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MedImmune

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Statistical Analysis Plan Approval

Date: 07SEP2018
To: Study File
From: [redacted]
Re: Statistical Analysis Plan Approval for Study CD-ID-MEDI4893-1139

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

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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)

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LIST OF ABBREVIATIONS

Abbreviation or Specialised Term	Definition
ACC-AHA	American College of Cardiology/American Heart Association Classification
ADA	anti-drug antibody
TEAE	treatment emergent adverse event
AESI	adverse event of special interest
APACHE II	Acute Physiology and Chronic Health Evaluation II
AT	alpha toxin
BAL	bronchoalveolar lavage
BMI	body mass index
CHF	Congestive Heart Failure
CI	confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CPIS	Clinical Pulmonary Infection Score
CRP	C-reactive protein
CT	Cycle threshold
DMC	Data Monitoring Committee
EAC	Endpoint Adjudication Committee
EU	European Union
[redacted]	[redacted]
GOLD	Global Initiative for Chronic Obstructive Lung Disease Classification
ICU	intensive care unit
IgG	immunoglobulin G
ITT	intent-to-treat
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
MV	mechanical ventilation
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	neutrophil elastase
NYHA	New York Heart Association Functional Classification
P_aO_2/F_iO_2	ratio of partial pressure arterial oxygen and fraction of inspired oxygen
PK	Pharmacokinetics
PSB	protected specimen brush
PT	preferred term
S aureus	*Staphylococcus aureus*

Abbreviation or Specialised Term	Definition
SAE	serious adverse event
SOC	system organ class
SOFA	Sequential Organ Failure Assessment
SPP	Statistical Programming Plan
VAP	ventilator associated pneumonia
WBC	white blood cell

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

2.1.3 [redacted]

[redacted]

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 [redacted] mg MEDI4893, [redacted] 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 [redacted] mg MEDI4893 dose serum concentrations on Day 31 were lower than the MEDI4893 serum target level of [redacted] µg/mL in ≥ 2 subjects, a dose adjustment to [redacted] mg MEDI4893 was to be made; if the [redacted] mg MEDI4893 dose serum concentrations were lower than the target level of [redacted] µg/mL in ≥ 2 subjects, further enrolment was to be re-evaluated. After the DMC reviewed the interim analysis data (serum PK profiles of [redacted] and [redacted] mg MEDI4893), the DMC recommended that enrolment in the [redacted] mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [redacted] mg MEDI4893 and placebo groups instead of making a dose adjustment to [redacted] mg MEDI4893; 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, [redacted] 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 ≤ 48 hours) within the 72 hours prior to randomisation. As the study is blinded, it is estimated that approximately 15 subjects may have already been enrolled and randomised in the [redacted] mg dose, prior to the decision of discontinuing [redacted] dose arm, making the total number of study subjects to be approximately 221.

[redacted] 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, [redacted] endpoints), serum PK, ADA, and safety data collected through 30 days post dose for the last subject enrolled will be analysed. The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study (ie, approximately 190 days post dose), and will analyse [redacted] 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 [redacted] mg MEDI4893, [redacted] mg MEDI4893, or placebo. After the DMC reviewed the PK interim analysis data, the DMC recommended that enrolment in the [redacted] mg MEDI4893 group be discontinued, and that the study proceed with enrolment in the [redacted] mg MEDI4893 and placebo groups. Thus, subsequent to Protocol Amendment 4, subjects will be randomised at a 1:1 ratio to receive either [redacted] mg MEDI4893 or placebo. Randomisation will be stratified by country and then by whether or not subjects received anti-*S aureus* systemic antibiotic (treatment for ≤ 48 hours) within the 72 hours prior to investigational product administration. Detailed instructions for the randomisation process will be provided in the IVRS manual.

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: [redacted] mg MEDI4893 (n = 103) or placebo (n = 103). As the study is blinded, it is estimated that approximately 15 subjects may have already been enrolled and randomized in the [redacted] mg dose, prior to the decision of discontinuing [redacted] 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 [redacted] As such, a study with a sample size of N=184 ([redacted] mg MEDI4893 [N = 92] or placebo [N = 92]) will allow 70% power at 2-sided significance level of $\alpha = 0.1$ to detect a relative risk reduction 50% comparing MEDI4893 versus placebo. A Poisson regression with robust variance (Zou, 2004) is employed in the calculation. A total of 221 subjects is derived when considering 10% attrition and adding an estimated 15 subjects in the [redacted] mg dose.

- [redacted] 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 [redacted] mg MEDI4893 and placebo subjects. Subjects who received [redacted] 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

Population	Description
Intent-to-treat (ITT) population	All randomised subjects. Subjects will be analysed according to their randomised 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 analysed according to the treatment they actually receive.

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-*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-*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-*S aureus* systemic antibiotic stratum, by country, and by pre-dose anti-*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 (≤ 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.

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, [redacted] mL). The actual total amount of investigational product infused (mg) = dose intensity * treatment group (mg). For this study, the IV treatment group is either [redacted] mg, [redacted] 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 [redacted] mg and placebo, using the term of treatment group as a covariate. The relative risk reduction, defined as 1 – Relative Risk (RR), and its corresponding 2-sided 90% CI will be estimated from the model. In addition, the 2-sided p-value testing null the hypothesis that the incidence of having *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 ≤ 0.1.

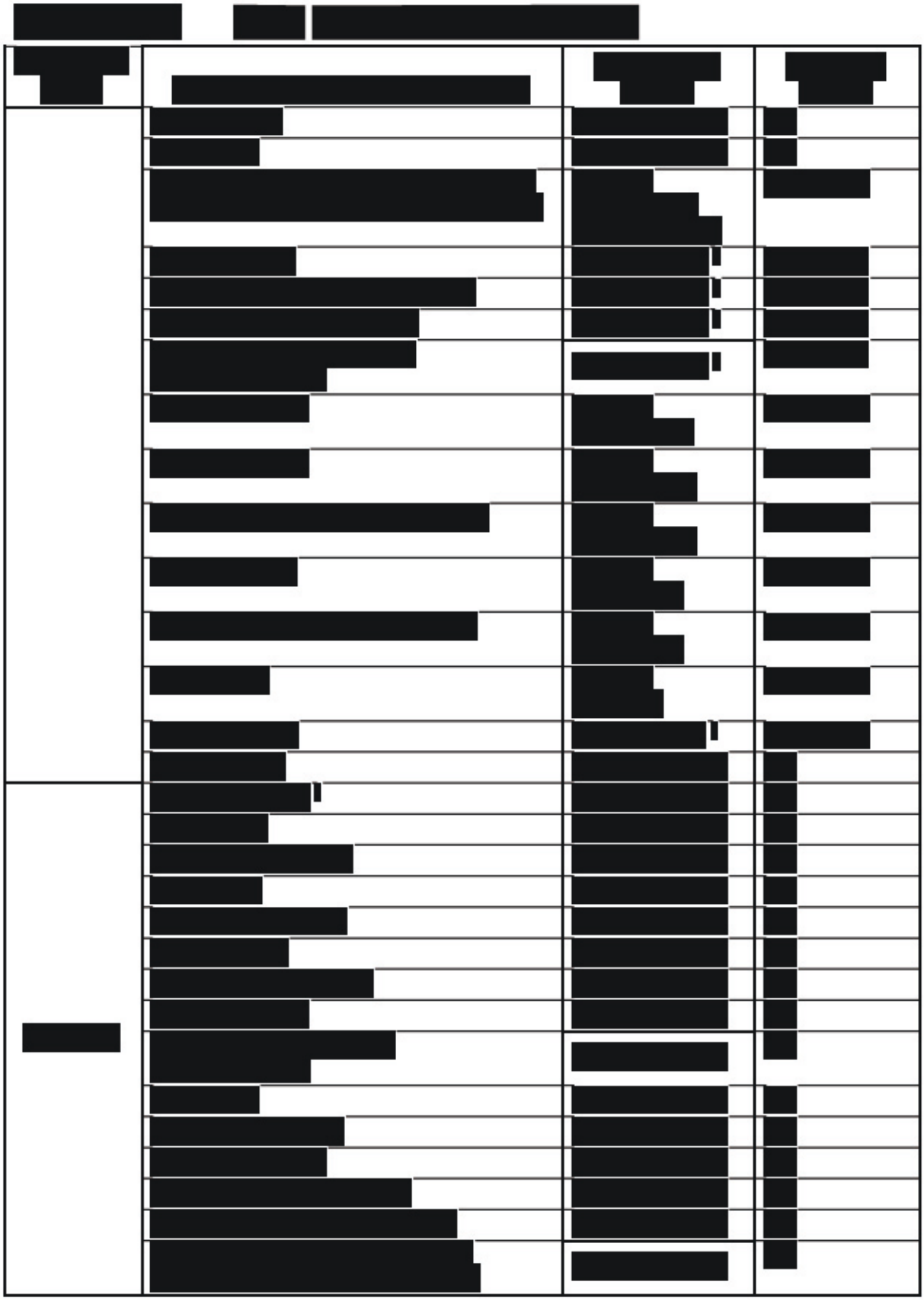
The Poisson regression with robust variance analysis will be implemented using the SAS PROC GENMOD procedure with the REPEATED statement for subject ID and logarithm link. The estimated parameter $\hat{\beta}$ [ie, $\log(\widehat{RR})$], 2-sided 90% confidence interval for $\hat{\beta}$, and the

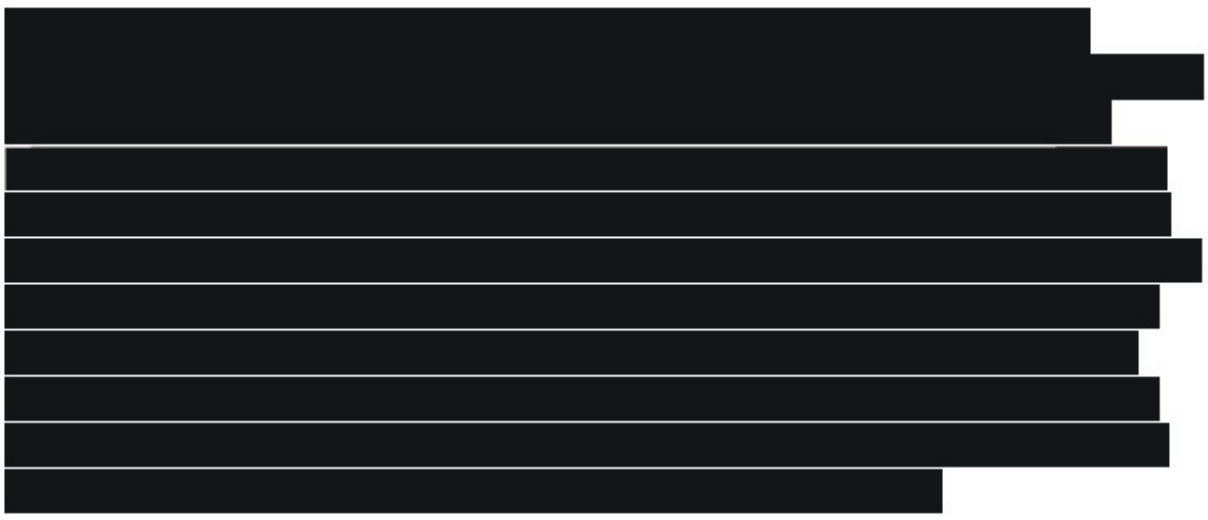
2-sided p-value will be provided from the SAS outputs. The estimated relative risk ($\widehat{RR}$) and corresponding confidence interval for the relative risk is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of relative risk reduction is given by [(1 – exp($\hat{\beta}$)) * 100%]. The confidence interval for the percent of relative risk reduction is given by ([1 – exp(upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp(lower confidence limit for $\hat{\beta}$) * 100%]).

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.





[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

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 (eg, 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 (eg, lupus, rheumatoid arthritis), and neurological disease (eg, 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.

3.6 [redacted]

[redacted]

[redacted]

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. [redacted] 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

3.9.1 [redacted]

[redacted]

3.9.1.2 [redacted]

[redacted]

3.9.1.3 [redacted]

[redacted]

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

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 (ie, primary, secondary, and exploratory efficacy endpoints), serum PK, ADA, and safety data collected through 30 days post dose for the last subject enrolled will be analysed. The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study. During the Stage 2 analysis, the [redacted] safety through study completion will be analysed.

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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:

Version	Date	Summary of Changes	Reason for Change
3.0	31May2018	• [redacted]	• Alignment with protocol
		• Reduction in sample size	• Alignment with protocol
		• Removal of futility analysis (and Appendix 2 for conditional power calculation) and blinded sample size re-estimation	• Alignment with protocol
		• Added modified ITT (mITT) population to be used in primary efficacy analysis	• Alignment with protocol
		• Removed stratification factors from primary analysis model	• Alignment with protocol
		• [redacted]	• [redacted]
		• Modified text regarding summaries for severity of [redacted], *S aureus* pneumonia, and	• Provide additional clarification
		• [redacted]	• [redacted]
		• [redacted]	• [redacted]
4.0	07SEP2018	• [redacted]	[redacted]
		[redacted]	• [redacted]

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/mm^3, WBC count < 4500 cells/mm^3, or > 15% band neutrophils)
  - Production of purulent endotracheal secretions
  - Physical examination findings consistent with pneumonia/pulmonary consolidation (eg, rales, rhonchi, bronchial breath sounds), dullness to percussion
- Major criteria
  - Acute changes made in the ventilatory support system to enhance oxygenation, as determined by:
    - PaO_2/FiO_2 ratio < 240 mmHg maintained for at least 4 hours, or
    - A decrease in PaO_2/FiO_2 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 $\geq 38.3°C$ or hypothermia, defined as a core body temperature of $< 35°C$), and/or abnormal WBC (WBC count $> 10,000$ cells/mm^3, WBC count < 4500 cells/mm^3, or $> 15\%$ band neutrophils)
  - A new onset of cough (or worsening of cough)
  - Production of purulent sputum

- Physical examination findings consistent with pneumonia/pulmonary consolidation such as auscultatory findings (eg, rales, rhonchi, bronchial breath sounds), dullness to percussion, or pleuritic chest pain
- Dyspnea, tachypnea (respiratory rate > 30 breaths/minute), or hypoxemia defined as:
  - O_2 saturation < 90% or PaO_2 < 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 O_2 saturations

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

AND

c. Microbiologic confirmation:

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

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

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Delegation of Authority

[redacted] (for the Oncology Therapeutic Area (TA)), [redacted] (for the Cardiovascular, Renal, and Metabolic Disease (CVRM) TA), and [redacted] (for all other TA)

May act on behalf of

[redacted] (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 [redacted] 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: [redacted]

Signatur [redacted]

Role: Acting Head of CBDM

Date: 20 August 2018

MedImmune

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Name:	[redacted]	Signatur	[redacted]
Role:	Acting Statistics TA Head for Oncology	Date:	20 August 2018
Name:	[redacted]	Signatur	[redacted]
Role:	Acting Statistics TA Head for CVRM	Date:	20 August 2018
Name:	[redacted]	Signature:	[redacted]
Role:	Statistics TA Head for All Other TA	Date:	24 August 2018

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