room air if lower than baseline, or
 - A need to initiate or increase sustained (≥ 3 hours) supplemental oxygen to maintain pre-event baseline O₂ saturations
- Major criteria
 - A need to initiate non-invasive mechanical ventilation or re-initiate invasive mechanical ventilation because of respiratory failure or worsening of respiratory status

AND

c. Microbiologic confirmation:

At least **1** of the following (obtained within 72 hours of onset of the event):

- Respiratory specimen is positive for *S aureus* 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. Respiratory samples from expectoration must show < 10 squamous epithelial cells and > 25 polymorphonuclear neutrophils per 100x field to be suitable.
- Blood culture positive for *S aureus* (and no other apparent primary source of infection outside the lung)
- Pleural fluid aspirate or lung tissue culture positive for *S aureus* (only if obtained as part of the subject's necessary clinical management)

4.3.2

[REDACTED]

[REDACTED]



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

Medical history and 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 will include blood pressure, heart rate, respiratory rate, and temperature (rectal/core, oral, or tympanic). All vital signs will be collected at screening, Day 1, and Day 2 according to the schedule in [Table 4.2.1-1](#) and [Table 4.2.2-1](#). Vital signs will also be used to monitor for clinical symptoms of suspected pneumonia and bacteremia as clinically indicated through Day 91.

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](#) and [Table 4.2.2-1](#) for the schedule of tests):

Serum Chemistry

- Calcium
- Chloride
- Potassium
- Sodium
- Bicarbonate
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Gamma glutamyl transferase (GGT)
- Creatinine
- Blood urea nitrogen (BUN)
- Glucose (fasting or non-fasting)
- Total bilirubin
- Creatine kinase

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

Hematology

- WBC count with differential
- RBC count
- Hematocrit
- Hemoglobin
- Platelet count

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Leukocytes
- Nitrite
- Glucose
- Ketones
- Blood
- Bilirubin
- Microscopy including WBC/high-power field (HPF), RBC/HPF

Pregnancy Test (females of childbearing potential only)

Serum beta-hCG (at screening, prior to randomisation [if > 24 hours after screening], and on Day 91)

4.3.5 Pharmacokinetic Evaluation and Methods

Blood [REDACTED] samples will be collected to evaluate PK of MEDI4893 in serum [REDACTED], according to the schedule in [Table 4.2.2-1](#). For subjects with a suspected pneumonia and bacteremia, blood [REDACTED] samples will be collected for PK evaluation on the day of onset of illness (see [Table 4.2.2-2](#)).

[REDACTED]. The PK of MEDI4893 in serum [REDACTED] will be measured using a validated sandwich enzyme-linked immunosorbent assay (ELISA) method.

4.3.6 Anti-drug Antibody Evaluation and Methods

Blood samples will be collected to evaluate ADA responses to MEDI4893 in serum according to the schedule in [Table 4.2.2-1](#). For subjects with a suspected pneumonia and bacteremia, 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. A drug-tolerant electrochemiluminescent assay will be used

to detect ADA because it is expected to be less susceptible to interference in the presence of residual drug levels 90 days post dose. 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.

4.3.7 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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 72 hours.

Table 4.3.9-1 Estimated Volume of Blood to be Collected per Visit

Visit	Estimated Volume of Blood (mL)
Screening	10
Day 1	30
Day 2	30
Day 4	10
Day 6	10
Day 8	10
Day 15	10
Day 22	10
Day 31	20
Day 61	10
Day 91	10
Total	160
Subjects with Suspected or Confirmed Pneumonia or Bacteremia	
Day 1 of illness	30
Day 2 of illness	10
Day 3 of illness	10
Day 4 of illness	20
Day 6 of illness and every other day through resolution (only for subjects positive for <i>S aureus</i> bacteremia)	10
Day of resolution	20

S aureus = *Staphylococcus aureus*.

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 MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune 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, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune 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 Independent Ethics Committee (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 IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Products

MedImmune will provide the investigators with investigational product (Table 4.5.1-1) using designated distribution centers.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI4893	MedImmune	[REDACTED]
Placebo	MedImmune	[REDACTED]

Investigational product should be stored at 2°C to 8°C.

Investigational product will be supplied to the site in open-labeled kits. Each kit has a unique number printed on all labels within the kit (ie, the outer carton label and the label of each vial).

Refer to Section 4.6.2 for information on coding of the container for blinding purposes.

4.5.1.1 Investigational Product Dose Preparation

Preparation of MEDI4893 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 MEDI4893 or placebo for investigational product preparation to start of administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new dose must be prepared from new vials and the study monitor must be notified *immediately*.

4.5.1.2 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. MEDI4893 is supplied as a solution at a concentration of [REDACTED] mg/mL.

If there are any defects noted with the investigational product, the Investigator and Site Monitor should be notified immediately. Refer to Section 4.5.1.6 for further instructions.

4.5.1.3 Dose Preparation Steps

The dose preparation steps are as follows:

1. The required volume of investigational product (MEDI4893 or placebo) will be prepared in [REDACTED]-mL infusion bags. Infusion bags should be composed of polyolefin, polyethylene, polypropylene, or ethylene vinyl acetate, and be free of latex, polyvinyl chloride (PVC), and di(2-ethylhexyl)phthalate (DEHP). Polypropylene syringes should be used for dose preparation.
2. To prepare investigational product, the investigational product manager should remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent and allowed to air dry. *To avoid foaming, the vial should not be shaken.*
3. From a [REDACTED]-mL infusion bag of 0.9% normal saline, withdraw and discard the entire contents of the bag using a syringe with no more than 2 punctures to the IV bag port.
4. To prepare the dose, the required volumes of investigational product and commercially available saline (Table 4.5.1.3-1) should be added either through an intermittent injection port that would allow multiple needle sticks, to the intermittent injection port, or by using a syringe with no more than 2 punctures to the IV bag port. For ease of preparation, a 1.5-inch 19-gauge withdrawal needle is recommended. Use a new needle for withdrawing investigational product from each vial.
5. Gently mix the contents of the infusion bag. The resulting mixture should be inspected to ensure that the solution is clear.

Table 4.5.1.3-1 Investigational Product Dose Preparation

Treatment Group	Capacity of Infusion Bag (mL)	Investigational Product Dose Volume (mL)	Number of Vials Required	Volume of Saline to be Added to Infusion Bag (mL)	Total Filled Bag Volume (mL)
[REDACTED] mg MEDI4893	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] mg MEDI4893	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Placebo	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

4.5.1.4 Treatment Administration

The day of dosing with investigational product is considered Day 1.

All subjects must receive the [REDACTED]-mL investigational product (MEDI4893 or placebo) solution IV through a dedicated line (either central or peripheral) until the entire investigational product solution has been infused. MEDI4893 or placebo must be administered through a low-protein binding 0.22-µm inline filter using an IV infusion pump over a minimum duration of [REDACTED] minutes. (Table 4.5.1.4-1). *MEDI4893 or placebo must never be administered via IV push or bolus.*

Table 4.5.1.4-1 Duration of Infusion by Treatment Group and Investigational Product Solution Volume

Treatment Group	Total Investigational Product Solution Volume Per Bag (mL)	Minimum Duration ^a of Infusion (min)
█ mg MEDI4893	█	█
█ mg MEDI4893	█	█
Placebo	█	█

^a If the maximum infusion duration exceeds 8 hours, the medical monitor must be notified *immediately* in case of such a delay.

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 █ mL, the IV tubing should be primed with █ 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 █ mL of 0.9% 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.

4.5.1.5 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 before the start of investigational product infusion (2 pre-dose blood pressure and heart rate readings should be obtained 5 minutes apart), every 30 minutes (± 5 minutes) during investigational product infusion, at completion of the infusion (± 5 minutes), every 30 minutes (± 5 minutes) for 2 hours after infusion of investigational product, and again 24 hours post dose.

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

4.5.1.6 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 product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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 label 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 MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorisation by MedImmune.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IVRS/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 IVRS/IWRS that the subject meets eligibility criteria and the IVRS/IWRS assigns a treatment arm and blinded investigational product kit number to the subject. The IVRS/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.

At study start, subjects were randomly assigned in a 1:1:1 ratio to receive a single IV dose of [REDACTED] mg MEDI4893, [REDACTED] mg MEDI4893, or placebo. After the DMC reviewed the PK interim analysis data, the DMC recommended that enrolment in the [REDACTED] mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [REDACTED] mg MEDI4893 and placebo groups. Thus, subsequent to Protocol Amendment 4, subjects will be randomised at a 1:1 ratio to receive either [REDACTED] mg MEDI4893 or placebo. Randomisation will be stratified by country and then by whether or not subjects received anti-*S aureus* systemic antibiotic (treatment for ≤ 48 hours) within the 72 hours prior to investigational product administration. Detailed instructions for the randomisation process will be provided in the IVRS manual.

The subject should be randomised no later than 6 hours after obtaining approval from the CCC. In case of a delay, the CCC should be contacted again to confirm that the subject still meets the requirements for randomisation.

Investigational product (MEDI4893 or placebo) infusion must be initiated the same day and within 6 hours after randomisation 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 be within 8 hours. In the event of a delay that prevents completion of infusion within 12 hours of start of investigational product preparation, the medical monitor must be notified immediately. Details of the administration procedure are presented in Section 4.5.1.4.

4.6.2 Methods for Ensuring Blinding

This is a double-blind study in which MEDI4893 and placebo are identical in appearance. 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 (ICH E9) (see Section 4.6.3.2 for unblinding related to interim analysis).

Investigational product will be handled by an unblinded investigational product manager at the site. An independent investigational product monitor will also be unblinded to perform investigational product accountability. 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 needs to be known to treat an individual subject for an AE, the investigator must notify the sponsor *immediately* and, if possible, before unblinding the treatment allocation. 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 should first attempt to contact the medical monitor, prior to unblinding the investigational product allocation for the 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 IVRS/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 and will occur after at least 10 subjects from each treatment group are followed through 30 days post dose. 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 or potential study termination as outlined in the criteria specified 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.

4.6.3.3 Unblinding for Stage 1 Analysis Purposes

The Stage 1 analysis will be conducted after the last subject has completed follow-up through 30 days post dose, and will be the primary analysis for efficacy. In this analysis, the safety, serum PK and ADA data will be summarised through 30 days post dose. In addition, all available data as of the data cut-off date will also be summarised. Description of this analysis is provided in Section 4.8.12. Sponsor personnel will be unblinded at this primary analysis. Study site personnel and the subjects will remain blinded to the treatment assignment of individual subjects until the last subject completes the study and the database is locked.

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 effective method of contraception for 190 days after receipt of investigational product;

cessation of contraception after this point should be discussed with a responsible 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
<ul style="list-style-type: none"> • Vasectomised sexual partner • Tubal occlusion • IUD 	<ul style="list-style-type: none"> • 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 = ethinyl estradiol; IUD = intrauterine device

4.7.2 Concomitant Medication

The Investigator must be notified as soon as possible about concomitant medication use. Any concomitant medication(s), including herbal preparations, taken from the time of screening through Day 91 must be reported to the Investigator and recorded. After Day 91 through end of study, only concomitant medication used to treat SAEs, AESIs, or NOCDs must be reported to the Investigator and recorded.

4.7.2.1 Permitted Concomitant Medications

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 Day 91. The sponsor must be notified in the event that a subject was to receive an investigational product.

4.8 Statistical Evaluation

4.8.1 General Considerations

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 to the 30-day post-dose follow-up will be included in the primary efficacy (ie, modified Intent-to-treat [mITT]) population as described in the primary efficacy analysis section below. Due to the decision to discontinue the lower dose arm, no dose adjustment will occur. The key efficacy analyses will be based on [REDACTED] mg MEDI4893 and placebo subjects. Subjects who received [REDACTED] mg MEDI4893 will be summarized descriptively.

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 randomized 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.

4.8.2 Sample Size and Power Calculations

Approximately 206 colonised subjects will be enrolled and randomised in a 1:1 ratio to one of 2 treatment groups: [REDACTED] mg MEDI4893 (N = 103) or placebo (N = 103). As the study is blinded, it is estimated that approximately 15 subjects may have already been enrolled and randomised in the [REDACTED] mg dose, prior to the decision of discontinuing this lower dose arm, making the total number of study subjects to be approximately 221.

[REDACTED]
[REDACTED] As such, a study with a sample size of N = 184 ([REDACTED] mg MEDI4893 [N = 92] or placebo [N = 92]) will allow 70% power at 2-sided significance level of $\alpha = 0.1$ to detect a

relative risk reduction 50% comparing [REDACTED] mg MEDI4893 versus placebo. A Poisson regression with robust variance ([Zou, 2004](#)) is employed in the calculation. A total of 221 subjects is derived when considering 10% attrition and adding an estimated 15 subjects in the [REDACTED] mg dose.

- [REDACTED]
[REDACTED] 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.

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

The percent reduction of incidence of *S aureus* pneumonia following administration of investigational product through 30 days post dose will be the primary efficacy endpoint. For subjects with multiple *S aureus* pneumonia events, only the first occurrence will be used in the primary analysis.

The primary analysis of the primary endpoint will be evaluated using the mITT Population. *S aureus* pneumonia that occurs prior to discontinuation will contribute to the primary efficacy analysis. If no *S aureus* pneumonia occurs prior to discontinuation, the subject will be considered as having no *S aureus* 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 *S aureus* pneumonia through 30 days post dose between [REDACTED] MEDI4893 and placebo, using the term of treatment group as a covariate. The primary analysis will be implemented using the SAS PROC GENMOD procedure with the REPEATED statement for subject ID and logarithm link. The percent of relative risk reduction $[(1 - \text{relative risk}) * 100\%]$, 2-sided p-value and corresponding 2-sided 90% CI around the estimated percent relative risk reduction will be provided from the model. Statistically significant treatment effect will be claimed if the 2-sided p-value ≤ 0.1 .

4.8.3.2 [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]

4.8.3.3 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.8.4 Safety

In the Stage 1 analysis, the safety data will be summarised by treatment group through 30 days post dose. In addition, all available data as of the data cut-off date will also be summarised. For Stage 2 analysis, safety data through 90 days post dose and through the end of the study will be summarised by treatment group. All safety analyses will be conducted using the As-treated Population.

4.8.4.1 Analysis of Adverse Events

Safety of MEDI4893 will primarily be assessed and measured by the occurrence of all TEAEs and TESAEs.

- Occurrence of AEs from the period immediately following administration of investigational product through 30 days and 90 days post dose
- Occurrence of SAEs from the period immediately following administration of investigational product through 190 days post dose
- Occurrence of AESIs to include targeted AEs of hepatic function abnormalities, anaphylaxis and serious allergic reactions (including hypersensitivity), infusion-related reactions, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis) from the period immediately following investigational product administration through 190 days post dose
- Occurrence of NOCDs from the period immediately following investigational product administration through 190 days post dose

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, hematology, and urinalysis) will be summarised from baseline through 30 days post dose.

4.8.5 [REDACTED]

[REDACTED]

[REDACTED]

4.8.6 Pharmacokinetics

Individual MEDI4893 concentrations in serum will be tabulated for all subjects by treatment group along with descriptive statistics through 90 days post dose. Individual MEDI4893 concentrations in tracheal aspirate will be assessed for intubated subjects who are intubated for any duration through 90 days post dose as an exploratory endpoint. Noncompartmental PK data analysis will be performed for MEDI4893 data obtained from treatment group with scheduled PK sample collection where data allows. Relevant descriptive statistics of noncompartmental PK parameters for MEDI4893 will be provided and may include area under the concentration-time curve, maximum observed concentration, clearance, and half-life.

4.8.7 Anti-drug Antibody Response

The immunogenic potential of MEDI4893 will be assessed by summarising the number and percentage of subjects who develop detectable ADAs in serum through 90 days post dose. The impact of ADA on PK will be assessed if data allow. Safety data will also be assessed in subjects with ADA.

4.8.8 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

PK profile of MEDI4893 in mechanically ventilated subjects in this study with healthy adult subjects dosed in the Phase 1 study (Study CD-ID-MEDI4893-1133). An independent DMC was responsible for recommending dose adjustment or potential study termination as outlined in the following criteria: If the [REDACTED] mg MEDI4893 dose serum concentrations on Day 31 were lower than the MEDI4893 serum target level of [REDACTED] $\mu\text{g/mL}$ in ≥ 2 subjects, a dose adjustment to [REDACTED] mg MEDI4893 was to be made; if the [REDACTED] mg MEDI4893 dose serum concentrations were lower than the MEDI4893 target level of [REDACTED] $\mu\text{g/mL}$ in ≥ 2 subjects, further enrolment was to be re-evaluated. After the DMC reviewed the interim analysis data (serum PK profiles of [REDACTED] and [REDACTED] mg MEDI4893), the DMC recommended that enrolment in the [REDACTED] mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [REDACTED] mg MEDI4893 and placebo groups instead of making a dose adjustment to [REDACTED] mg MEDI4893.

4.8.12 Planned Analysis

Two formal analyses (Stage 1 and Stage 2) are planned. The Stage 1 analysis will be conducted after the last subject has completed follow-up through 30 days post dose and will be the primary analysis for efficacy, for which the study is powered. During the Stage 1 analysis, all efficacy (ie, primary, secondary, [REDACTED] endpoints), serum PK, ADA, and safety data collected through 30 days post dose for the last subject enrolled will be analysed. The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study (ie, approximately 190 days post dose). During the Stage 2 analysis, safety, serum PK, and ADA through 90 days post dose will be analyzed. In addition, [REDACTED] [REDACTED] safety through study completion will be analysed.

5 ASSESSMENT OF SAFETY

For this study, AEs, SAEs, AESIs, and NOCDs will be assessed. Definitions, collection, and reporting are described in the subsections below.

5.1 Definition of Adverse Events

The International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) 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 (including electrocardiogram 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 requires close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious.

5.3.1 Hepatic Function Abnormality

Hepatic function abnormality meeting the definition of Hy's law is considered an AESI. Adverse events of hepatic function abnormality of special interest to the sponsor are defined as any increase in ALT or AST equal to or greater than $3 \times$ upper limit of normal (ULN) **and concurrent** increase in bilirubin equal to or greater than $2 \times$ ULN.

In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

5.3.2 Anaphylaxis and Serious Allergic Reactions (Including Hypersensitivity) and Infusion-related Reactions

Administration of polyclonal immunoglobulin preparations and mAbs have been associated with anaphylaxis and serious allergic reactions (including hypersensitivity) and infusion-related reactions that occur during or after dosing. 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). 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). 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 anaphylaxis and serious allergic reactions (including hypersensitivity) 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 oedema, bronchospasm, dyspnoea, tachypnoea, cyanosis, respiratory arrest, tachycardia, hypotension, arrhythmia, chest pain, ischemia or infarction, cardiac arrest, erythema, pruritus, urticaria, angio-oedema, maculopapular rash, nausea, vomiting, cramping, and diarrhoea ([Kang and Saif, 2007](#)).

It should be noted that all subjects in this study will be mechanically ventilated (and therefore intubated) at the time of study drug infusion. Although laryngeal oedema is considered a relatively common complication of intubation, it can also be a manifestation of hypersensitivity reaction, especially in subjects with prior hypersensitivity reaction to the investigational product. Therefore, subjects with prior hypersensitivity reaction to the investigational product should be closely monitored for any additional signs and symptoms of hypersensitivity, including (but not limited) to post-extubation laryngeal oedema.

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 New Onset Chronic Disease

New onset chronic disease is a newly diagnosed medical condition that is of a chronic, ongoing nature. It is observed after receiving the investigational product and is assessed by the investigator as medically significant. Examples of NOCDs include but are not limited to diabetes, asthma, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy). Events that would not be considered as NOCDs are mild eczema, diagnosis of a congenital anomaly present at study entry, or acute illness (eg, upper respiratory infection, otitis media, bronchitis).

5.5 Collection of Adverse Events

Adverse events will be recorded using a recognised medical term or diagnosis that accurately reflects the event. Adverse events 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 MedImmune Patient Safety. See Section 5.2 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.

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](#).

5.5.1 Time Period for Collection of Adverse Events

For any randomised subjects, AEs will be collected from time of signature of informed consent through Day 91 according to the schedule in [Table 4.2.1-1](#) and [Table 4.2.2-1](#). For screening failure subjects, AEs will be collected from time of signature of informed consent until they are a confirmed screen failure in IXRS.

All SAEs will be recorded from the time of informed consent through Day 191 according to the schedule in [Table 4.2.1-1](#) and [Table 4.2.2-1](#). Assessments for SAEs after Day 91 will be conducted by telephone contact.

Time period for collection of AESIs and NOCDs is presented in Section [5.5.3](#) and Section [5.5.4](#), respectively.

5.5.2 Follow-up of Unresolved Adverse Events

Any AEs/SAE(s) that are unresolved at the subject's last AE/SAE assessment in the study are followed up by the investigator until resolution, until the subject returns to baseline status, or until the condition has stabilised with the expectation that it will remain chronic, even if this extends beyond study participation. 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.

5.5.3 Collection of Adverse Events of Special Interest

Adverse events of special interest (which include hepatic function abnormality, anaphylaxis and serious allergic reactions, infusion-related reactions and immune complex disease) will be collected from the period immediately following investigational product administration through Day 191 according to the schedule in [Table 4.2.2-1](#).

5.5.3.1 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 the hepatic function abnormality is known (including progression of pre-existing disease), the diagnosis should be recorded as an AE or SAE per Section [5.5](#) or Section [5.6](#), 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 [5.5](#) or Section [5.6](#), respectively.

Medications used to treat these events should be recorded.

Events of hepatic function abnormality of unknown etiology or that are considered related to investigational product must be reported within 24 hours of knowledge of the event to MedImmune Patient Safety or designee (see Section 5.7.2).

5.5.3.2 Anaphylaxis and Serious Allergic Reactions (Including Hypersensitivity) and Infusion-related Reactions

Events of anaphylaxis and serious allergic reactions (including hypersensitivity) 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 Section 5.2, respectively). Medications used to treat these events should be recorded.

In order to characterise and understand their association with the investigational product, non-serious AESIs of allergic reactions (including hypersensitivity) and infusion-related reactions must be recorded within 48 hours of knowledge of the event into the eCRF.

5.5.3.3 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.

5.5.4 Collection of New Onset Chronic Disease

New onset chronic disease will be recorded using a recognised medical term or diagnosis that accurately reflects the event from the period after investigational product administration through Day 191 according to the schedule in Table 4.2.2-1. New onset chronic disease events will be assessed by the investigator for relationship to the investigational product. Events associated with NOCDs as defined in Section 5.4, should be recorded according to the definitions of AE and SAE (Section 5.1 and Section 5.2, respectively). Medications used to treat NOCDs should be recorded.

5.6 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 procedures. SAEs should not be reported for subjects once they have failed screening and are no longer being followed in the study.

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety or designee.

MedImmune or designee contact information:



The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements. The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

5.7 Other Events Requiring Immediate Reporting

5.7.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in this protocol (ie, [REDACTED] mg MEDI4893).

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported *within 24 hours of knowledge of the event* to MedImmune Patient Safety or designee using the Safety Fax Notification Form (see Section 5.6 for contact information). If the overdose results in an AE, the AE must also be recorded (see Section 5.5). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalisation, the event is serious and must be reported as an SAE (see Section 5.6). MedImmune does not recommend

specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

5.7.2 Hepatic Function Abnormality

An AESI of hepatic function abnormality (as defined in Section 5.3.1) of unknown etiology or that is considered attributable to investigational product, is required to be reported as “hepatic function abnormal” *within 24 hours of knowledge of the event* to MedImmune Patient Safety using the SAE Report Form, even if the event is considered to be non-serious (see Section 5.6 for contact information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor.

5.7.3 Pregnancy

Pregnancy in a female subject who has received investigational product is required to be reported *within 24 hours of knowledge of the event* to MedImmune Patient Safety or designee using the Safety Fax Notification Form (see Section 5.6 for contact information).

Subjects who become pregnant during the study period will not be withdrawn from the study. If the subject requests to know which treatment she received, this information will be provided to her. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety or designee after outcome.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported *within 24 hours of knowledge of the event* to MedImmune Patient Safety or designee using the Safety Fax Notification Form (see Section 5.6 for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative or designee 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 electronic case report forms (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 or designee 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 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).

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Sections 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] 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/GCP, and applicable regulatory requirements.

7.2 Subject Data Protection

The Informed Consent Form 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 IEC should approve the final study protocol, including the final version of the Informed Consent Form 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 IEC should be given in writing. The investigator should submit the written approval to MedImmune or designee before enrolment of any subject into the study.

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

MedImmune or designee should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

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

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

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

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

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

7.4 Informed Consent

The Principal Investigators at each centre will:

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

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 IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

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

If a protocol amendment requires a change to a site's Informed Consent Form, MedImmune or designee and the site's IEC are to approve the revised Informed Consent Form before the revised form is used.

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

7.6 Audits and Inspections

Authorised representatives of MedImmune, a regulatory authority, or an 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, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

8 REFERENCES

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9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

9.1 Protocol Amendment 1, 07Aug2014

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

1. The synopsis was updated to be consistent with the protocol body.
2. Section 3.1.1 (Overview): Text was added to indicate that enrolment will continue in only the [REDACTED] mg MEDI4893 and placebo arms while the interim analyses are being performed. A second interim analysis for futility assessment was added, to be conducted when approximately 33-40% of the enrolled subjects are followed through 30 days post dose.
3. Section 4.1.2 (Inclusion Criteria): Bilateral tubal ligation was stricken from the definition of surgical sterility in order to be consistent with Table 4.7.1-1.
4. Section 4.1.4 (Subject Enrolment and Randomisation): A statement was added to indicate that subjects who have failed screening may be rescreened.
5. Section 4.2.2 (Treatment and Follow-up Periods): Assessments of CPIS assessment, SOFA, PaO₂/FiO₂ ratio were removed from Table 4.2.2-1. Serum for biomarkers was added to Table 4.2.2-1 and Table 4.2.2-2. A footnote was added to Microbiology to clarify that if pleural fluid aspirate or lung tissue is obtained as part of a subject's necessary clinical management, the sample should also be sent for Gram stain and culture.
6. Section 4.3.1.4 (Definition of *S aureus* Pneumonia): Under Microbiologic confirmation, it was clarified that at least one of the bulleted confirmations (ie, not just the first bullet) should be obtained within 24 hours of onset of the event for mechanically ventilated subjects and within 72 hours of onset of the event for non-mechanically ventilated subjects.
7. Section 4.3.4 (Clinical Laboratory Tests): Leukocytes and nitrite were added to the list of urinalysis assessments.
8. [REDACTED]
9. Section 4.3.9 (Estimate of Volume of Blood to be Collected): Instructional text was deleted.


10. Section 4.5.1.4 (Treatment Administration): The instruction indicating that MEDI4893 administration should not exceed a rate of [REDACTED] mg/minute was deleted. Footnote a in Table 4.5.1.4-1 was modified to note that if the maximum infusion duration exceeds [REDACTED] hours, the medical monitor must be notified.
11. Section 4.6.3.3 (Unblinding for Futility Analysis Purposes): This section was added to indicate that the sponsor site personnel will remain blinded to the treatment assignment of individual subjects until the last subject completes the study and the database is locked and the sponsor personnel will remain blinded to the treatment assignment of individual subjects until the Stage 1 analysis (ie, primary analysis).
12. Section 4.7.2.2 (Prohibited Concomitant Medications): Other experimental/investigational drugs were prohibited through Day 91 and the sponsor must be notified in the event a subject were to receive an investigational product.
13. Section 4.8.2 (Sample Size and Power Calculations): The point at which the sample size may be modified was changed from after 40% to 50% of subjects are enrolled to after 33% to 40% of subjects are enrolled, and the sample size reassessment was to be performed prior to the futility assessment.
14. Section 4.8.3 (Efficacy): Subsections describing efficacy analyses were modified to indicate that *S aureus* systemic antibiotic use will be analyzed.
15. [REDACTED]
16. Section 4.8.10 (Data Review Committees): Under Data Monitoring Committee, the interim analysis for futility was added.
17. Section 4.8.11 (Interim Analyses): A description of the interim analysis for futility was added.
18. Appendix 2 (Additional Safety Guidance): Text was modified to correct the definition of Grade 4 (life threatening) AEs/SAEs to remove reference to disabilities, which was previously inadvertently added to this definition.

9.2 Protocol Amendment 2, 04Jun2015

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

1. Title Page: Information for Contract Research Organisation [REDACTED] was deleted.
2. The synopsis was updated to be consistent with the protocol body.
3. Section 1.4 (Summary of Clinical Experience): Text was updated with final clinical safety and PK data from the first-time-in-human Study CD-ID-MEDI4893-1133.

4. Figure 3.1.1.-1 (Study Flow Diagram): Text was modified to indicate that the DMC will review PK data and recommend dose adjustment or study termination during the interim analysis.
5. Section 4.1.2 (Inclusion Criteria): Text was modified to clarify the time window for positive samples for *S aureus*, and that the samples will be analyzed by PCR.
6. Section 4.1.3 (Exclusion Criteria): Criteria for SOFA score based on the GCS score was modified.
7. Section 4.1.4 (Subject Enrolment and Randomisation): Clarification was added regarding subjects who are considered for rescreening.
8. Section 4.1.8 (Withdrawal of Informed Consent for Data and Biological Samples; Samples Obtained for Future Research): Text was modified to reflect current practices.
9. Table 4.2.1-1 (Schedule of Screening Procedures): Text was modified to clarify that *S aureus* colonisation in tracheal or bronchial aspirates is evaluated by PCR.
10. Table 4.2.2-1 (Schedule of Treatment and Post-dose Follow-up Procedures): Text was modified to clarify that *S aureus* colonisation is evaluated by PCR. Oxygen status was added as a parameter to monitor for clinical symptoms/signs of pneumonia/serious *S aureus* infection, and a new footnote with examples of those parameters was also added.
11. Table 4.2.2-2: Title was changed from “Schedule of Procedures for Subjects with Suspected Serious *S aureus* Infection” to “Schedule of Procedures for Subjects with Suspected or Confirmed Pneumonia or Bacteremia.” It was also clarified that the term “resolution” refers specifically to “clinical resolution.” A new footnote defining the term “clinical resolution” was added.
12. Section 4.3.1.4 (Definition of *S aureus* Pneumonia): Text was modified to clarify that the criterion of dullness to percussion is not elicited by auscultation and it is a separate criterion. It was clarified that the acute changes in PaO₂/FiO₂ have to be maintained for at least 4 hours.
13. Section 4.3.4 (Clinical Laboratory Tests): Text was modified to include fasting glucose test.
14. Table 4.3.9-1 (Estimate Volume of Blood to be Collected per Visit): “Subjects with Suspected Serious *S aureus* infection” was replaced with “Subjects with Suspected or Confirmed Pneumonia or Bacteremia.”
15. Section 4.5.1.3 (Dose Preparation Steps): Ethylene vinyl acetate was added as an infusion bag material.
16. Section 4.6.3.1 (Unblinding in the Event of a Medical Emergency): It was clarified that the investigator should first attempt to contact the medical monitor prior to unblinding the investigational product allocation for an individual subject as long as this does not jeopardise the safety of the subject.
17. Section 4.6.3.2 (Unblinding for Interim Pharmacokinetic Analysis Purposes): Details regarding the PK analysis and presentation to the DMC were added to further describe how the DMC will recommend dose adjustments or potential study termination.
18. [REDACTED]

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19. Section 4.8.4.1 (Analysis of Adverse Events): “hypersensitivity (including anaphylaxis)” was replaced with “anaphylaxis and serious allergic reactions (including hypersensitivity).”
 20. Section 4.8.11 (Interim Analyses): It was added that the DMC will be responsible for recommending dose adjustment or potential study termination.
 21. Section 5.3.2: Title changed from “Hypersensitivity (including Anaphylaxis) and Infusion-related Reactions” to “Anaphylaxis and Serious Allergic Reactions (including Hypersensitivity) and Infusion-related Reactions.” In addition, definitions for anaphylaxis and infusion-related reactions, as well as signs and symptoms of anaphylaxis and serious allergic reactions (including hypersensitivity) were added. Information on the risk of post-extubation laryngeal oedema in subjects with prior hypersensitivity reaction to investigational product was also added.
 22. Section 5.5.3.2: Title changed from “Hypersensitivity (including Anaphylaxis) and Infusion-related Reactions” to “Anaphylaxis and Serious Allergic Reactions (including Hypersensitivity) and Infusion-related Reactions.” Text was also modified accordingly.
 23. Section 6.2.2 (Study Agreements): Text was modified to reflect current practices.

9.3 Administrative Change 1, 26Jun2015

1. Section 4.1.2 (Inclusion Criteria): Text was modified in criterion 7 to correct a typographical error.

9.4 Protocol Amendment 3, 14Aug2015

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

1. Table 4.2.1-1(Schedule of Screening Procedures): Table was modified to include tracheal/bronchial aspirates for both Gram stain and culture in the screening procedures.
2. Table 4.2.2-1 (Schedule of Treatment and Post-dose Follow-up Procedures): Tracheal/bronchial aspirates for Gram stain and for culture were deleted from the post-dose procedures.
3. Section 4.8.10 (Data Review Committees): Text was added to clarify that the adjudication committee may request to review all data relevant to a potential case, including radiographic and imaging studies, as well as other clinical and/or microbiologic data.

9.5 Protocol Amendment 4, 20Oct2016

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 4. Major changes to the protocol are summarised below:

1. Updated synopsis to be consistent with the protocol body.
2. [REDACTED]
3. [REDACTED]
4. Section 3.1.1 (Overview) and Section 3.2.2 (Dose Rationale): Modified text to reflect that an independent DMC reviewed the PK interim analysis data and per protocol, recommended that the [REDACTED] mg MEDI4893 group be discontinued and that a dose adjustment to [REDACTED] mg MEDI4893 should not be made, since the lower dose PK profile in mechanically ventilated subjects was well below the target drug exposure, thus unlikely to offer efficacy. In addition, modified text to reflect the new number of subjects that will be enrolled and randomized to one of 2 treatment groups: [REDACTED] mg MEDI4893 or placebo.
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-*S aureus* systemic antibiotic (treatment for ≤ 48 hours [rather than ≤ 24 hours]) within the 72 hours (rather than within the 48 hours) prior to randomization to align with the updated exclusion criterion 6 language. In addition, the restriction to ensure that no more than approximately 75% of the study population will consist of subjects in either stratification level of prior anti-*S aureus* systemic antibiotic treatment was removed. These changes were made in order to facilitate study enrolment and randomisation.
6. Section 3.1.1 (Overview), Section 4.8.2 (Sample Size and Power Calculations), and Section 4.8.11 (Interim Analyses): Modified text to reflect that as the [REDACTED] mg MEDI4893 will no longer be enrolled and randomized, the overall sample size of the study has been reduced. Consequently, due to the smaller overall sample size, futility analysis will be performed at a later time point based on the operating characteristics; thus, modified text to clarify that futility assessment will be conducted when 100-120 (40% to 50%) subjects enrolled are followed through 30 days instead of 33% to 40% of enrolled patients.
7. Figure 3.1.1 (Study Flow Diagram): Updated diagram to reflect the recommendations by the DMC. The study flow diagram now illustrates how the 2 treatment groups, [REDACTED] mg

MEDI4893 and placebo will continue to be enrolled and randomised in a 1:1 ratio (N = 135 for each treatment group). Additionally, modified diagram to reflect the new follow-up times of 190 days post dose.

8. Section 3.1.2 (Treatment Regimen), Section 4.1.1 (Number of Subjects), and Section 4.8.2 (Sample Size and Power Calculation): Modified text to reflect the new number of subjects who will be enrolled and randomised to one of 2 treatment groups: [REDACTED] mg MEDI4893 or placebo. For Section 3.1.2 (Treatment Regimen) only, a sentence was also added to explain that subjects who were enrolled and randomised into the [REDACTED] mg MEDI4893 group prior Protocol Amendment 4 will continue to be followed through the end of study. For Section 4.1.1 (Number of Subjects), a sentence was added to note the approximate number of subjects enrolled in the [REDACTED] mg dose.
9. Section 4.1.2 (Inclusion Criteria): Modified criterion 9 to reflect new follow-up times of 190 days post dose instead of 360 days.
10. Section 4.1.3 (Exclusion Criteria): Modified criterion 6 to exclude enrolment of subjects who receive anti-*S aureus* antibiotics for > 48 hours (instead of > 24 hours) within 72 hours (instead of 48 hours) prior to randomisation. Modified criterion 8 to exclude enrolment of subjects with SOFA score of ≥ 9 at time of randomisation and to clarify that vasopressors only used to improve cerebral perfusion pressure will not be entered in the calculation of the cardiovascular component of the SOFA score. Modified criterion 11 to allow enrolment of subjects with asymptomatic HIV infection. Modified criterion 14 to change the time frame for exclusion of patients receiving chemotherapy from 6 months to 2 months. All these changes were introduced to facilitate study enrolment and randomisation.
11. Table 4.2.2-1 (Schedule of Treatment and Post-dose Follow-up Procedures): Modified table to reflect the new follow-up times of 190 days post dose. Modified footnote 'd' to reflect that the call to CCC to confirm requirements for randomisation has to be made within 6 hours. A similar change was made to the text in Section 4.6.1 (Methods for Assigning Treatment Groups).
12. Table 4.2.2-2 (Schedule of Procedures for Subjects with Suspected or Confirmed Pneumonia or Bacteremia): Added a new footnote to the PK/ADA/Other Assessments to clarify the handling of samples taken for subjects with suspected pneumonia.
13. Section 4.3.1.4 (Definition of *S aureus* Pneumonia): Under *S aureus* Pneumonia Criteria for Subjects Who are Mechanically Ventilated at the Time of Diagnosis, clarified that in subjects who are not intubated but meet the protocol definition of mechanical ventilation, a specimen of expectorated sputum would be acceptable for microbiologic confirmation.
14. Section 4.3.1.4 (Definition of *S aureus* Pneumonia): Under *S aureus* Pneumonia Criteria for Subjects Who are Not Mechanically Ventilated at the Time of Diagnosis, clarified that a subject is not considered to be mechanically ventilated when an endotracheal or nasotracheal tube is not in place and that the subject does not require positive ventilation support for at least 8 hours.
15. Table 4.5.1.3-1 (Investigational Product Dose Preparation) and Table 4.5.1.4-1 (Duration of Infusion by Treatment Group and Investigational Product Solution Volume): Modified tables to remove information for the [REDACTED] and [REDACTED] mg doses, as subjects will no longer be enrolled at these dose levels.

16. Section 4.6.1 (Methods for Assigning Treatment Groups): Modified text to clarify DMC's recommendation to discontinue the [REDACTED] mg dose.
17. Section 4.8.1 (General Considerations): Modified text to clarify that no adjustments were made when the [REDACTED] mg dose was discontinued. In addition, the [REDACTED] mg dose was removed from the key efficacy analyses.
18. Section 4.8.2 (Sample Size and Power Calculations) and Section 4.8.3.4 (Exploratory Efficacy Analysis): The sample size methodology was modified to use Poisson regression with robust variance in order to be consistent with the planned primary efficacy analysis.
19. Section 4.8.3.1 (Primary Efficacy Analysis): Added text to clarify the use of covariates if the number of subjects in either stratum is too small.
20. Section 4.8.11 (Interim Analyses): Removed language mentioning that enrolment will resume in the lower dose arm after futility analysis as it is no longer applicable.
21. Section 5 (Assessment of Safety): Added text to clarify that AEs, SAEs, AESIs, and NOCDs are assessed in the study.
22. Section 5.3 (Definition of Adverse Events of Special Interest): The last sentence regarding rapid reporting was removed, in order to avoid confusion with the requirements for reporting stated in other sections.
23. Section 5.3.1 (Hepatic Function Abnormality): Updated text for Hy's law per new protocol template. Text that did not apply to this study was removed.
24. Section 5.5 (Collection of Adverse Events): Changed title from "Recording of Adverse Events" to "Collection of Adverse Events" for added clarity on the process.
25. Section 5.5.1 (Time Period for Collection of Adverse Events): Modified text to clarify the time of collection of AEs for subjects who had failed screening.
26. Section 5.5.3 (Collection of Adverse Events of Special Interest): Changed title from "Recording of Adverse Events of Special Interest" to "Collection of Adverse Events of Special Interest" for added clarity.
27. Section 5.5.3.2 (Anaphylaxis and Serious Allergic Reactions (Including Hypersensitivity) and Infusion-related Reactions): Update text to clarify when these events must be recorded in order to understand their association with the investigational product.
28. Section 5.5.4 (Collection of New Onset Chronic Disease): Changed title from "Recording of New Onset Chronic Disease" to "Collection of New Onset Chronic Disease" for added clarity.
29. Section 5.6 (Reporting of Serious Adverse Events): Modified text to clarify that SAEs should not be reported for subjects once they have failed screening and are no longer being followed in the study.
30. Appendix 6 (Sequential Organ Failure Assessment): Note added to clarify that vasopressors only used to improve cerebral perfusion pressure will not be entered in the calculation of the cardiovascular component of the SOFA score.

9.6 Protocol Amendment 5, 15Mar2018

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 5. Major changes to the protocol are summarised below:

1. Updated synopsis to be consistent with the protocol body.
2. [REDACTED]
3. [REDACTED]
4. [REDACTED]
5. [REDACTED]
6. Section 3.1.1 (Overview), Section 3.1.2 (Treatment Regimen), Section 3.2.2 (Dose Rationale), Section 4.1.1 (Number of Subjects), Section 4.8.2 (Sample Size and Power Calculations): Due to challenges with enrollment and the need to maintain the development timeline for MEDI4893, the total number of subjects planned to be enrolled was reduced from 285 to approximately 221.
7. Section 3.1.1 (Overview), Section 4.8.2 (Sample Size and Power Calculations), Section 4.8.10 (Data Review Committees – Data Monitoring Committee), and Section 4.8.11 (Interim Analysis): Text was modified to remove mentions of futility analysis, as the analysis would not be performed, since it would not be informative due to the smaller planned sample size.
8. Figure 3.1.1-1 (Study Flow Diagram): Figure caption text was updated with new enrollment numbers.
9. Section 4.1.5 (Withdrawal from Study): In the sub-section “Lost to Follow-up” text was modified to clarify that subjects will be considered lost to follow-up if no contact has been established by the time the subject’s last protocol-specified visit assessment has been reached, instead of when the entire study is completed.
10. Section 4.1.7 (Replacement of Subjects): Text was modified to indicate subjects will not be replaced.
11. Table 4.2.2-1 (Schedule of Treatment and Post-dose Follow-up Procedures): For the parameter “Monitor for clinical symptoms/signs of pneumonia/serious *S aureus* infection (physical exam, vital signs, oxygen status, as indicated),” the footnote stating that the CPIS was to be assessed daily while the subject remained on mechanical ventilation, was removed since it was not meant to be a mandatory assessment. [REDACTED]

- [REDACTED]
12. Table 4.2.2-2 (Schedule of Procedures for Subjects With Suspected or Confirmed Pneumonia or Bacteremia): In footnote “a” text was added to clarify that for subjects with an onset of a suspected pneumonia or bacteremia from Days 2 through 31, assessments will be collected at onset and through resolution of disease, even if it extends past Day 31.
 13. [REDACTED]
 14. Section 4.6.3.3 (Unblinding for Futility Analysis): This section was removed completely as no futility analysis will be performed.
 15. Section 4.6.3.4 (Unblinding for Stage 1 Analysis Purposes): Text was modified to indicate that Stage 1 analysis will be conducted after the last subject has completed follow-up through 30 days post dose (instead of 90 days), and that this analysis will be the primary analysis for efficacy only. In addition, it was clarified that the safety, serum PK and ADA will be summarized through 30 days post dose. New text regarding the Stage 1 analysis was also included in Section 3.1.1 (Overview), Section 4.8.4 (Safety), and Section 4.8.12 (Planned Analysis). These changes were introduced to keep with the development timelines for MEDI4893.
 16. Section 4.8.1 (General Considerations): The primary analysis population was changed from the ITT population to the mITT population to account for those subjects who were randomized and not dosed. In addition, under sub-Section Analysis Populations, a definition for the mITT population was added.
 17. Section 4.8.2 (Sample Size and Power Calculations): Text was modified to change the power calculation number from 80% to 70%, due to the smaller planned sample size. Text describing sample size reassessment was removed.
 18. Section 4.8.3.1 (Primary Efficacy Analysis): Per feedback from regulators, text was modified to indicate that the stratification factors for country and prior systemic antibiotics will not be included in the analysis model. Further clarification regarding the analysis was also added.
 19. [REDACTED]
 20. Section 4.8.4 (Safety), Section 4.8.12 (Planned Analysis): Text was modified to indicate that for Stage 2 analysis safety data will be summarized through 90 days post dose and through the end of the study. These changes were introduced to keep with the development timelines for MEDI4893.

Appendix 1 Signatures

Sponsor Signature

A Phase 2 Randomised, Double-blind, Placebo-controlled, Single-dose, Dose-ranging Study
of the Efficacy and Safety of MEDI4893, a Human Monoclonal Antibody Against
Staphylococcus aureus Alpha Toxin in Mechanically Ventilated Adult Subjects

I agree to the terms of this protocol.

Signature and date: _____

Clinical Development Therapeutic Area Head


One MedImmune Way, Gaithersburg MD, 20878, USA

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

A Phase 2 Randomised, Double-blind, Placebo-controlled, Single-dose, Dose-ranging Study
of the Efficacy and Safety of MEDI4893, a Human Monoclonal Antibody Against
Staphylococcus aureus Alpha Toxin in Mechanically Ventilated Adult Subjects

I agree to the terms of this protocol.


Signature and date



Senior Director, Clinical Research and Development

Infectious Disease and Vaccines, MedImmune

One MedImmune Way, Gaithersburg MD, 20878, USA



Signature of Coordinating Principal Investigator

A Phase 2 Randomised, Double-blind, Placebo-controlled, Single-dose, Dose-ranging Study of the Efficacy and Safety of MEDI4893, a Human Monoclonal Antibody Against *Staphylococcus aureus* Alpha Toxin in Mechanically Ventilated Adult Subjects

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 Independent Ethics Committee (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 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



Site/Center number (if available) _____

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 Randomised, Double-blind, Placebo-controlled, Single-dose, Dose-ranging Study of the Efficacy and Safety of MEDI4893, a Human Monoclonal Antibody Against *Staphylococcus aureus* Alpha Toxin in Mechanically Ventilated Adult Subjects

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Signature and date: _____

Name and title: _____

Address including postal code: _____

Telephone number: _____

Site/Center Number (if available) _____

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.

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.
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 nontreatment-emergent SAEs (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 (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) Guidance for Anaphylaxis Diagnosis

This definition was a product of a symposium convened by the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network ([Sampson et al, 2006](#)). 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, hypoxemia)
 - b. Reduced blood pressure (see #3 below for definition) 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 subject (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 blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours); for adults a systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that subject's baseline blood pressure (taken at or immediately prior to start of the infusion), whichever blood pressure is lower.

Appendix 4 Clinical Pulmonary Infection Score

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

ABG = arterial blood gas; APS = Acute Physiology Score; CHE = Chronic Health Evaluation; GCS = Glasgow Coma Scale; 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	≥5.0 <500 mL/day <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 PaO₂ and FiO₂

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



