Statistical Analysis Plan Approval

Date: *17Feb2020*
To: Study File
From: Redacted
Re: Statistical Analysis Plan Approval for Study *D5470C00004*

The Statistical Analysis Plan, version 3, for Study *D5470C00004* has been reviewed and approved.

Name:	Redacte	Signature:	Redacted 17 February 2020
Role:	Statistician	Date:	
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Statistical Analysis Plan

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

Protocol Number: D5470C00004

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

List of Abbreviations

Abbreviation or Specialized Term	Definition
ACC-AHA	American College of Cardiology/American Heart Association classification
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
APACHE II	Acute Physiology and Chronic Health Evaluation II
ATP	according to protocol
BMI	body mass index
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CLSI	Clinical and Laboratory Standards Institute
CPIS	Clinical pulmonary infection score
CRP	C reactive protein
CSR	clinical study report
DBL	database lock
DMC	Data Monitoring Committee
EAC	endpoint adjudication committee
eCRF	electronic case report form
ECG	electrocardiogram
EU	European Union
GOLD	Global initiative for chronic Obstructive Lung Disease classification
HADS	hospital anxiety and depression scale
ICU	intensive care unit
Ig	immunoglobulin
IM	immunogenicity
ITT	intent-to-treat
IV	intravenous
IXRS	interactive voice/web response system
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation or Specialized Term	Definition
NYHA	New York Heart Association functional classification
P aeruginosa	*Pseudomonas aeruginosa*
P_aO_2/F_iO_2	ratio of partial pressure arterial oxygen and fraction of inspired oxygen
PT	preferred term
PK	pharmacokinetics
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SID	subject identification number
SOC	system organ class
SOFA	sequential organ failure assessment
SPP	statistical programming plan
SSR	Sample size re-estimation
TFL	tables, figures and listings
VAP	Ventilator-associated pneumonia
WBC	white blood cell

1 INTRODUCTION

This document describes the statistical analysis for protocol D5470C00004, a proof-of-concept study to evaluate the efficacy and safety of MEDI3902 in mechanically ventilated patients for the prevention of nosocomial pneumonia caused by *Pseudomonas aeruginosa*.

A separate Statistical Programming Plan (SPP) will be created to give details for the planned Tables, Figures and Listings for this study.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

1 To evaluate the effect of MEDI3902 in reducing the incidence of nosocomial pneumonia caused by *P aeruginosa*

2 To evaluate the safety of a single IV dose of MEDI3902 in mechanically ventilated patients

2.1.2 Secondary Study Objectives

1 To evaluate the serum pharmacokinetics (PK) of MEDI3902

2 To evaluate the serum ADA responses to MEDI3902

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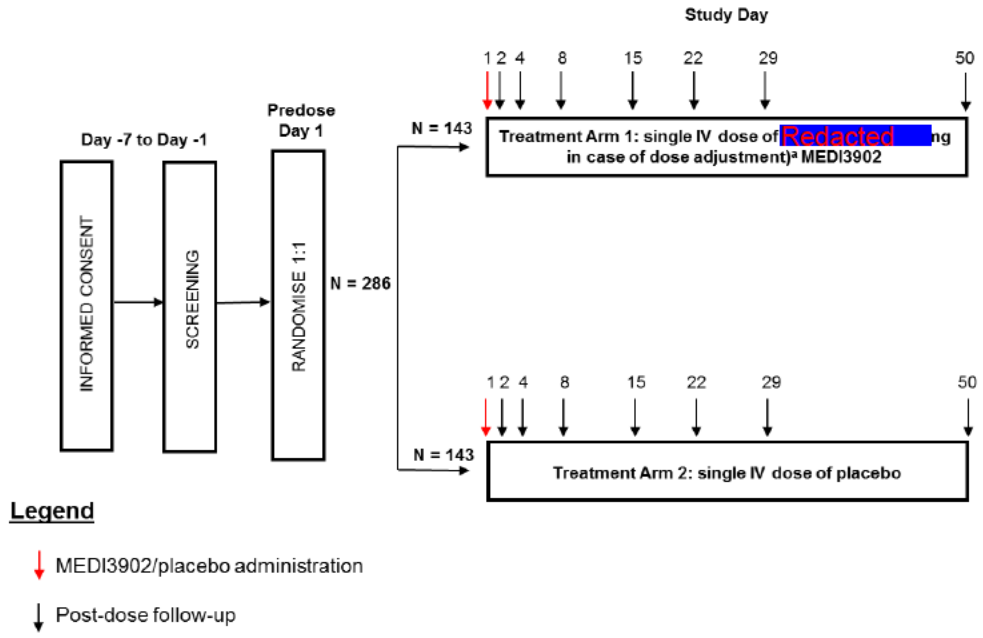
2.2 Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, single-dose, dose-ranging, proof-of-concept study evaluating 2 dosage levels of MEDI3902 in mechanically ventilated patients in the intensive care unit (ICU) who are at high risk for *P aeruginosa* infections and who are currently free of *P aeruginosa*-related disease but are colonised with *P aeruginosa* in the lower respiratory tract. At study start, approximately 429 subjects were to be enrolled and dosed at approximately 120 sites primarily in Europe. Subjects were to be randomly assigned in a 1:1:1 ratio to receive a single IV dose of [redacted] or [redacted] mg MEDI3902, or placebo. However, based on data from a separate study in a similar population with another monoclonal antibody, data from a PK study in mice (see Protocol Section 3.2.1) and from simulation results using data from the Phase 1 study (Study D5470C00002), a single dose of [redacted] mg MEDI3902 is not expected to maintain the target level of [redacted] µg/mL for 21 days. Therefore, enrolment in the [redacted] mg MEDI3902 group will be discontinued. Approximately 286 subjects will be randomized in a 1:1 ratio to one of 2 treatment groups, [redacted] mg MEDI3902 or placebo (N = 143 for each treatment group).

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

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

Randomization will be stratified by country and by whether subjects received anti-*P aeruginosa* antibiotic treatment (no antibiotics use, duration of $\leq$ 72 hours, duration > 72 hours) within the 96 hours prior to randomization. Subjects will be followed through Day 50.



Redacted; IV = intravenous; N = number of subjects; PK = pharmacokinetics

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

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

2.3 Treatment Assignment and Blinding

An interactive web response system (IWRS) will be used for randomization to a treatment group and assignment of blinded investigational product kit number. Subjects will be randomized at a 1:1 ratio to receive either MEDI3902 Reda mg or placebo (or in case of dose adjustment Reda mg MEDI3902). Randomization will be stratified by country and by whether subjects received anti-*P aeruginosa* antibiotic treatment (no antibiotics use, duration of ≤ 72 hours, duration of > 72 hours) within the 96 hours prior to randomization.

2.4 Sample Size

Approximately 286 colonised subjects will be enrolled and randomly assigned (1:1 ratio) to Reda mg MEDI3902 (n = 143) or placebo (n = 143). In case of a dose adjustment from Reda mg to Reda mg MEDI3902, approximately 143 subjects will be randomized to receive the Reda mg MEDI3902 dose to maintain 1:1 ratio with the placebo group. Subjects who have

been enrolled and randomized in the Re mg and Reda mg MEDI3902 groups will be followed until the end of the study period (Day 50).

Key assumptions used for sample size/power calculations: placebo group *P aeruginosa* pneumonia incidence 20%, relative reduction 50%, at least 80% power, 20% adjustment for attrition. Relative reduction of 50% was recommended to Sponsor as a clinically meaningful effect by experts in critical care, pulmonary medicine, and infectious diseases.

Statistical methods: power calculations are based on Poisson regression with robust variance comparing MEDI3902 versus placebo, 2-sided, with $\alpha = 0.2$.

2.4.1 Blinded Sample Size Re-estimation

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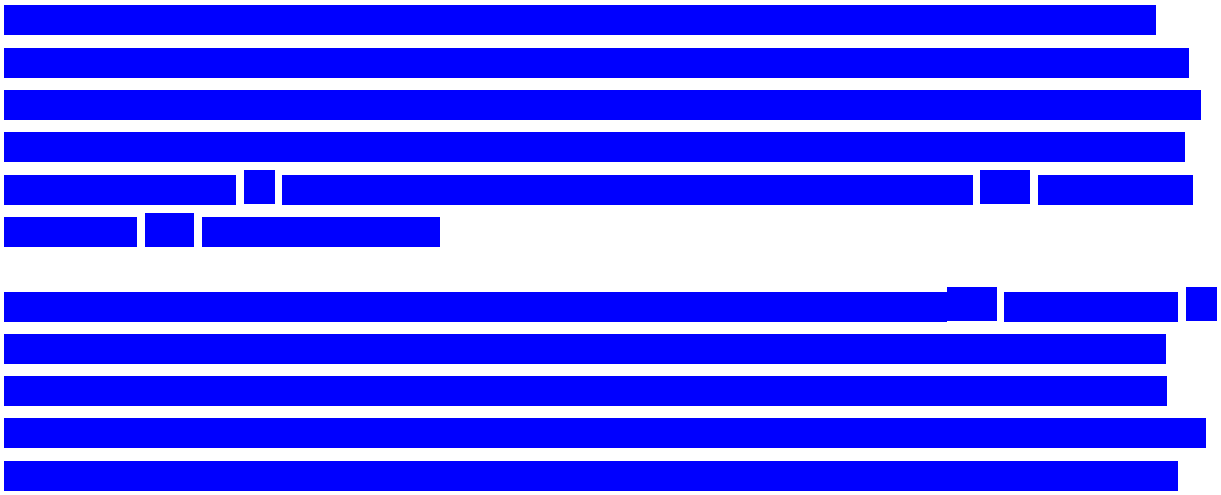

3 STATISTICAL METHODS

3.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject identification number (SID). Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. No multiplicity adjustments will be made to any of the analyses. In general, unless stated otherwise, baseline will be defined as the last value prior to dosing.

The key efficacy analyses will be based on Reda mg MEDI3902 and placebo subjects. Subjects who received Red mg MEDI3902 will be summarized descriptively for both efficacy and safety.

All statistical tests will be 2-sided at an alpha = 0.2 significance level unless stated otherwise.

Data analyses will be conducted using the SAS® System Version 9.3 or higher (SAS Institute Inc., Cary, NC) in a UNIX platform.

3.2 Analysis Populations

The analysis populations are defined in Table 1.

Table 1 Analysis Populations

Population	Description
ITT	All subjects who are randomized. Subjects will be analyzed according to their randomized treatment group.
modified ITT (mITT) population	Subjects who receive any study investigational product will be included in the mITT population and subjects will be analyzed according to their randomized treatment group.
As-Treated population	Subjects who receive any study investigational product will be included in the As Treated population and subjects will be analyzed according to the treatment they actually receive.

ITT = intent-to-treat

3.3 Strata

Many analyses are presented by, or adjusted for, the stratification factor 'anti-*P aeruginosa* antibiotic treatment (no antibiotics use, duration of ≤ 72 hours, duration of > 72 hours) within the 96 hours prior to randomization'. For subjects who were assigned to an incorrect stratum at randomization, the stratum recorded on the electronic case report form (eCRF) will differ from the stratum recorded for the subject in the IXRS database. Unless stated otherwise, the stratum on the eCRF will be used.

3.4 Study Subjects

3.4.1 Subject Disposition and Completion Status

Subject disposition will summarise the total number of subjects screened and the reasons for screen failure: did not meet inclusion/exclusion criteria, lost to follow-up, withdrawal of consent, and other. The summary will also include the number of subjects randomized, the number of subjects randomized and dosed, and the number of subjects randomized and not dosed and the reason the subject was not dosed: AE, or other. The summary of subject status at the end of the study will include the number and percentage of subjects who completed the study (i.e. completed the Day 50 follow-up visit) and the number and percentage of subjects who discontinued the study due to reasons such as: lost to follow-up, withdrawal of consent, death, or other. This summary will be presented by treatment group, for MEDI3902 total, and for all subjects combined. The denominators for this summary will include all subjects who were randomized and dosed.

A further summary showing eligibility of subjects for each of the study analysis populations will be provided. The denominator for this summary will include all subjects who were randomized into the study.

3.4.2 Demographics and Baseline Characteristics

Enrolment will be summarized by site and by country and site for each treatment group, for MEDI3902 total, and for all subjects combined. The total number of subjects randomized into each treatment group will be used as the denominator.

Enrolment will also be summarized by country and pre-dose anti-*P aeruginosa* antibiotic stratum for each treatment group, for MEDI3902 total, and for all subjects combined. The total number of subjects in the mITT population will be used as the denominator. The number of mis-stratified subjects (i.e. the true pre-dose anti-*P aeruginosa* antibiotic recorded on the eCRF does not match the IXRS database) will be noted. This will be done for each country as well as for all countries combined.

Demographic will be summarized in the intent-to-treat (ITT) and the modified intent-to-treat (mITT) population by treatment group, for MEDI3902 total, and for all subjects combined. Subjects will be excluded from the summary (e.g. means and percentages) of an individual parameter if data are missing.

Demographic information related to gender, age (years), age category (< 65 years, ≥ 65 years), ethnicity, race, weight (kg), height (cm), body mass index (BMI) (kg/m^2), and BMI category (≤ 30, > 30) will be summarised. Actual weight will be recorded when available. If actual weight is not available, estimated weight will be recorded. BMI will be calculated based on the weight (actual or estimated) provided.

Baseline characteristics (i.e. clinical severity scores, comorbidities, risk factors within the last 3 months prior to randomization, and ventilator associated pneumonia (VAP) prevention) will be summarized for subjects in the mITT population by treatment group, for MEDI3902 total, and for all subjects combined. Subjects will be excluded from the summary (e.g. means and percentages) of an individual parameter if data are missing.

Summaries of clinical severity scores at baseline (defined as the last assessment prior to dosing) will include Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Clinical Pulmonary Infection Score (CPIS). For CPIS and SOFA, the total scores are sums of the individual score components, respectively. For any component which is 'Not Done', a total score cannot be calculated. For APACHE-II, the total score is the sum of A+B+C, where (A) = Acute Physiology Score (APS) Points, (B) = Age points, and (C) = Chronic Health Points. The calculation for APS Points (A) is below:

- Total APS Points = [Temperature + Mean Arterial Pressure + Heart Rate + Respiratory Rate + [((A-aDO2 or PaO2) + Arterial pH) or Serum HCO3] + Serum Sodium + Serum potassium + Serum creatinine + Hematocrit + WBC + Glasgow Coma Scale Score]

- If Arterial Blood Gas (ABGs) are not performed (ie, no result for Oxygenation (both AaDo2 and PaO2 are 'Not Done') and Arterial pH is 'Not Done'), use the serum HCO3 value in the APS Score calculation. If Oxygenation and Arterial pH are both 'Not Done' and serum HCO3 is also 'Not Done', APS points cannot be calculated and therefore, APACHE-II cannot be calculated.

The following comorbidities will be summarized:

- Chronic obstructive pulmonary disease (COPD)
- Congestive heart failure (CHF)
- Severe COPD (GOLD Stage III/IV) without advanced CHF
- Advanced CHF (NYHA Class III/IV or ACC-AHA Stage C/D) without severe COPD
- Both severe COPD and advanced CHF
- Any other comorbidity:
  - Coronary Artery Disease (including Myocardial Infarction)
    - Angina (chest pain/discomfort)
    - History of angioplasty
  - Peripheral vascular disease
  - Cerebrovascular disease
  - Hypertension
  - Chronic liver disease
  - Diabetes
  - Pulmonary artery hypertension
  - Renal insufficiency or renal failure
  - Thoracic malignancy or any malignancies
  - Known immunodeficiency

The Minimum Inhibitory Concentration (MIC) Clinical and Laboratory Standards Institute (CLSI) susceptibility profile of *P aeruginosa* strain in tracheal aspirate at baseline will summarize multidrug-resistant (MDR), extensively drug-resistant (XDR), pandrug-resistant (PDR), and non-MDR. Baseline is defined as the last value prior to dosing.

Risk factors history within 3 months prior to randomization will summarise supplemental oxygen use prior to hospital admission, history of previous staph infections or colonization, history of *P aeruginosa* infections or colonization, history of other infection(s) (which required either oral or IV antibiotic) (yes/no), antibiotic usage (yes/no), hospitalized (yes/no), and resided in long term care prior to hospitalization (yes/no).

VAP prevention measures at baseline will summarise elevation of the head of the bed (yes/no), daily 'sedation vacations' and assessment of readiness to extubate (yes/no), peptic

ulcer disease prophylaxis (yes/no), deep venous thrombosis prophylaxis (yes/no), daily oral care with chlorhexidine (yes/no), and all 5 measures used (yes/no).

3.4.3 Study Drug Exposure

The amount of investigational product infused will be summarized by milligrams (mg) for subjects in the 'As-Treated' population by treatment group. The actual total amount of investigational product infused will be calculated based on the treatment group to which the subject was assigned and the dose intensity. If the entire dose was administered, the dose intensity will be assumed to be 100%. If the entire dose was not administered, dose intensity will be calculated as a percentage of actual volume of investigational product given (mL) against the volume that was intended to be administered (ie, 100 mL). The actual total amount of investigational product infused (mg) = dose intensity * treatment group (mg). For this study, the IV treatment group is either Re mg, orReda mg orR mg Redacte R

An additional table will summarise the number of infusion interruptions and the median length of interruptions (minutes).

3.5 Efficacy Analyses

3.5.1 Primary Efficacy Endpoint and Analyses

3.5.1.1 Primary Efficacy Endpoint

The primary endpoint is the incidence of nosocomial pneumonia caused by *P aeruginosa* (as determined by the Endpoint Adjudication Committee [EAC]) through 21 days postdose. For subjects with multiple *P aeruginosa* pneumonia events, only the first occurrence will be used in the primary analysis. Subjects with mixed culture results, which include *P aeruginosa,* will be counted towards the primary endpoint.

The analysis of *P aeruginosa* pneumonia rates will be based on the protocol-specified definition as described in the Protocol (Section 4.3.1.4). The EAC will determine the onset and resolution date and time of the *P aeruginosa* pneumonia event. In general, the onset will be the date and time when the first criteria were met (ie, radiographic, clinical, or microbiologic). For clinical criteria, for example, if a subject starts with fever, then the next day develops purulent secretions and meets the radiographic and microbiologic criteria later, the date of onset would typically be the date of the fever, subject to EAC review.

3.5.1.2 Handling of Dropouts and Missing Data

It is anticipated that the main cause of missing data for the primary analysis will be subjects who discontinue early as a result of death due to their underlying disease in the ICU. If no *P aeruginosa* pneumonia occurs prior to discontinuation, the subject will be considered having no *P aeruginosa* pneumonia infection in the primary efficacy analysis. No other imputation will be applied to the primary efficacy analysis.

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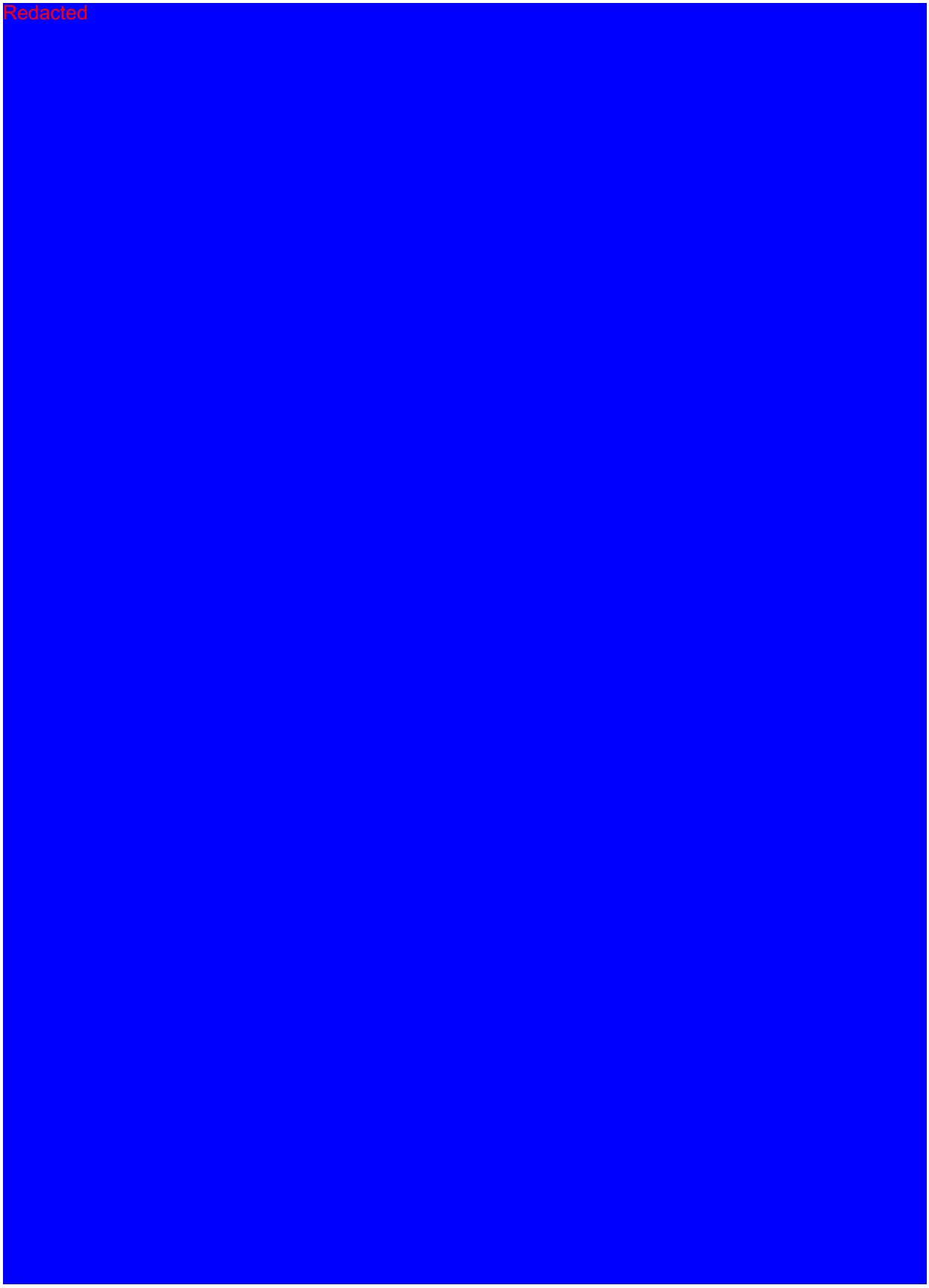
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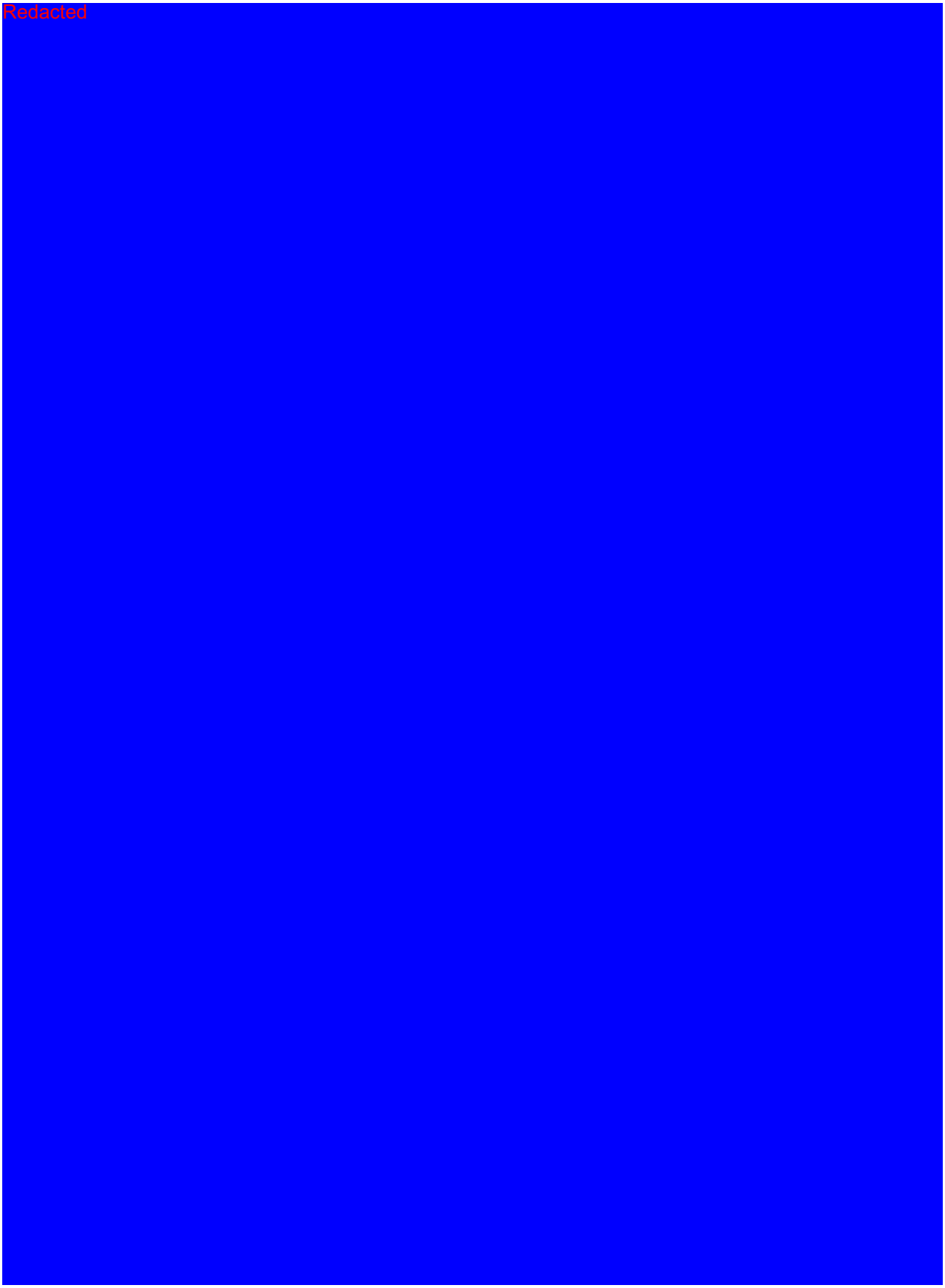

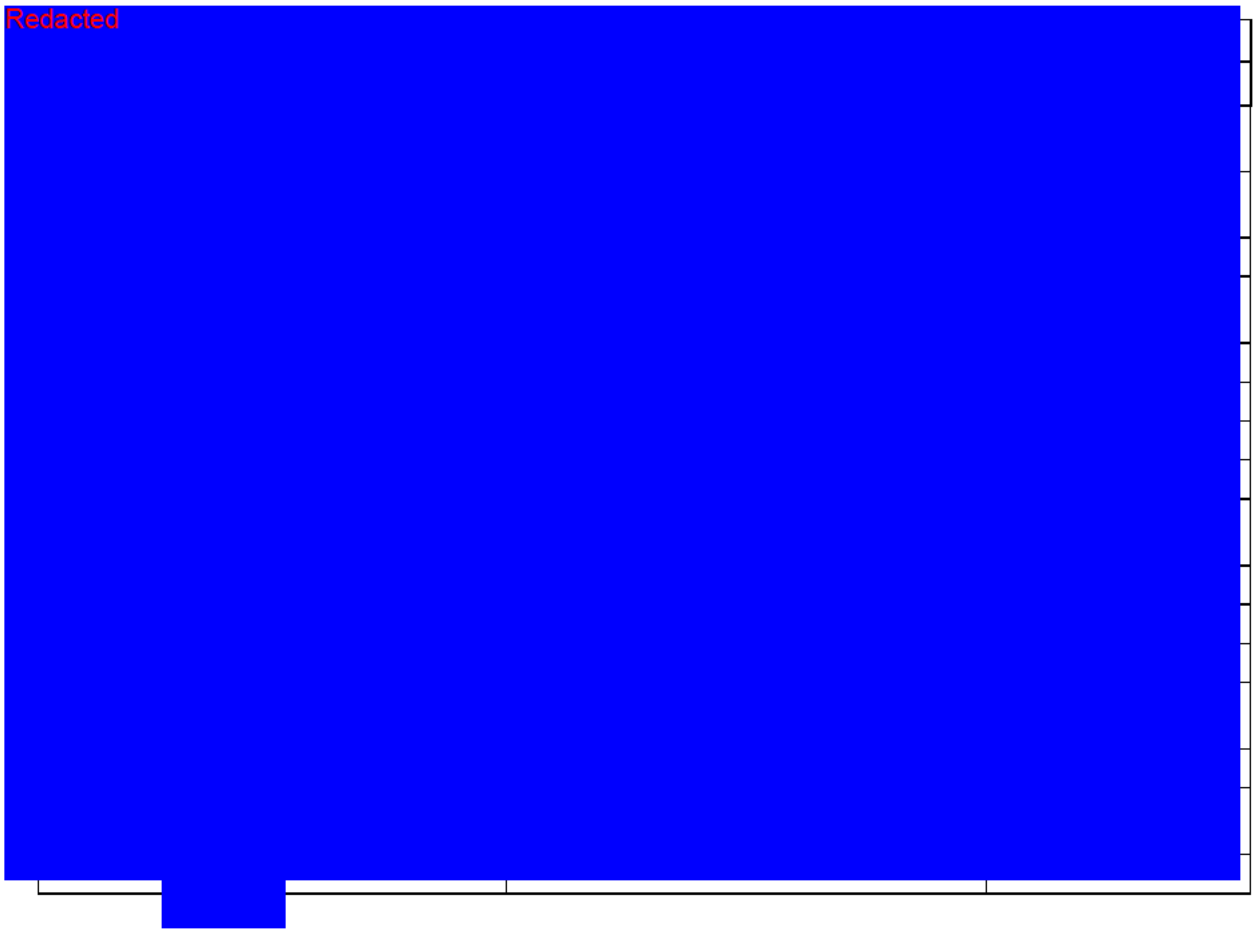

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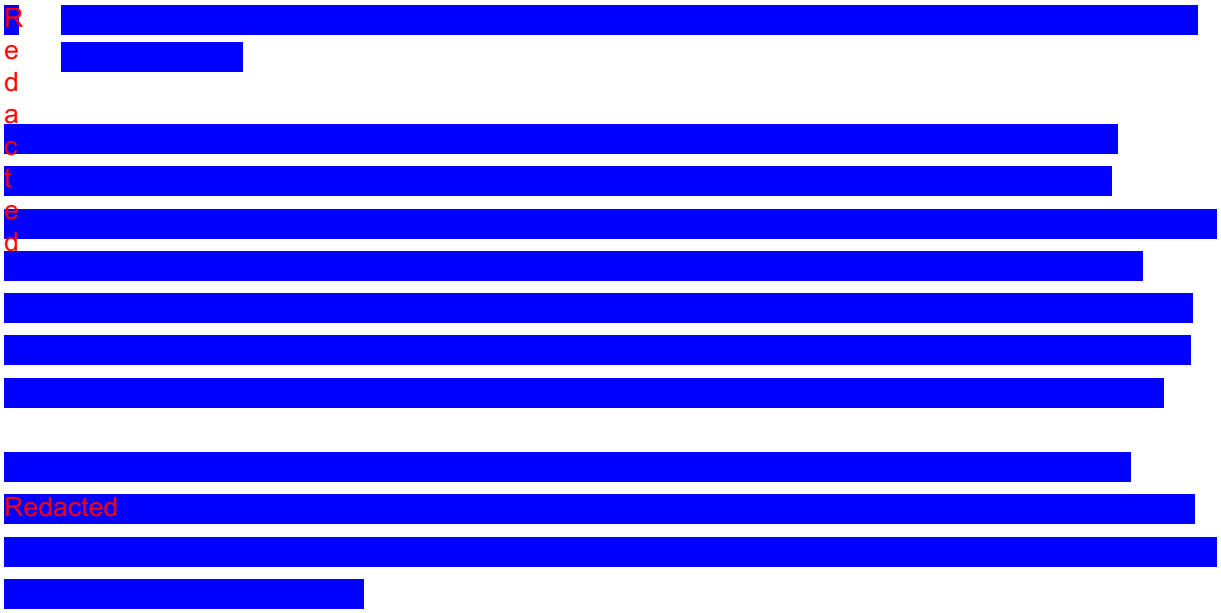

3.8 Safety Analyses

3.8.1 Adverse Events and Serious Adverse Events

Adverse events (AEs) will be coded by MedDRA version 21.0 and the type incidence, severity and relationship to study investigational product will be summarized for subjects in the As-treated population by treatment group and for MEDI3902 total. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same adverse event occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. All TEAEs will be summarized overall, as well as categorized by MedDRA System Organ Class and Preferred Term.

Serious Adverse Events (SAEs) will be summarized for each treatment group by MedDRA System Organ Class (SOC) and Preferred Term (PT).

The overall summary of AEs will summarise the number and percentage of subjects with at least one event, at least one investigational product related event, at least one event with at least Grade 3 severity, death due to AEs, at least one SAE, at least one serious and/or at least one Grade 3 severity event, at least one investigational product related serious event, at least one event leading to discontinuation of investigational product, at least one AESI, at least one investigational product related AESI, and at least one AESI >= Grade 3 severity.

3.8.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will include targeted AEs of hypersensitivity (including anaphylaxis), infusion-related reactions, hepatic function abnormalities, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, arthralgias) and will be summarized by treatment group and for MEDI3902 total

overall, and by SOC and PT based on MedDRA. Additional groupings may be added by the Medical Monitor if warranted.

An additional table will summarise duration and time to onset from dosing start for AESIs including hypersensitivity reactions, infusion related reactions and anaphylactic reactions.

3.8.3 Deaths and Treatment Discontinuations due to Adverse Events

AEs that resulted in death and AEs that led to discontinuation of study treatment will be summarized for each treatment group by SOC and PT.

3.8.4 Clinical Laboratory Evaluation

Laboratory parameters will be summarized for subjects in the As-treated population by treatment group and for MEDI3902 total as observed and change from baseline. Frequencies of worst observed toxicity and Grade 3-4 toxicities, as defined by NCI CTCAE, 2010, v4.03, will be presented for each laboratory parameter by treatment group and for MEDI3902 total.

Also, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts from baseline.

For laboratory values reported as lower than the lower limit of quantification (LLOQ), a value equal to half of the limit of quantification will be imputed in the summaries. However, < LLOQ will be reported in the listings.

3.8.5 Other Safety Evaluations

Additional data collected throughout the study include important protocol deviations, screen failure data, significant findings in medical history and physical exam, vital signs, chest X-ray, oxygenation status, oxygen log, microbiology data, antibiotics, and concomitant medications through 49 days post dose.

Data listings will be provided and no formal analyses will be conducted on these data. Upon review of the listings, additional summary tables may be generated as appropriate.

3.9 Antidrug antibody Response

The number and percentage of subjects who develop anti-MEDI3902 antibodies will be summarized at each visit by treatment group and for MEDI3902 total. Subjects will be excluded from the summary of an individual visit if data to that specific visit are missing. For those with a positive assessment or borderline positive assessment, the ADA titer results will also be summarized. Antidrug antibody values reported as borderline positive (ie, ≤ LLOQ), a value equal to LLOQ will be imputed in the summaries. An additional table will summarise the number and percentage of subjects positive for ADA at baseline (ie, ADA prevalence) and positive at any post-baseline time point (ie, ADA incidence). For those with a positive post-

baseline assessment, the percentage who were persistent positive and transient positive will also be presented.

5. Persistent positive is defined as positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment.
6. Transient positive is defined as negative at last post-baseline assessment and positive at only one post-baseline assessment or at ≥ 2 post-baseline assessments (with < 16 weeks between first and last positive).

AEs will be summarized by SOC and PT based on MedDRA for subjects with ADA to MEDI3902 at any time post-baseline. The impact of ADA on PK will be included in the PK report as mentioned in Section 3.10.

3.10 Pharmacokinetics

Individual MEDI3902 concentrations in serum will be tabulated for all subjects by treatment group along with descriptive statistics through 49 days post dose. Individual MEDI3902 concentrations in tracheal aspirate will be assessed for intubated subjects who are intubated for any duration through 21 days post dose as an exploratory endpoint. Noncompartmental PK data analysis will be performed for MEDI3902 data obtained from treatment group with scheduled PK sample collection where data allows. Relevant descriptive statistics of noncompartmental PK parameters for MEDI3902 will be provided and may include area under the concentration-time curve, maximum observed concentration, clearance, volume of distribution and half-life.

The details of the analyses and presentation of these data will be included in a separate PK Report.

4 INTERIM ANALYSIS

An interim PK data analysis will be performed after at least 10 subjects in each of the Reda mg MEDI3902 and placebo groups are followed through 21 days postdose. The interim PK analysis will allow the determination of serum PK profile of MEDI3902 in mechanically ventilated subjects. Enrolment will continue in both theReda mg MEDI3902 and placebo groups while the PK interim analysis is conducted. An independent DMC will be responsible for recommending dose adjustment as outlined in the following criteria: If the mean serum concentration of MEDI3902 on Day 22 in theReda mg MEDI3902 dose group is lower than the target concentration of Re µg/mL, a dose adjustment to 3000 mg MEDI3902 will be considered. Details of the interim analyses will be provided in the Interim Analysis Plan.

A blinded sample size re-estimation will be carried out as described in section 2.4.1.

Safety data will be reviewed regularly by the sponsor and an independent data monitoring committee (DMC). The independent DMC will review make recommendations regarding further study conduct. Additional details will be provided in the DMC charter.

5 REFERENCES

Agresti A, Min Y. On Small-Sample Confidence Intervals for Parameters in Discrete Distributions. *Biometrics* 2001; 57: 963-971.

Gray, R. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *The Annals of Statistics* 1988; 16:1141–1154.

NCI CTCAE, 2010, U.S. Department Of Health And Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, Published: May 28, 2009 (v4.03: June 14, 2010).

Shaw JW, Johnson JA, Coons SJ. US Valuation of the EQ-5D Health States: Development and Testing of the D1 Valuation Model. *Med Care* 2005; 43(3): 203-220.

Zou, G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *Am J Epidemiol* 2004; 159:702–706.

6 VERSION HISTORY

A significant number of major and minor updates were completed throughout the document. Major updates are included in the table below:

Table 3 Version History

Version	Date	Summary of Changes	Reason for Change
2.0	28Feb2019	• Clarified key efficacy analyses will be based on Red mg MEDI3902 and placebo subjects. • Added modified ITT (mITT) population to be used in primary efficacy analysis; Removed PK population as analyses will be provided in a separate report • R e • NOCDs as a safety assessment has been removed • Added language regarding interim PK analysis; Details are provided in the IUAP • Redacted • Removed secondary efficacy endpoints and analyses • Removed stratification factors from primary analysis model	Alignment with protocol
		• Modified text for baseline and demographic summaries • Modified text regarding summaries for severity of Redact *aeruginosa* Redacted R • Redacted • R e d	• Provide additional clarification
		• Redacted	R e
3.0	17Feb2020	• Redacted • Redacted	• R e

Table 3 Version History

Version	Date	Summary of Changes	Reason for Change
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Certificate Of Completion

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Source Envelope:

Document Pages: 38 Signatures: 4 Envelope Originator:

Certificate Pages: 3 Initials: 0 Reda

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Record Tracking

Status: Original Redacted Location: DocuSign

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Electronic Record and Signature Disclosure:

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In Person Signer Events	Signature	Timestamp
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	2/17/2020 11:39:12 AM
Certified Delivered	Security Checked	2/17/2020 12:26:05 PM
Signing Complete	Security Checked	2/17/2020 12:26:39 PM
Completed	Security Checked	2/17/2020 12:26:39 PM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

I hereby consent to that AstraZeneca Worldwide https://www.astrazeneca.com may disclose personal information such as; full name, email address, and any other information you may supply on the electronic form to AstraZeneca affiliates and third party service providers throughout the world in relation to the handling and administration of the Electronic Signature Service solution. This consent relates to any electronic records or signatures associated with the electronic contract.

AstraZeneca and the third party administering this service store and process personal information that AstraZeneca collects from you for the purposes of operating the Electronic Signature Service solution.

This also applies after termination of the Agreement. Processing of your personal information will be done in accordance with applicable law.

You may request access to your personal data and withdraw agreement to this processing at any time by contacting us in writing at Redacted

Personal details and electronic signatures of signatories contained in contracts cannot be removed once the contract has been executed and will remain part of such contracts until these are destroyed in accordance with applicable law and AstraZeneca internal data retention policies.