The Statistical Analysis Plan, version 4, for Study CD-ID-MEDI4893-1139 has been reviewed and approved.

<table>
<thead>
<tr>
<th>Name:</th>
<th>Role:</th>
<th>Signature:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistician</td>
<td></td>
<td>09 September 2018</td>
</tr>
<tr>
<td></td>
<td>Statistical Programmer</td>
<td></td>
<td>10 September 2018</td>
</tr>
<tr>
<td></td>
<td>Clinical Development Lead</td>
<td></td>
<td>10 September 2018</td>
</tr>
<tr>
<td></td>
<td>Clinical Biostatistics Therapeutic Area Head</td>
<td></td>
<td>10 September 2018</td>
</tr>
<tr>
<td></td>
<td>Head of Clinical Biostatistics &amp; Data Management</td>
<td></td>
<td>10 September 2018</td>
</tr>
</tbody>
</table>
Statistical Analysis Plan

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

Protocol Number: CD-ID-MEDI4893-1139 (SAATELLITE)
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>1</th>
<th>INTRODUCTION</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>STUDY OVERVIEW</td>
<td>6</td>
</tr>
<tr>
<td>2.1</td>
<td>Study Objectives</td>
<td>6</td>
</tr>
<tr>
<td>2.1.1</td>
<td>Primary Study Objective</td>
<td>6</td>
</tr>
<tr>
<td>2.1.2</td>
<td>Secondary Study Objectives</td>
<td>6</td>
</tr>
<tr>
<td>2.2</td>
<td>Study Design</td>
<td>7</td>
</tr>
<tr>
<td>2.3</td>
<td>Treatment Assignment and Blinding</td>
<td>8</td>
</tr>
<tr>
<td>2.4</td>
<td>Sample Size</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>STATISTICAL CONSIDERATIONS</td>
<td>10</td>
</tr>
<tr>
<td>3.1</td>
<td>General Considerations</td>
<td>10</td>
</tr>
<tr>
<td>3.2</td>
<td>Analysis Populations</td>
<td>10</td>
</tr>
<tr>
<td>3.3</td>
<td>Study Subjects</td>
<td>11</td>
</tr>
<tr>
<td>3.3.1</td>
<td>Subject Disposition and Completion Status</td>
<td>11</td>
</tr>
<tr>
<td>3.3.2</td>
<td>Demographics and Baseline Characteristics</td>
<td>12</td>
</tr>
<tr>
<td>3.3.3</td>
<td>Investigational Product Exposure</td>
<td>13</td>
</tr>
<tr>
<td>3.4</td>
<td>Efficacy Analyses</td>
<td>14</td>
</tr>
<tr>
<td>3.4.1</td>
<td>Primary Efficacy Endpoint and Analyses</td>
<td>14</td>
</tr>
<tr>
<td>3.4.1.1</td>
<td>Primary Efficacy Endpoint</td>
<td>14</td>
</tr>
<tr>
<td>3.4.1.2</td>
<td>Primary Efficacy Analyses</td>
<td>14</td>
</tr>
<tr>
<td>3.4.1.3</td>
<td>Handling of Dropouts and Missing Data</td>
<td>15</td>
</tr>
<tr>
<td>3.5</td>
<td>Safety Analyses</td>
<td>20</td>
</tr>
<tr>
<td>3.5.1</td>
<td>Adverse Events and Serious Adverse Events</td>
<td>20</td>
</tr>
<tr>
<td>3.5.2</td>
<td>Adverse Events of Special Interest</td>
<td>21</td>
</tr>
<tr>
<td>3.5.3</td>
<td>New Onset Chronic Disease</td>
<td>22</td>
</tr>
<tr>
<td>3.5.4</td>
<td>Clinical Laboratory Parameters</td>
<td>22</td>
</tr>
<tr>
<td>3.6</td>
<td>Pharmacokinetics</td>
<td>26</td>
</tr>
<tr>
<td>3.7</td>
<td>Pharmacodynamics</td>
<td>28</td>
</tr>
<tr>
<td>3.8</td>
<td>Antidrug antibody Response</td>
<td>30</td>
</tr>
<tr>
<td>3.9</td>
<td></td>
<td>31</td>
</tr>
</tbody>
</table>
 Statistical Analysis Plan for Protocol CD-ID-MEDI4893-1139 (SAATELITE)  
07Sep2018; Final v4.0

LIST OF IN-TEXT TABLES
Table 3.2-1 Analysis Populations ......................................................... 11

LIST OF APPENDICES
Appendix 1 Definition of S aureus Pneumonia ...................................... 37
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation or Specialised Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC-AHA</td>
<td>American College of Cardiology/American Heart Association Classification</td>
</tr>
<tr>
<td>ADA</td>
<td>anti-drug antibody</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment emergent adverse event</td>
</tr>
<tr>
<td>AESI</td>
<td>adverse event of special interest</td>
</tr>
<tr>
<td>APACHE II</td>
<td>Acute Physiology and Chronic Health Evaluation II</td>
</tr>
<tr>
<td>AT</td>
<td>alpha toxin</td>
</tr>
<tr>
<td>BAL</td>
<td>bronchoalveolar lavage</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CPIS</td>
<td>Clinical Pulmonary Infection Score</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Cycle threshold</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>EAC</td>
<td>Endpoint Adjudication Committee</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease Classification</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>ITT</td>
<td>intent-to-treat</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous(ly)</td>
</tr>
<tr>
<td>IVRS</td>
<td>interactive voice response system</td>
</tr>
<tr>
<td>IWRS</td>
<td>interactive web response system</td>
</tr>
<tr>
<td>LLOQ</td>
<td>lower limit of quantification</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MRSA</td>
<td>methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MSSA</td>
<td>methicillin-susceptible <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MV</td>
<td>mechanical ventilation</td>
</tr>
<tr>
<td>NCI CTCAE</td>
<td>National Cancer Institute Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>NE</td>
<td>neutrophil elastase</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association Functional Classification</td>
</tr>
<tr>
<td>$P_{O_2}/F_{O_2}$</td>
<td>ratio of partial pressure arterial oxygen and fraction of inspired oxygen</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PSB</td>
<td>protected specimen brush</td>
</tr>
<tr>
<td>PT</td>
<td>preferred term</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Abbreviation or Specialised Term</td>
<td>Definition</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SOC</td>
<td>system organ class</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment</td>
</tr>
<tr>
<td>SPP</td>
<td>Statistical Programming Plan</td>
</tr>
<tr>
<td>VAP</td>
<td>ventilator associated pneumonia</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

This document describes the statistical analysis for protocol CD-ID-MEDI4893-1139, an investigation of MEDI4893 in mechanically ventilated adult subjects. 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 *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 intravenous (IV) dose of MEDI4893 [redacted] mg administered to mechanically ventilated subjects in the ICU will have an acceptable safety profile. These hypotheses will be evaluated by results of the incidence of *S aureus* pneumonia and descriptive statistics from safety. This document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used.

In addition, a set of table templates and specifications is planned to be created in a statistical programming plan to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective

Primary objectives are:

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

2.1.2 Secondary Study Objectives

Secondary objectives are:

- To evaluate the serum pharmacokinetics (PK) of MEDI4893
- To evaluate the serum anti-drug antibody (ADA) responses to MEDI4893
2.2 Study Design

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 **mg** MEDI4893, **mg** MEDI4893, or placebo. A planned 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 **mg** MEDI4893 dose serum concentrations on Day 31 were lower than the MEDI4893 serum target level of **μg/mL** in ≥ 2 subjects, a dose adjustment to **mg** MEDI4893 was to be made; if the **mg** MEDI4893 dose serum concentrations were lower than the target level of **μg/mL** in ≥ 2 subjects, further enrolment was to be re-evaluated. After the DMC reviewed the interim analysis data (serum PK profiles of **and ** mg MEDI4893), the DMC recommended that enrolment in the **mg** MEDI4893 group be discontinued, and that the study proceed with enrolment in the **mg** MEDI4893 and placebo groups instead of making a dose adjustment to **mg** MEDI4893; subsequently the sample size was modified to 270 subjects. Approximately 206 subjects will now be randomized in a 1:1 ratio to one of 2 treatment groups, **mg** MEDI4893 or placebo (N = 103 for each treatment group) at sites primarily in Europe and the United States (US). Randomisation will be stratified by country and then by whether or not subjects received anti-*S. aureus* systemic...
antibiotic (treatment for $\leq 48$ 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 [mg dose] prior to the decision of discontinuing [dose arm], making the total number of study subjects to be approximately 221.

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.

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 which the study is powered. During the Stage 1 analysis, all efficacy (ie, primary, secondary, [endpoint] 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), and will analyse [ ] safety through study completion.

2.3 Treatment Assignment and Blinding

At study start, subjects were randomly assigned in a 1:1:1 ratio to receive a single IV dose of [mg MEDI4893, mg MEDI4893, or placebo. After the DMC reviewed the PK interim analysis data, the DMC recommended that enrolment in the [mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [mg MEDI4893 and placebo groups. Thus, subsequent to Protocol Amendment 4, subjects will be randomised at a 1:1 ratio to receive either [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 $\leq 48$ hours) within the 72 hours prior to investigational product administration. Detailed instructions for the randomisation process will be provided in the IVRS manual.
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.

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. 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 adverse event (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.

2.4 Sample Size

Approximately 206 colonised subjects will be enrolled and randomised in a 1:1 ratio to one of 2 treatment groups: 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 randomized in the mg dose, prior to the decision of discontinuing dose arm, making the total number of study subjects to be approximately 221.

In the sample size calculation, it is assumed the placebo group S. aureus pneumonia incidence rate is As such, a study with a sample size of N=184 ( mg MEDI4893 [N = 92] or placebo [N = 92]) will allow 70% power at 2-sided significance level of a = 0.1 to detect a relative risk reduction 50% comparing 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 mg dose.
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.

3 STATISTICAL CONSIDERATIONS

3.1 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. 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 [ ] mg MEDI4893 and placebo subjects. Subjects who received [ ] mg MEDI4893 will be summarised descriptively.

There are two planned analyses for this study: the Primary Analysis (Stage 1) and the Final Analysis (Stage 2). The Primary Analysis will be conducted after all randomized subjects have completed the Day 31 visit. At the time of this primary analysis, approximately 85% (183 subjects) of all subjects enrolled will have completed the study. MEDI4893’s efficacy will be evaluated in the Primary Analysis as intended by the study design. In addition, all available PK, ADA, and safety data will be analyzed. The final analysis will be conducted when all subjects have completed the last visit of the study.

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

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1. Subject populations will be identified for each endpoint in the sections that follow. A summary of the number and percentage of subjects in each analysis population will be provided by treatment group, for MEDI4893 total, and for all subjects combined.
### Table 3.2-1: Analysis Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat (ITT) population</td>
<td>All randomised subjects. Subjects will be analysed according to their randomised treatment group.</td>
</tr>
<tr>
<td>modified mITT (mITT) population</td>
<td>Subjects who receive any study investigational product will be included in the mITT population and subjects will be analyzed according to their randomised treatment group.</td>
</tr>
<tr>
<td>As-treated population</td>
<td>Subjects who receive any study investigational product will be included in the as-treated population and subjects will be analysed according to the treatment they actually receive.</td>
</tr>
</tbody>
</table>

Many of the planned analyses presented in the following sections include summaries by pre-dose anti-*S. aureus* systemic antibiotic stratum (“yes” or “no?”). 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 IVRS database. Unless stated otherwise, the stratum on the eCRF will be used.

Many analyses will also be summarised by country.

**Analysis Datasets**

- The Primary Dataset contains all data (efficacy, safety, ADA, PK) from all randomized subjects through the Day 31 visit and all available safety data as of the data cutoff date. The Primary Analysis will be performed on the Primary Dataset.

- The Final Dataset contains all data collected in this study, including data in the Primary Dataset and data from the subjects who were ongoing at the time when the Primary Dataset was locked. The Final Analysis will be performed on the Final Dataset.

### 3.3 Study Subjects

#### 3.3.1 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 randomised, the number of subjects randomised and treated, and the number of subjects randomised and not treated and the reason the subject was not treated: 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 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 MEDI4893 total, and for all subjects
combined. The denominators for this summary will include all subjects who were randomised and dosed.

3.3.2 Demographics and Baseline Characteristics

Enrolment will be summarised by site, and by country and site for each treatment group, for MEDI4893 total, and for all subjects combined. The total number of subjects randomised into each treatment group will be used as the denominator.

Enrolment will also be summarised by country and pre-dose anti-\textit{S. aureus} systemic antibiotic stratum for each treatment group, for MEDI4893 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 (ie, the true pre-dose anti-\textit{S. aureus} systemic antibiotic stratum recorded on the eCRF does not match the IVRS database) will be noted. This will be done for each country as well as for all countries combined.

Demographic and baseline characteristics (ie, clinical severity scores, comorbidities, risk factors within the last 3 months prior to randomization, and Study Day 0 ventilator associated pneumonia (VAP) prevention) will be summarised for subjects in the mITT population by treatment group, for MEDI4893 total, and for all subjects combined. Summaries will be created overall, by pre-dose anti-\textit{S. aureus} systemic antibiotic stratum, by country, and by pre-dose anti-\textit{S. aureus} systemic antibiotic stratum and country. Subjects will be excluded from the summary (eg, means and percentages) of an individual parameter if data are missing.

Demographic information related to gender, age (years), age category (\leq 65 years, > 65 years), ethnicity, race, weight (kg), height (cm), body mass index (BMI) (kg/m\textsuperscript{2}), and BMI category (\leq 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.

Clinical severity scores at screening will summarise Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Clinical Pulmonary Infection Score (CPIS).

The following comorbidities will be summarised:

- 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
  - History of bypass surgery
  - Peripheral vascular disease
  - Cerebrovascular disease
  - Hypertension
  - Chronic liver disease
  - Diabetes
  - Pulmonary artery hypertension
  - Renal insufficiency or renal failure
  - Thoracic malignancy or any malignancies

Risk factors history within 3 months prior to randomization will summarise history of previous staph infections, history of other infection(s) (which required either oral or IV antibiotic) (yes/no), antibiotic usage (yes/no), hospitalised (yes/no), and resided in long term care prior to hospitalization (yes/no).

Study Day 0 VAP prevention 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), and daily oral care with chlorhexidine (yes/no).

**3.3.3 Investigational Product Exposure**

The amount of investigational product infused will be summarised by 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, mL). The actual total amount of investigational product infused (mg) = dose intensity * treatment group (mg). For this study, the IV treatment group is either mg, mg or 0 (placebo).
An additional table will summarise the number of infusion interruptions and the median length of interruptions (minutes).

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint and Analyses

3.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent reduction of incidence of an Endpoint Adjudication Committee (EAC)-determined *S. aureus* pneumonia following administration of investigational product through 30 days post dose, will be performed on the Primary Dataset. For subjects with multiple *S. aureus* pneumonia events, only the first occurrence will be used in the primary analysis. Subjects with mixed cultures results which include *S. aureus* will be counted towards the primary endpoint.

The analysis of *S. aureus* pneumonia rates will be based on the protocol-specified definition as described in Appendix 1 and in the Protocol (Section 4.3.14) and will be performed on the Primary Dataset. Efficacy analyses performed on the Primary Dataset will be refreshed in the Final Dataset to make sure statistical inferences on MEDI4893 efficacy made from the Primary Analysis are consistent with those from the Final Dataset.

3.4.1.2 Primary Efficacy Analyses

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 MEDI4893 [mg] and placebo, using the term of treatment group as a covariate. The relative risk reduction, defined as $1 - \text{Relative Risk (RR)}$, and its corresponding 2-sided 90% CI will be estimated from the model. In addition, the 2-sided p-value testing null the hypothesis that the incidence of having *S. aureus* pneumonia between MEDI4893 and placebo groups are the same will also be obtained from the model. Statistically significant treatment effect will be claimed if the 2-sided p-value $\leq 0.1$.

The Poisson regression with robust variance analysis will be implemented using the SAS PROC GENMOD procedure with the REPEATED statement for subject ID and logarithm link. The estimated parameter $\hat{\beta}$ [ie, log($\text{RR}$)], 2-sided 90% confidence interval for $\hat{\beta}$, and the
2-sided p-value will be provided from the SAS outputs. The estimated relative risk ($\hat{RR}$) and corresponding confidence interval for the relative risk is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of relative risk reduction is given by $[(1 - \exp(\hat{\beta})) \times 100\%]$. The confidence interval for the percent of relative risk reduction is given by $[(1 - \exp(\text{upper confidence limit for } \hat{\beta}) \times 100\%), (1 - \exp(\text{lower confidence limit for } \hat{\beta}) \times 100\%)]$.

The above described analysis on the primary efficacy endpoint will also be conducted on the intent-to-treat (ITT) population.

### 3.4.1.3 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 *S aureus* pneumonia occurs prior to discontinuation, the subject will be considered having no *S aureus* pneumonia infection in the primary efficacy analysis. No other imputation will be applied to the primary efficacy analysis.
3.5 Safety Analyses

3.5.1 Adverse Events and Serious Adverse Events

In the Stage 1 analysis, the safety data will be summarized through 30 days post dose. In addition, all available data as of the data cut-off will also be summarized. For Stage 2 analysis, safety data will be summarized by treatment group for the different follow-up periods specified in the course of the study, including (1) ≤ 90 days post dose, (2) ≤ 190 days post dose, (3) ≤ 240 days post dose and (4) through the end of the study.

Adverse events will be coded by Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and the type incidence, severity and relationship to study investigational product will be summarised for subjects in the As-treated population by treatment group and for MEDI4893 total. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. All treatment-emergent AEs (including treatment-emergent infusion related reactions) will be summarised overall, as well as categorised by MedDRA system organ class (SOC) and preferred term (PT). Nontreatment-emergent AEs/SAEs will be presented in the listings.
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, at least one AESI with at least Grade 3 severity, a least one NOCD, and at least one investigational product related NOCD.

### 3.5.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will include targeted AEs of hypersensitivity (including anaphylaxis), infusion-related reactions, thrombocytopenia, hepatic function abnormalities, and immune complex disease (e.g., vasculitis, endocarditis, neuritis, glomerulonephritis) and will be summarised by treatment group and for MEDI4893 total overall, and by SOC and PT based on MedDRA. All TEAEs will be reviewed by the Medical Monitor to decide which terms should be included for these summaries. Additional groupings may be added by the Medical Monitor if warranted.

### 3.5.3 New Onset Chronic Disease

New onset chronic diseases include but are not limited to diabetes, asthma, autoimmune disease (e.g., lupus, rheumatoid arthritis), and neurological disease (e.g., epilepsy) and will be provided in the listings.

### 3.5.4 Clinical Laboratory Parameters

Laboratory parameters will be summarised for subjects in the As-treated population by treatment group and for MEDI4893 total as observed and change from baseline. Frequencies of worst observed toxicity and Grade 3-4 toxicities, as defined by NCI CTCAE, 2010, will be presented for each laboratory parameter by treatment group and for MEDI4893 total. Also, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts from baseline. Urinalysis parameters will be presented in the data listings.

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.
3.7 Pharmacokinetics

Individual MEDI4893 concentrations in serum will be tabulated for all subjects by treatment group along with descriptive statistics through 90 days post dose. 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.

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

3.8 Antidrug antibody Response

In the Stage 1 analysis, all available data as of the data cut-off will also be summarized. For Stage 2 analysis, anti-MEDI4893 antibody data will be summarized through 90 days post dose.

The number and percentage of subjects who develop anti-MEDI4893 antibodies will be summarised at each visit by treatment group and for MEDI4893 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, the ADA titre results will also be summarised.

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.

1. 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
2. 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)
Adverse events will be summarised by SOC and PT based on MedDRA for subjects with ADA to MEDI4893 at any time post-baseline.

The impact of ADA on PK will be included in the PK report as mentioned in Section 3.7.

3.9 Additional Analyses
3.9.2 Other Summaries

Additional data collected throughout the study include 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. 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.

3.9.3 Data Review Committees

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

3.9.3.1 Data Monitoring Committee

An independent DMC will review safety data regularly and make recommendations regarding further study conduct.

3.9.3.2 Adjudication Committee

A blinded independent endpoint adjudication committee will review clinical, radiographic, and microbiologic data for adjudication of efficacy endpoints. Additional details will be provided in the Adjudication Committee charter.

4 INTERIM ANALYSES

One interim analysis is 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 [mg] MEDI4893 dose serum concentrations on Day 31 were lower than the MEDI4893 serum target level of [μg/mL in ≥ 2 subjects, a dose adjustment to [mg] MEDI4893 was to be made; if the [mg] MEDI4893 dose serum concentrations were lower than the MEDI4893 target level of [μg/mL in ≥ 2 subjects, further enrolment was to be re-evaluated. After the DMC reviewed the interim analysis data (serum PK profiles of [mg] and [mg] MEDI4893), the DMC recommended that enrolment in the [mg] MEDI4893 group be discontinued, and that the study proceed with enrolment in the [mg] MEDI4893 and placebo groups instead of making a dose adjustment to [mg] MEDI4893.
Details of the interim analyses will be provided in the Interim Analysis Plan.

5 PLANNED ANALYSES

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 which the study is powered. During the Stage 1 analysis, all efficacy (i.e., 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. During the Stage 2 analysis, the [REDACTED] safety through study completion will be analysed.
6 REFERENCES


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).


7 VERSION HISTORY

7.1 Statistical Analysis Plan v3.0, 31May2018

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

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Summary of Changes</th>
<th>Reason for Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>31May2018</td>
<td>• Reduction in sample size</td>
<td>• Alignment with protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Removal of futility analysis (and Appendix 2 for conditional power calculation) and blinded sample size re-estimation</td>
<td>• Alignment with protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Added modified ITT (mITT) population to be used in primary efficacy analysis</td>
<td>• Alignment with protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Removed stratification factors from primary analysis model</td>
<td>• Alignment with protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Modified text regarding summaries for severity of &quot;Staphylococcus aureus pneumonia, and &quot;</td>
<td>• Provide additional clarification</td>
</tr>
<tr>
<td>4.0</td>
<td>07SEP2018</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 1  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°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)
     - 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 bronchoalveolar lavage (BAL) or protected specimen brush (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 (e.g., 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 *Staphylococcus 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)
Certificate Of Completion

Envelope Id: 0502DC3FCC3D4906AB583DB040E51863
Source Envelope:
Document Pages: 40
Certificate Pages: 2
AutoNav: Enabled
EnvelopeStmping: Disabled
TimeZone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking
Status: Original
9/9/2018 10:44:33 PM
Holder: [Masked]
Location: DocuSign

Signer Events | Signature | Timestamp
--------------|-----------|-------------
Senior Director | [Masked] | Sent: 9/9/2018 10:47:51 PM
AstraZeneca | Signature Adoption: Pre-selected Style | Signed using mobile
| | Viewed: 9/10/2018 5:36:19 AM
Senior Principal Statistician | [Masked] | Sent: 9/9/2018 10:47:52 PM
AstraZeneca | Signature Adoption: Pre-selected Style | Signed using mobile
| | Viewed: 9/9/2018 10:48:30 PM
AstraZeneca | Signature Adoption: Pre-selected Style | Signed using mobile
| | Viewed: 9/9/2018 4:47:09 PM
| | Signed: 9/9/2018 4:47:14 PM
AstraZeneca | Signature Adoption: Pre-selected Style | Signed using mobile
| | Viewed: 9/9/2018 5:18:46 PM
| | Signed: 9/10/2018 5:18:46 PM
In Person Signer Events | Signature | Timestamp
--------------|-----------|-------------
AstraZeneca | Signature Adoption: Pre-selected Style | Signed using mobile
| | Viewed: 9/9/2018 5:18:46 PM
| | Signed: 9/10/2018 5:18:46 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign
<table>
<thead>
<tr>
<th>Event Type</th>
<th>Status</th>
<th>Timestamp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editor Delivery Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agent Delivery Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediary Delivery Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certified Delivery Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon Copy Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notary Events</td>
<td>Signature</td>
<td></td>
</tr>
<tr>
<td>Envelope Summary Events</td>
<td>Status</td>
<td>Timestamps</td>
</tr>
<tr>
<td>Envelope Sent</td>
<td>Hashed/Encrypted</td>
<td>9/9/2018 10:47:54 PM</td>
</tr>
<tr>
<td>Certified Delivered</td>
<td>Security Checked</td>
<td>9/10/2018 5:18:39 PM</td>
</tr>
<tr>
<td>Signing Complete</td>
<td>Security Checked</td>
<td>9/10/2018 5:18:46 PM</td>
</tr>
<tr>
<td>Completed</td>
<td>Security Checked</td>
<td>9/10/2018 5:18:46 PM</td>
</tr>
<tr>
<td>Payment Events</td>
<td>Status</td>
<td>Timestamps</td>
</tr>
</tbody>
</table>
Delegation of Authority

(acting Head of Clinical Biostatistics and Data Management (CBDM))

In the role as

Head of CBDM for the approval of the Statistical Analysis Plan

Period of Delegation
From: 24 August 2018
To: 31 December 2018 (or until the time is no longer the acting Head of CBDM)

Cause for Delegation
☐ Vacation
☐ Business journey
☒ Other, please specify

Departure of previous Head of CBDM and requisite recruitment and replacement period

May the authority be re-delegated?
☐ Yes
☒ No

Name:
Role: Acting Head of CBDM
Signatur
Date: 20 August 2018
<table>
<thead>
<tr>
<th>Name:</th>
<th>Signature:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role: Acting Statistics TA Head for Oncology</td>
<td>Date: 20 August 2018</td>
</tr>
<tr>
<td>Name:</td>
<td>Signature:</td>
</tr>
<tr>
<td>Role: Acting Statistics TA Head for CVRM</td>
<td>Date: 20 August 2018</td>
</tr>
<tr>
<td>Name:</td>
<td>Signature:</td>
</tr>
<tr>
<td>Role: Statistics TA Head for All Other TA</td>
<td>Date: 24 August 2018</td>
</tr>
</tbody>
</table>
**Certificate Of Completion**

- **Envelope Id:** 46A42C0D85FD406EB5DB7F00AC89A9DE
- **Status:** Completed
- **Subject:** Please DocuSign: Delegation of Authority_SAP approval_2018-08-24.docx
- **iSave Workspace ID:**
- **Document Pages:** 2
- **Signatures:** 4
- **Certificate Pages:** 6
- **Initials:** 0
- **AutoNav:** Enabled
- **Envelope Stamping:** Disabled
- **Time Zone:** (UTC-05:00) Eastern Time (US & Canada)

**Record Tracking**

- **Status:** Original
- **Date:** 6/20/2013 2:13:07 AM
- **Holder:**
- **Location:** DocuSign

**Signer Events**

<table>
<thead>
<tr>
<th>Signer</th>
<th>Signature</th>
<th>Timestamp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8/20/2018 2:31:55 AM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8/20/2018 5:44:00 AM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8/20/2018 5:44:18 AM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8/20/2018 1:22:28 PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8/20/2018 1:23:08 PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8/20/2018 3:56:22 PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8/20/2018 3:56:27 PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8/24/2018 2:49:56 PM</td>
</tr>
</tbody>
</table>

**Signatures**

- **Signature Adoption:** Pre-selected Style
- **Signed using mobile**

**Electronic Record and Signature Disclosure**

- Accepted: 8/20/2018 5:44:00 AM
- ID: aa138ac9-7d4a-48e8-8464-74504e07863a

**AstraZeneca**

- Security Level: Email, Account Authentication (None)
- Signature Adoption: Pre-selected Style

**Electronic Record and Signature Disclosure**

- Not Offered via DocuSign
<table>
<thead>
<tr>
<th>In Person Signer Events</th>
<th>Signature</th>
<th>Timestamp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editor Delivery Events</td>
<td>Status</td>
<td>Timestamp</td>
</tr>
<tr>
<td>Agent Delivery Events</td>
<td>Status</td>
<td>Timestamp</td>
</tr>
<tr>
<td>Intermediary Delivery Events</td>
<td>Status</td>
<td>Timestamp</td>
</tr>
<tr>
<td>Certified Delivery Events</td>
<td>Status</td>
<td>Timestamp</td>
</tr>
<tr>
<td>Carbon Copy Events</td>
<td>Status</td>
<td>Timestamp</td>
</tr>
</tbody>
</table>

**Copied:**

- **Sent:** 8/20/2018 2:31:56 AM
- **Viewed:** 8/20/2018 7:56:02 AM

---

<table>
<thead>
<tr>
<th>Carbon Copy Events</th>
<th>Status</th>
<th>Timestamp</th>
</tr>
</thead>
</table>

---

<table>
<thead>
<tr>
<th>Notary Events</th>
<th>Signature</th>
<th>Timestamp</th>
</tr>
</thead>
</table>

**Envelope Summary Events**

- Envelope Sent: Hashed/Encrypted
- Certified Delivered: Security Checked
- Signing Complete: Security Checked
- Completed: Security Checked

**Timestamps**

- 8/20/2018 2:31:58 AM
- 8/24/2018 2:49:55 PM
- 8/24/2018 2:49:58 PM

**Payment Events**

<table>
<thead>
<tr>
<th>Status</th>
<th>Timestamp</th>
</tr>
</thead>
</table>

**Electronic Record and Signature Disclosure**
ELECTRONIC RECORD AND SIGNATURE DISCLOSURE
From time to time, AstraZeneca (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through your DocuSign, Inc. (DocuSign) Express user account. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Getting paper copies
At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. For such copies, as long as you are an authorized user of the DocuSign system you will have the ability to download and print any documents we send to you through your DocuSign user account for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent
If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind
If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. To indicate to us that you are changing your mind, you must withdraw your consent using the DocuSign 'Withdraw Consent' form on the signing page of your DocuSign account. This will indicate to us that you have withdrawn your consent to receive required notices and disclosures electronically from us and you will no longer be able to use your DocuSign Express user account to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically
Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through your DocuSign user account all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.
How to contact AstraZeneca:
You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: [redacted]

To advise AstraZeneca of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to us at [redacted] and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address.
In addition, you must notify DocuSign, Inc to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in DocuSign.

To request paper copies from AstraZeneca
To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an e-mail to [redacted] and in the body of such request you must state your e-mail address, full name, US Postal address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with AstraZeneca
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:
   i. decline to sign a document from within your DocuSign account, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
   ii. send us an e-mail to [redacted] and in the body of such request you must state your e-mail, full name, IS Postal Address, telephone number, and account number. We do not need any other information from you to withdraw consent. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process.

Required hardware and software
<table>
<thead>
<tr>
<th>Operating Systems:</th>
<th>Windows2000? or WindowsXP?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Browsers (for SENDERS):</td>
<td>Internet Explorer 6.0? or above</td>
</tr>
<tr>
<td>Browsers (for SIGNERS):</td>
<td>Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)</td>
</tr>
<tr>
<td>Email:</td>
<td>Access to a valid email account</td>
</tr>
<tr>
<td>Screen Resolution:</td>
<td>800 x 600 minimum</td>
</tr>
<tr>
<td>Enabled Security Settings:</td>
<td>*Allow per session cookies</td>
</tr>
<tr>
<td></td>
<td>*Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection</td>
</tr>
</tbody>
</table>

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time.
providing you with the revised hardware and software requirements, at which time you will have the right to withdraw your consent.

Acknowledging your access and consent to receive materials electronically
To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

By checking the 'I Agree' box, I confirm that:

- I can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC RECORD AND SIGNATURE DISCLOSURES document; and

- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and

- Until or unless I notify AstraZeneca as described above, I consent to receive from exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to me by AstraZeneca during the course of my relationship with you.
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.

Übersetzung der Datenschutzerklärung für DocuSign


Sie können Auskunft zu Ihren personenbezogenen Daten verlangen und jederzeit die Einwilligung in die entsprechende Datenverarbeitung widerrufen, indem Sie zu uns schriftlich Kontakt aufnehmen über [redacted].