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Statistical Analysis Plan Approval

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FROM: [redacted]

RE: Statistical Analysis Plan Approval for Study D5290C00003

The Statistical Analysis Plan, version 1, for Study D5290C00003 has been reviewed and approved.

[redacted] 18 November 2016

Statistician Date

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Statistical Analysis Plan

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

Protocol Number: D5290C00003

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List of Abbreviations

Abbreviation or Specialized Term	Definition
AAP	American Academy of Pediatrics
AE	adverse event
AESI	adverse event of special interest
CE	*Conformité Européenne* or European Conformity
CI	confidence interval
eCRF	electronic case report form
ER	emergency room
EU	European Union
hMPV	human metapneumovirus
HRU	healthcare resource utilization
ICU	intensive care unit
IDMC	independent data monitoring committee
IM	intramuscular
ITT	intent-to-treat
IWRS	interactive web response system
LRTI	lower respiratory tract infection
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOCD	new onset chronic disease
OTC	over-the-counter
PK	pharmacokinetics
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SID	subject identification
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
US FDA	United States Food and Drug Administration
USA	United States of America
wGA	weeks gestational age

1 INTRODUCTION

This document describes the statistical analysis for protocol D5290C00003, a pivotal Phase 2b study to determine if MEDI8897 is efficacious in reducing medically attended respiratory syncytial virus (RSV)-confirmed lower respiratory tract infection (LRTI) in healthy preterm infants entering their first RSV season. The primary efficacy hypothesis of

this study is that, compared to placebo, a single 50-mg intramuscular (IM) dose of MEDI8897 will be efficacious in reducing medically attended LRTI caused by RT-PCR-confirmed RSV in healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable. The secondary hypotheses are that (1) there will be a reduction in the incidence of hospitalizations attributable to RSV, (2) the predicted extended $t_{1/2}$ will be adequate for the duration of the RSV season, and (3) ADA to MEDI8897 will not significantly impact the serum concentrations or safety of MEDI8897 over the 5-month RSV season. These hypotheses will be assessed by the incidence of RSV LRTI, RSV hospitalization, ADA, pharmacokinetics parameters, and descriptive statistics from safety data. 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(s)

To assess the efficacy of MEDI8897 when administered as a single 50 mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo.

2.1.2 Secondary Study Objectives

1. To assess the efficacy of MEDI8897 for the reduction of hospitalizations due to RT-PCR-confirmed RSV, compared to placebo
2. To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared to placebo
3. To evaluate single-dose serum concentrations of MEDI8897
4. To evaluate ADA responses to MEDI8897 in serum

2.1.3 Exploratory Study Objectives

To assess healthcare resource utilization (HRU) and caregiver burden for MEDI8897 recipients compared to placebo recipients.

2.2 Study Design

The population to be enrolled is healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who would not receive RSV prophylaxis based on the AAP or other local or national guidelines. These infants will not be receiving palivizumab, allowing for a placebo comparator group for the determination of efficacy and the safety profile. A total of 1,500 infants will be randomized 2:1 to receive a 50 mg IM dose of MEDI8897 (N = 1000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. All infants will be followed for approximately 360 days after dosing.

2.3 Treatment Assignment and Blinding

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized at a 2:1 ratio to receive a 50 mg IM dose of MEDI8897 (N = 1,000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500.

The procedure for using IWRS is as follows:

- The investigator or designee contacts the IWRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject
- Placebo (provided by site) or a vial from a MEDI8897 kit will be assigned to the subject
- Confirmation of this information is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log

Investigational product (MEDI8897 or placebo) must be administered the same day the investigational product is assigned. Total in-use storage time from needle puncture of the investigational product vial to administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used. If there is a delay in the administration of investigational product such that it will not be administered within the

specified timeframe, the unblinded investigational product monitor must be notified immediately.

2.4 Sample Size

The sample size of 1,500 is necessary based on advice from the US FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size has approximately > 99% power to detect 70% relative risk reduction, assuming a placebo group medically attended RSV LRTI incidence of 8%. Power calculations are based on Poisson regression model with robust variance (Zou, 2004) comparing MEDI8897 50 mg versus placebo, with 2-sided, $\alpha = 0.049$ (due to 0.001 alpha spend at the interim analysis; refer to Interim Analysis Section 4).

- The 70% relative risk reduction assumption is based on a placebo-controlled study in Native American infants in which there was 87% relative reduction in the incidence of RSV hospitalization (11.3% placebo; 1.5% motavizumab; $p < 0.001$) and 71% relative reduction in the incidence of outpatient RSV LRTI (10.0% placebo; 2.9% motavizumab; $p < 0.001$) in infants who received motavizumab prophylaxis (O'Brien et al, 2015)

In order to evaluate risk, a sample size of 1,000 subjects exposed to MEDI8897 will provide a 90% probability of observing at least one AE if the true event rate is 0.2%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.3%.

3 STATISTICAL METHODS

3.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. In general, unless stated otherwise, baseline will be defined as the last value prior to dosing.

For the primary efficacy analysis for the primary endpoint of medically attended RSV LRTI [and similarly for RSV LRTI hospitalization (Protocol-Defined) and medically attended RSV outpatient LRTI (Protocol-Defined)], if a subject does not experience a medically attended RSV LRTI prior to discontinuation from participation through 150 days post dose, their event status will be imputed assuming the observed placebo medically attended RSV LRTI rate conditional on stratification value. For the sensitivity analyses for the primary endpoint, similar approaches will be used with various assumed medically attended RSV LRTI event rates, with or without stratification adjustment in the imputation.

For additional analyses on the primary endpoint, secondary efficacy analyses, and exploratory efficacy analyses, if no RSV LRTI occurs prior to discontinuation, the subject will be considered as having no RSV LRTI in the analysis, unless stated otherwise.

All analyses, with the exception of safety, will be performed on the ITT Population. Summaries presented for > 150 days post dose will include subjects in the ITT population who are still on study after day 150.

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

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	Subjects who are randomized will be included in the ITT population and subjects will be analyzed according to their randomized treatment group.
As-treated population	Subjects who receive any study investigational product will be included in the as-treated population and subjects will be analyzed according to the treatment they actually receive.
Per-protocol population	The per-protocol population includes all subjects in the as-treated population who are either followed through 150 days post dose or not followed through 150 days post dose but had medically attended RSV LRTI.

3.3 Stratification Factors

Many of the planned analyses presented in the following sections include summaries by age at randomization [age ≤ 3 months (ie, age ≤ 91 days), age > 3 to ≤ 6 months (ie, age > 91 to ≤ 183 days), age > 6 months (ie, age > 183 days)] and hemisphere (northern hemisphere, southern hemisphere). For subjects who were assigned to an incorrect age stratum at randomization, the age stratum as calculated from the electronic case report form (eCRF) will differ from the stratum recorded for the subject in the IWRS database. Unless stated otherwise, the age stratum based on the CRF calculation will be used.

CRF calculation for age when full DOB is available:

- Age at randomization (months) = (randomization date – date of birth) / (365.25/12)

When full DOB is unavailable, age at screening will be used. Since screening may be collected in terms of days, weeks, or months, it will be first converted in terms of months as follows:

- Age at screening (days) / (365.25/12) = Age at screening (months)
- Age at screening (weeks) / (52/12) = Age at screening (months)

Once Age at screening is converted to months,

- Age at randomization (months)= Age at screening (months) + [(randomization date – screening date) / (365.25/12)]

Many analyses will also be summarized by hemisphere. The sites have been grouped together by country into the following two hemispheres: Northern Hemisphere (Bulgaria, Canada, Czech Republic, France, Hungary, Italy, Poland, Russian Federation, Spain, United Kingdom, and USA) and Southern Hemisphere (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa).

3.4 Study Subjects

3.4.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment received (including summary of subjects randomized but not treated) will be provided. In addition, disposition of subjects throughout the study with respect to follow-up will be provided. This summary will be presented by treatment group and for all subjects combined. The denominators for this summary will include all subjects who were randomized into the study.

3.4.2 Demographics and Baseline Characteristics

Enrollment will be summarised by hemisphere, country and site, and by hemisphere, country, and age at randomization stratum for each treatment group and for all subjects combined. The total number of subjects randomized into each treatment group will be used as the denominator. For the summary of hemisphere, country, and age at randomization stratum, the number of mis-stratified subjects (ie, age stratum as calculated from the eCRF does not match the IWRS database) will be summarized.

Demographic information related to gender, age at randomization (months) calculated from the CRF, age at randomization category determined using the CRF age calculation (age $\leq$ 3 months, age $>$ 3 to $\leq$ 6 months, age $>$ 6 months), gestational age (weeks), gestational age

category (29-32 weeks, > 32 weeks), ethnicity, race, weight (kg) on day 1, weight on day 1 category (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg), birth weight (kg), birth weight category (weight ≤ 2.5 kg, weight > 2.5 kg), multiple birth (yes/no), and siblings enrolled in the study (yes/no) will be summarized by treatment group and for all subjects combined using the ITT population. Subjects will be excluded from the summary (eg, means and percentages) of an individual parameter if data are missing. This will be done for all subjects, each age category at randomization, country, and by hemisphere.

3.4.3 Study Drug Exposure

Due to the simplicity of dosing for this study, exposure is summarized in the Subject Disposition and Completion Status table under the summary "Randomized and dosed." No other summary will be reported.

3.5 Efficacy Analyses

An interim analysis for safety and efficacy will be conducted by an independent data monitoring committee (IDMC) after approximately 750 infants have been randomized and followed for at least 150 days post dose. There is no provision to stop early due to an efficacy claim, however 0.001 alpha will be spent at the interim analysis based on advice from the US FDA. The final analysis will be tested at 2-sided alpha 0.049 accordingly.

For the final analysis, the secondary efficacy hypothesis will be assessed only if the primary efficacy hypothesis has been demonstrated. Due to this preplanned sequential testing procedure, the overall Type I error is controlled at 0.049. Therefore, no further multiplicity adjustment is necessary.

3.5.1 Primary Efficacy Endpoint and Analyses

3.5.1.1 Primary Efficacy Endpoint

The primary endpoint is the incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose. For subjects with multiple medically attended RSV LRTI events (inpatient or outpatient), only the first occurrence will be used in the primary analysis.

The analysis of medically attended RSV LRTI will be based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from analyzing the respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A and RSV B performed in a central laboratory. These LRTI events may occur in the inpatient or outpatient visit setting.

Prior to analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as an medically attended RSV LRTI if they occurred in a respiratory sample collected within this window relative to the initial date seen by the healthcare provider (eg, admission/deterioration date associated with the event, urgent care visit, outpatient ED visit, or outpatient clinic visit). The actual window used will be documented prior to unblinding. In addition, deaths which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as primary medically attended RSV LRTI events.

3.5.1.2 Handling of Dropouts and Missing Data

RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo medically attended RSV LRTI rate conditional on stratification factors as described below.

The primary analysis uses Poisson regression with robust variance with stratification factors as covariates, which requires a subject-level dataset. A repeated imputation approach is introduced to impute medically attended RSV LRTI status for missing observations at the subject-level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and confidence interval estimation of the treatment effect is expected through the repeated imputation (Little and Rubin, 2002). To cope with the primary analysis including stratification factors/covariates, the missing values will be imputed at the medically attended RSV LRTI risk level adjusted for subject's stratification value using SAS PROC MI with, e.g., logistic regression method.

The details for the repeated imputation placebo medically attended RSV LRTI rate adjusted for stratification values are provided below. Note that the placebo rate is applied equally to both placebo and MEDI8897 groups in the imputation.

- Step 1: For the subjects in the MEDI8897 arm who do not have an RSV LRTI and are not followed through 150 days post dose, their treatment code of "MEDI8897" will be substituted with "placebo" to ensure the placebo RSV LRTI risk is equally applied in the imputation for both the MEDI8897 and placebo subjects adjusted for their stratification values. The imputation will be executed using SAS PROC MI (e.g., logistic regression with stratification factors).
- Step 2: The original treatment code will be restored after the RSV LRTI event statuses have been imputed. A complete dataset comprises the imputed RSV LRTI status and observed RSV LRTI status.

- Step 3: Analyze the complete dataset using a Poisson regression model with robust variance to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, categorical age at randomization, and dichotomous temperate hemispheres as covariates. The point estimate and variance will be extracted from the model.
- Steps 2-3 will be repeated multiple times. The set of point estimates and variances for the model parameter for each complete dataset will be used to generate statistical inferences using the multiple imputation procedure (eg, SAS MIANALYZE procedure).

3.5.1.3 Primary Efficacy Analysis

The primary (ie, final) efficacy analysis of the primary endpoint will be evaluated using the ITT Population. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary efficacy analysis to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo groups, including treatment group, age at randomization based on CRF calculation (ie, age $\leq$ 3 months, age > 3 to $\leq$ 6 months, age > 6 months) and dichotomous temperate (northern and southern) hemispheres as covariates. If the number of subjects in any stratum is too small and/or convergence cannot be achieved, the covariate(s) may not be included in the model. In addition, the 2-sided p-value and corresponding 2-sided 95.1% CI on the relative risk will be provided from the model. Relative risk reduction is defined as (1 - Pn/Ps) where Pn is the incidence of medically attended RSV LRTI through 150 days post dose in the MEDI8897 group and Ps is the incidence of RSV LRTI through 150 days post dose in the placebo group. Statistical significance will be achieved if the 2-sided p-value is < 0.049.

3.5.1.4 Additional Analyses of the Primary Efficacy Endpoint

Additional analyses will be based on observed events and available follow-up through 150 days, unless stated otherwise.

To allow for differences in follow-up time, the primary analysis using Poisson Regression with robust variance will be repeated, adjusting for the same covariates as well as log(follow-up time) as an offset.

- For subjects who meet the medically attended RSV LRTI endpoint within 150 days postdose, the follow-up time will be calculated as (Date of Onset of RSV LRTI) – (Date of Dosing) +1.
- For subjects who do not experience a medically attended RSV LRTI event within 150 days post dose, the efficacy follow-up will be determined based on the following:
    - If an end of study date occurs within 150 days post dose (or end of study date is missing and last assessment date occurs within 150 days post dose), the efficacy

follow-up will be calculated as (Date of End of Study or Date of Last Assessment, whichever is later) – (Date of Dosing) +1.

- If an end of study date occurs after 150 days post dose (or end of study date is missing and last assessment date is after 150 days post dose), the efficacy follow-up will be set to 150 days.

Medically attended RSV LRTI will be summarized by treatment group for the per-protocol population. Relative risk and 95.1% CI will be constructed using an exact conditional method based on the number of RSV LRTIs.

A CMH (Cochran-Mantel-Haenszel) test stratified by hemisphere and age at randomization (ie, age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months) will be used to compare between treatment groups through 150 days post dose as a sensitivity analysis for the primary endpoint.A Kaplan-Meier curve for time to first medically attended RSV LRTI will be used as a sensitivity analysis for the primary endpoint. Subjects who have not had a medically attended RSV LRTI through 150 days post dose will be considered censored. For these subjects time will be defined in days from the date of randomization to date of last follow-up (see above for calculation). For subjects experiencing a medically attended RSV LRTI through 150 days post dose, time will be defined from randomization to date of first medically attended RSV LRTI. A plot presenting the Kaplan-Meier curves will be created. Treatment groups will be compared using the stratified log-rank and Wilcoxon tests.

The incidence of medically attended RSV LRTI by subtype (RSV A, RSV B) through 150 days post dose will be summarized for each treatment group using the Poisson regression approach as described for the primary efficacy analysis (Section 3.5.1.3). The analysis will include the relative efficacy, 2-sided p-value and 2-sided 95.1% CI on the relative risk reduction from the model.

The total number of new onset medically attended RSV LRTIs since the previous medically attended RSV LRTI will be calculated for each subject. A new onset medically attended RSV LRTI will be defined as an adverse event (for which at least one healthcare visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV LRTI (see Table 3.5-1). The total number of medically attended RSV LRTIs occurring for each subject through 150 days post dose will be summarized by numbers and percentages of subjects who have X number of medically attended RSV LRTIs (ie, 0, 1, 2, 3... medically attended RSV LRTIs). This summary will be repeated for medically attended RSV LRTIs occurring > 150 days post dose and for ≤ 360 days post dose.

Additional summaries will present the incidence of medically attended RSV LRTI through for ≤ 360 days post dose and occurring > 150 days post dose.

Adverse events associated with medically attended RSV LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days.

Sensitivity Analyses for Subjects who are Not Followed through 150 Days Post Dose

Sensitivity analyses for RSV LRTI through 150 days post dose will be performed to address subjects who do not have an RSV LRTI and are not followed through 150 days post dose. The imputed rates of medically attended RSV LRTI through 150 days post dose will be as follows:

1. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having not met the RSV LRTI endpoint within each treatment group.
2. Impute the missing values in each treatment group using 2-times the placebo RSV LRTI event rate through 150 days post dose (ie, Bernoulli distribution with expected value equal to 2-times placebo RSV LRTI event rate)
3. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 2-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 1 or 2-times placebo RSV LRTI event rate)
4. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 3-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 1 or 3-times placebo RSV LRTI event rate)
5. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having met the RSV LRTI endpoint within each treatment group (ie, clinical failures).
6. Multiple imputation

The sensitivity analyses 2-4 will be carried out following the steps below:

- Step 1: Determine the observed placebo RSV LRTI rate through 150 days post dose, which is calculated as the proportion of all randomized placebo subjects with observed RSV.
- Step 2: Impute the event status for subjects who do not have an RSV LRTI and are not followed through 150 days post dose in each treatment arm or the MEDI8897 arm only (depending on the sensitivity analysis assumption above) using the Bernoulli distribution with X-times the observed placebo RSV LRTI rate.

- Step 3: The subjects with imputed values of RSV LRTI status will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose, to form a complete dataset.
- Step 4: Analyze the complete dataset using a Poisson regression model with robust variance to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, categorical age at the time of randomization, and dichotomous temperate hemispheres as covariates. The point estimate and variance will be provided from the model.
- The steps 2-4 will be repeated multiple times. The point estimate and variance for the model parameters for each complete dataset will be used to generate statistical inferences using the multiple imputation procedure (eg, SAS MIANALYZE procedure).

For sensitivity analyses 1 and 5, all subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be assumed to either (1) have an RSV LRTI event (sensitivity analysis #5) or (2) not have an RSV LRTI event (sensitivity analysis #1). The subjects with imputed values of RSV LRTI status will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose, to form a complete dataset. The primary efficacy analysis using the Poisson regression model with robust variance adjusting for the same covariates will be run according to this new dataset.

For sensitivity analysis 6, the same missing data imputation steps described above in Section 3.5.1.2 for the primary efficacy analysis will be followed, except step 1 (ie, the "MEDI8897" treatment code will not be substituted with "placebo" prior to the SAS PROC MI imputations); the actual treatment codes will be used.

3.5.1.5 Subgroup Analyses

The following subgroups analysis will be provided including the efficacy of MEDI8897 relative to placebo and corresponding confidence intervals in each subgroup given there are sizable numbers of subjects in each level of the subgroups:

- Hemisphere/Country
- Age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg)
- Gestational age (29-32 weeks, > 32 weeks)

- Sibling also participating in the study (yes/no)
- Post-baseline detection of ADA (detected, not detected) – only incidence rates will be provided for this summary

Forest plots may be provided showing the relative risk reduction ratio and 95.1% confidence interval for each level of the subgroup.

Subgroup analysis will be conducted:

- in the ITT population using the same method as for the primary analysis, when applicable;
- in the per-protocol population using the same method as for the per-protocol analysis described in Section 3.5.1.4.

3.5.2 Secondary Efficacy Endpoint and Analyses

3.5.2.1 Secondary Efficacy Endpoint

The secondary efficacy endpoint is the incidence of RSV LRTI hospitalization through 150 days post dose. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis.

The analysis of RSV LRTI hospitalizations will be based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from central laboratory analysis respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A and RSV B.

Prior to analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as an RSV LRTI hospitalization if they occurred in a respiratory sample collected within this window relative to the admission/deterioration date. The actual window used will be documented prior to unblinding. In addition, deaths which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as RSV LRTI hospitalization endpoints.

3.5.2.2 Handling of Dropouts and Missing Data

RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. For subjects who do not have an RSV LRTI hospitalization and were not followed through 150 day post dose, their event status will be imputed assuming the observed placebo RSV LRTI hospitalization rate conditional on stratification factors as described below.

A repeated imputation approach is introduced at the subject-level for the model fitting to impute RSV LRTI hospitalization status for missing observations. The same methods described above for the primary efficacy endpoint will be used (see Section 3.5.1.2). However, the imputation by covariates may not be applicable if the total number of RSV LRTI hospitalization events is not adequate (eg, the anticipated number of RSV LRTI hospitalizations is < 40% of the primary RSV LRTI endpoints). In this case the imputation will be performed using the Bernoulli distribution with the observed placebo RSV LRTI hospitalization rate (see Section 3.5.1.4).

3.5.2.3 Secondary Efficacy Analyses

A Poisson regression model with robust variance (Zou, 2004) will be used to compare the incidence of RSV LRTI hospitalization between MEDI8897 and placebo, including treatment group, age at randomization stratum based on CRF calculation (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months) and dichotomous temperate (northern and southern) hemispheres as covariates (similar analysis as described above for the primary endpoint of medically attended RSV LRTI). In addition, the 2-sided p-value and corresponding 2-sided 95.1% CI on the relative risk will be provided from the model. Relative risk reduction is defined as (1 - Pn/Ps) where Pn is the incidence of RSV LRTI hospitalization through 150 days post dose in the MEDI8897 group and Ps is the incidence of RSV LRTI hospitalization through 150 days post dose in the placebo group. Medically attended RSV LRTI hospitalization will be summarized by treatment group for the per-protocol population. Relative risk and 95.1% CI will be constructed using an exact conditional method based on the number of RSV LRTI hospitalization.

The secondary efficacy hypothesis will be assessed only if the primary efficacy hypothesis has been demonstrated. Statistical significance will be achieved if the 2-sided p-value is < 0.049.

3.5.2.4 Additional Analyses of the Secondary Efficacy Endpoint

The additional analyses (except CMH, Kaplan-Meier, and the sensitivity analyses for subjects who were not followed through 150 days post dose) as described for the primary endpoint will be provided for RSV LRTI hospitalization.

3.5.2.5 Subgroup Analyses

The same subgroups analyses as described for the primary endpoint will be provided for RSV LRTI hospitalization.

3.5.3 Other Efficacy Analyses

An analysis will also include the incidence of all medically attended LRTI, protocol-defined LRTI, non-protocol defined LRTI, and incidence by RSV positive RT-PCR and/or local testing results, and RSV negative LRTI by RT-PCR or local testing. This will be repeated for LRTI hospitalizations and medically attended outpatient LRTI events. The same analysis window as described in above sections for the RT-PCR central tests will be used for the local tests. For subjects with multiple events, only the first occurrence will be used in each incidence summary, respectively. The observed and imputed counts from the primary and secondary endpoint analysis will be presented in this summary. For medically attended RSV outpatient LRTI (Protocol-Defined), if a subject does not have an event prior to discontinuation from participation, their event status will be imputed assuming the observed placebo event rate conditional on stratification value (see Section 3.5.1.2). However, the imputation by covariates may not be applicable if the total number of events is not adequate. In this case the imputation will be performed using the Bernoulli distribution with the observed placebo event rate (see Section 3.5.1.4). All other summaries will be based on observed events and available follow-up through 150 days. . This summary will be presented for the ITT population through 150 days post dose, after 150 days post dose, and through 360 days post dose.

Similar to the primary endpoint (as described in Section 3.5.1.4), the total number of new onset events since previous events will be summarized for the following events:

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset medically attended RSV LRTI	A new onset medically attended RSV LRTI will be defined as an adverse event (for which at least one healthcare visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV LRTI.
New onset RSV LRTI **hospitalization**	A new onset medically attended RSV LRTI hospitalization will be defined as an adverse event (for which at least one hospitalization is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV LRTI hospitalization.
New onset medically attended RSV **outpatient** LRTI	A new onset medically attended RSV outpatient LRTI will be defined as an adverse event (for which at least one healthcare outpatient visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV outpatient LRTI.
New onset medically attended LRTI	A new onset medically attended LRTI will be defined as an adverse event of LRTI that occurs after the resolution date of the previous adverse event for a medically attended LRTI.
New onset LRTI **hospitalization**	A new onset medically attended LRTI hospitalization will be defined as an adverse event (with at least one hospitalization associated with LRTI) that occurs after the resolution date of the previous adverse event for a medically attended LRTI hospitalization.

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset medically attended **outpatient** LRTI	A new onset medically attended outpatient LRTI will be defined as an adverse event (with at least one outpatient healthcare visit associated with LRTI) that occurs after the resolution date of the previous adverse event for a medically attended outpatient LRTI.
New onset medically attended non-RSV LRTI	A new onset medically attended Non-RSV LRTI will be defined as an adverse event (for which at least one healthcare visit is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV LRTI.
New onset non-RSV LRTI **hospitalization**	A new onset medically attended Non-RSV LRTI hospitalization will be defined as an adverse event (for which at least one hospitalization is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV LRTI hospitalization.
New onset medically attended non-RSV **outpatient** LRTI	A new onset medically attended Non-RSV outpatient LRTI will be defined as an adverse event LRTI (for which at least one outpatient healthcare visit is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV outpatient LRTI.

Adverse events associated with medically attended LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days.

3.6 Exploratory Analyses

3.6.1 Healthcare Resource Utilization

The magnitude of HRU (eg, number of admissions to hospitals and ICUs and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and types of outpatient visits, eg, outpatient ED, urgent care, outpatient clinic; and number of prescription and OTC medications and duration of use) will be summarized by treatment group for all randomized subjects through 150 days post dose, after 150 days post dose, and through 360 days post dose.

Duration of hospitalization will be calculated from the admission or deterioration date to discharge. Durations for the other parameters will be calculated in a similar manner from start date to stop date. The subject's entire experience throughout the study (eg, separate occurrences of mechanical ventilation within a hospitalization or across separate hospitalizations) will be summed together. All randomized subjects will be included in the analysis; therefore, a subject who was not hospitalized or did not utilize the particular parameter (CPAP, supplemental oxygen use, ICU stay, or mechanical ventilation) will have a duration of 0 days. Unlike the other parameters, supplemental oxygen can also be used in the

outpatient setting, thus the summary of supplemental oxygen will include use in both hospital and outpatient settings.

Durations will be summarized by total days, mean and standard deviation number of days (mean calculated as total days divided by total number of randomized subjects per group), median days, and minimum/maximum number of days.

For duration of prescription and OTC medication summaries, missing or partial concomitant medication start/stop dates will be imputed as follows:

- Partial dates where only the year is known: For start dates assume January 1st; for stop dates assume December 31st.
- Partial dates where only the month and year are known: For start dates assume the first of the month; for stop dates assume the end of the month.

In addition to the overall HRU summary, the HRU for (1) medically attended RSV LRTI (Protocol-Defined), (2) medically attended non-RSV LRTI (Protocol-Defined), and (3) medically attended LRTI (Non-Protocol Defined) will be summarized for all randomized subjects by treatment group, through 150 days post dose, after 150 days post dose, and through 360 days post dose. The same conventions used for the overall summary will apply for the respective events; however, the HRU must occur during the event being summarized. For example, only supplemental oxygen use during a medically attended RSV LRTI (Protocol-Defined) will be counted for the medically attended RSV LRTI summary. A concomitant medication will be associated with the adverse event associated with the RSV LRTI event if the medication was taken to treat the LRTI (as recorded in the CRF) and the medication overlaps the adverse event being summarized. The duration of medications will be counted as the days of medication use residing within the adverse event associated with the RSV event.

Additional summaries of HRUs will evaluate HRUs among subjects who have an event. The summaries will only include subjects with the event (1) medically attended RSV LRTI (Protocol-Defined), (2) medically attended non-RSV LRTI (Protocol-Defined), and (3) medically attended LRTI (Non-Protocol Defined). These summaries will provide an estimate of the average HRU use among subjects who are experiencing an event.

The average number of prescriptions (and OTC medications) per medically attended non-RSV LRTI (Protocol-Defined) per subject will be summarized for each treatment group through 150 days post dose. The average number of prescriptions per medically attended non-RSV LRTI (Protocol-Defined) will be calculated as the total number of prescriptions

provided during the study divided by the total number of medically attended non-RSV LRTI (Protocol-Defined) events. Only subjects with a medically attended non-RSV LRTI (Protocol-Defined) will be included in the analysis. This summary will be provided for subjects with at least one non-RSV LRTI hospitalization and for subjects without any non-RSV LRTI hospitalizations. Similar summaries will be provided for medically attended LRTI (Non-Protocol-Defined).

3.6.2 Caregiver Burden

Caregiver burden (eg, caregiver missed work days, subject absence from day care/babysitting) for subjects with medically attended RSV LRTI (Protocol-Defined) will be summarized by treatment group for all randomized subjects and among subjects who have an event. If at least one healthcare visit occurring during an adverse event is associated with RSV, the caregiver burden collected for that adverse event will be counted in this summary. For example, consider a subject with an LRTI with three healthcare visits: outpatient ER (non-protocol defined LRTI and RSV negative), outpatient clinic (protocol-defined LRTI and RSV negative), and hospitalization (protocol-defined LRTI and RSV positive). Since the hospitalization for this subject meets the protocol definition for LRTI and is associated with RSV, the entire caregiver burden for the adverse event will be included in this summary. Similar summaries will be provided for medically attended non-RSV LRTI (Protocol-Defined) and medically attended LRTI (Non-Protocol-Defined) events. These summaries will be presented through 150 days post dose, after 150 days post dose, and through 360 days post dose.

The average caregiver burden (caregiver missed work days, subject absence from day care/babysitting) per medically attended non-RSV LRTI (Protocol-Defined) per subject will be summarized for each treatment group through 150 days post dose. The average caregiver burden (caregiver missed work days, subject absence from day care/babysitting) per medically attended non-RSV LRTI (Protocol-Defined) will be calculated as the total caregiver burden divided by the total number of medically attended non-RSV LRTI (Protocol-Defined). Only subjects with a medically attended non-RSV LRTI (Protocol-Defined) will be included in the analysis. This summary will be provided for subjects with at least one non-RSV LRTI hospitalization and for subjects without any non-RSV LRTI hospitalizations. As similar summary will be provided for medically attended LRTI (Non-Protocol-Defined).

3.7 Safety Analyses

3.7.1 Adverse Events and Serious Adverse Events

Adverse events will be coded by Medical Dictionary for Regulatory Activities (MedDRA) version 19 or higher and the type, incidence, severity and relationship to study investigational product will be summarized by treatment group. Specific adverse events (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 will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT).

Additional summaries will present treatment-emergent AEs by SOC and high-level term and by SOC and high-level group term. Nontreatment-emergent AEs/serious adverse events (SAEs) will be presented in the listings.

3.7.2 Adverse Events of Special Interest

Adverse events of special interest will include targeted AEs of hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA. Additional groupings may be added by the Medical Monitor if warranted.

3.7.3 Skin and Hypersensitivity Reactions

All skin reactions and skin reactions identified as hypersensitivity/allergic reactions and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA.

3.7.4 New Onset Chronic Disease

New onset chronic diseases include but are not limited to diabetes, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy) and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA.

3.7.5 Subgroup Analyses

All adverse events will be summarized by age at randomization stratum (age $\leq$ 3 months, age > 3 to $\leq$ 6 months, age > 6 months), and weight on day 1 (weight $\leq$ 2.5 kg, weight > 2.5 to $\leq$ 5 kg, weight > 5 kg).

3.7.6 Other Safety Evaluations

Adverse events, adverse events of special interest, skin reactions and skin hypersensitivity reactions will also be summarized by timing relative to dosing ('within 1 day'/'greater than 1 day', 'within 7 days/greater than 7 days').

Additional data collected throughout the study include screen failure data, significant findings in medical history and physical exam, vital signs, and concomitant medications through Day 361. 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.

3.8 Anti-drug Antibodies

The number and percentage of subjects who develop anti-MEDI8897 antibodies will be summarized at each visit by treatment group. For those with a positive assessment, the ADA titer results will also be summarized.

An additional table will summarize 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 summarized by SOC and PT based on MedDRA for subjects with ADA to MEDI8897 at any time post-baseline.

The impact of ADA on PK will be included in the PK report as mentioned in Section 3.9.

3.9 Pharmacokinetics

Following a single dose of MEDI8897, individual MEDI8897 serum concentrations data will be tabulated by treatment group along with description statistics. Terminal-phase half-life ($t_{1/2}$) will be estimated using non-compartmental analysis, if data permit. The details of the analyses and presentation of these data will be included in a separate PK report.

4 INTERIM ANALYSIS

An interim analysis for safety and efficacy will be conducted by an IDMC after approximately 750 infants have been randomized and followed for 150 days post dose. This analysis is being conducted to address the US FDA request that the benefit risk assessment should be performed after 500 infants have received MEDI8897 before moving forward into Phase 3 in infants > 35 wGA. There is no provision to stop the study early due to an efficacy claim; however 0.001 alpha will be spent at this interim analysis based on advice from the US FDA. The final analysis will be tested at 2-sided alpha 0.049 accordingly. Additional details will be provided in the IDMC charter.

Given an IDMC recommendation that the risk/benefit is favorable and a Phase 3 study may be initiated, a limited and controlled internal review of the unblinded interim results will be initiated in order to design the Phase 3 trial and prepare materials for further discussion with regulatory agencies. The site investigators, subjects' parent(s)/legal representative, site monitors, and all study team members at MedImmune having direct contact with the site or involved in the data collection and cleaning process will remain blinded to individual treatment allocation so that blinded follow-up can continue through Day 361. Details will be documented in a separate unblinding plan.

A final analysis is planned after all subjects have completed the 360-day safety follow-up period.

5 REFERENCES

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

Little, R. J. A. and Rubin, D. B. Statistical Analysis with Missing Data, 2nd Edition, Hoboken, NJ: John Wiley & Sons 2002; 257.

O'Brien KL, Chandran A, Weatherholtz R, Jafri HS, Griffin MP, Bellamy T, et al. Respiratory Syncytial Virus Prevention study group. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomized double-blind placebo-controlled trial. Lancet Infect Dis. 2015;15(12):1398-408.

Appendix 1 Elements to Evaluate for Case Definition of Medically Attended RSV LRTI

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive RT-PCR	**Documented PE findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration • Prescription medications (only for children with underlying lung disease)

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = real time reverse transcriptase-polymerase chain reaction;

Note: One item from each column is required to meet the case definition of RSV LRTI.

MedImmune

A member of the AstraZeneca Group

Statistical Analysis Plan Approval

DATE: 13Jan2017

TO: Study File

FROM: [redacted]

RE: Statistical Analysis Plan Version 2.0 Approval for Study D5290C00003

The Statistical Analysis Plan, version 2.0, for Study D5290C00003 has been reviewed and approved.

[redacted] 13 January 2017

Statistician Date

[redacted] 13 January 2017

Statistical Programmer Date

[redacted] 14 January 2017

Clinical Development Lead Date

[redacted] 14 January 2017

Head of Clinical Biostatistics and Data Management Date

Statistical Analysis Plan

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

Protocol Number: D5290C00003

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List of Abbreviations

Abbreviation or Specialized Term	Definition
AAP	American Academy of Pediatrics
AE	adverse event
AESI	adverse event of special interest
CE	*Conformité Européenne* or European Conformity
CI	confidence interval
eCRF	electronic case report form
ER	emergency room
EU	European Union
hMPV	human metapneumovirus
HRU	healthcare resource utilization
ICU	intensive care unit
IDMC	independent data monitoring committee
IM	intramuscular
ITT	intent-to-treat
IWRS	interactive web response system
LRTI	lower respiratory tract infection
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOCD	new onset chronic disease
OTC	over-the-counter
PK	pharmacokinetics
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SID	subject identification
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
US FDA	United States Food and Drug Administration
USA	United States of America
wGA	weeks gestational age

1 INTRODUCTION

This document describes the statistical analysis for protocol D5290C00003, a pivotal Phase 2b study to determine if MEDI8897 is efficacious in reducing medically attended respiratory syncytial virus (RSV)-confirmed lower respiratory tract infection (LRTI) in healthy preterm infants entering their first RSV season. The primary efficacy hypothesis of

this study is that, compared to placebo, a single 50-mg intramuscular (IM) dose of MEDI8897 will be efficacious in reducing medically attended LRTI caused by RT-PCR-confirmed RSV in healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable. The secondary hypotheses are that (1) there will be a reduction in the incidence of hospitalizations attributable to RSV, (2) the predicted extended $t_{1/2}$ will be adequate for the duration of the RSV season, and (3) ADA to MEDI8897 will not significantly impact the serum concentrations or safety of MEDI8897 over the 5-month RSV season. These hypotheses will be assessed by the incidence of RSV LRTI, RSV hospitalization, ADA, pharmacokinetics parameters, and descriptive statistics from safety data. 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(s)

To assess the efficacy of MEDI8897 when administered as a single 50 mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo.

2.1.2 Secondary Study Objectives

1. To assess the efficacy of MEDI8897 for the reduction of hospitalizations due to RT-PCR-confirmed RSV, compared to placebo
2. To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared to placebo
3. To evaluate single-dose serum concentrations of MEDI8897
4. To evaluate ADA responses to MEDI8897 in serum

2.1.3 Exploratory Study Objectives

To assess healthcare resource utilization (HRU) and caregiver burden for MEDI8897 recipients compared to placebo recipients.

2.2 Study Design

The population to be enrolled is healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who would not receive RSV prophylaxis based on the AAP or other local or national guidelines. These infants will not be receiving palivizumab, allowing for a placebo comparator group for the determination of efficacy and the safety profile. A total of 1,500 infants will be randomized 2:1 to receive a 50 mg IM dose of MEDI8897 (N = 1000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. All infants will be followed for approximately 360 days after dosing.

2.3 Treatment Assignment and Blinding

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized at a 2:1 ratio to receive a 50 mg IM dose of MEDI8897 (N = 1,000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500.

The procedure for using IWRS is as follows:

- The investigator or designee contacts the IWRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject
- Placebo (provided by site) or a vial from a MEDI8897 kit will be assigned to the subject
- Confirmation of this information is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log

Investigational product (MEDI8897 or placebo) must be administered the same day the investigational product is assigned. Total in-use storage time from needle puncture of the investigational product vial to administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used. If there is a delay in the administration of investigational product such that it will not be administered within the

specified timeframe, the unblinded investigational product monitor must be notified immediately.

2.4 Sample Size

The sample size of 1,500 is necessary based on advice from the US FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size has approximately > 99% power to detect 70% relative risk reduction, assuming a placebo group medically attended RSV LRTI incidence of 8%. Power calculations are based on Poisson regression model with robust variance (Zou, 2004) comparing MEDI8897 50 mg versus placebo, with 2-sided, $\alpha = 0.049$ (due to 0.001 alpha spend at the interim analysis; refer to Interim Analysis Section 4).

- The 70% relative risk reduction assumption is based on a placebo-controlled study in Native American infants in which there was 87% relative reduction in the incidence of RSV hospitalization (11.3% placebo; 1.5% motavizumab; $p < 0.001$) and 71% relative reduction in the incidence of outpatient RSV LRTI (10.0% placebo; 2.9% motavizumab; $p < 0.001$) in infants who received motavizumab prophylaxis (O'Brien et al, 2015)

In order to evaluate risk, a sample size of 1,000 subjects exposed to MEDI8897 will provide a 90% probability of observing at least one AE if the true event rate is 0.2%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.3%.

3 STATISTICAL METHODS

3.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. In general, unless stated otherwise, baseline will be defined as the last value prior to dosing.

For the primary efficacy analysis for the primary endpoint of medically attended RSV LRTI [and similarly for RSV LRTI hospitalization (Protocol-Defined) and medically attended RSV outpatient LRTI (Protocol-Defined)], if a subject does not experience a medically attended RSV LRTI prior to discontinuation from participation through 150 days post dose, their event status will be imputed assuming the observed placebo medically attended RSV LRTI rate conditional on stratification value. For the sensitivity analyses for the primary endpoint, unless otherwise specified, similar approaches will be used with various assumed medically attended RSV LRTI event rates, with or without stratification adjustment in the imputation.

For additional analyses on the primary endpoint, secondary efficacy analyses, and exploratory efficacy analyses, if no RSV LRTI occurs prior to discontinuation, the subject will be considered as having no RSV LRTI in the analysis, unless stated otherwise.

All analyses, with the exception of safety, will be performed on the ITT Population. Summaries presented for > 150 days post dose will include subjects in the ITT population who are still on study after day 150.

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

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	Subjects who are randomized will be included in the ITT population and subjects will be analyzed according to their randomized treatment group.
As-treated population	Subjects who receive any study investigational product will be included in the as-treated population and subjects will be analyzed according to the treatment they actually receive.
Per-protocol population	The per-protocol population includes all subjects in the as-treated population who are either followed through 150 days post dose or not followed through 150 days post dose but had medically attended RSV LRTI.

3.3 Stratification Factors

Many of the planned analyses presented in the following sections include summaries by age at randomization [age ≤ 3 months (ie, age ≤ 91 days), age > 3 to ≤ 6 months (ie, age > 91 to ≤ 183 days), age > 6 months (ie, age > 183 days)] and hemisphere (northern hemisphere, southern hemisphere). For subjects who were assigned to an incorrect age stratum at randomization, the age stratum as calculated from the electronic case report form (eCRF) will differ from the stratum recorded for the subject in the IWRS database. Unless stated otherwise, the age stratum based on the CRF calculation will be used.

CRF calculation for age when full DOB is available:

- Age at randomization (months) = (randomization date – date of birth) / (365.25/12)

When full DOB is unavailable, age at screening will be used. Since screening may be collected in terms of days, weeks, or months, it will be first converted in terms of months as follows:

- Age at screening (days) / (365.25/12) = Age at screening (months)
- Age at screening (weeks) / (52/12) = Age at screening (months)

Once Age at screening is converted to months,

- Age at randomization (months)= Age at screening (months) + [(randomization date – screening date) / (365.25/12)]

Many analyses will also be summarized by hemisphere. The sites have been grouped together by country into the following two hemispheres: Northern Hemisphere (Bulgaria, Canada, Czech Republic, France, Hungary, Italy, Poland, Russian Federation, Spain, United Kingdom, and USA) and Southern Hemisphere (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa).

3.4 Study Subjects

3.4.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment received (including summary of subjects randomized but not treated) will be provided. In addition, disposition of subjects throughout the study with respect to follow-up will be provided. This summary will be presented by treatment group and for all subjects combined. The denominators for this summary will include all subjects who were randomized into the study.

3.4.2 Demographics and Baseline Characteristics

Enrollment will be summarised by hemisphere, country and site, and by hemisphere, country, and age at randomization stratum for each treatment group and for all subjects combined. The total number of subjects randomized into each treatment group will be used as the denominator. For the summary of hemisphere, country, and age at randomization stratum, the number of mis-stratified subjects (ie, age stratum as calculated from the eCRF does not match the IWRS database) will be summarized.

Demographic information related to gender, age at randomization (months) calculated from the CRF, age at randomization category determined using the CRF age calculation (age $\leq$ 3 months, age $>$ 3 to $\leq$ 6 months, age $>$ 6 months), gestational age (weeks), gestational age

category (29-32 weeks, > 32 weeks), ethnicity, race, weight (kg) on day 1, weight on day 1 category (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg), birth weight (kg), birth weight category (weight ≤ 2.5 kg, weight > 2.5 kg), multiple birth (yes/no), and siblings enrolled in the study (yes/no) will be summarized by treatment group and for all subjects combined using the ITT population. Subjects will be excluded from the summary (eg, means and percentages) of an individual parameter if data are missing. This will be done for all subjects, each age category at randomization, country, and by hemisphere.

3.4.3 Study Drug Exposure

Due to the simplicity of dosing for this study, exposure is summarized in the Subject Disposition and Completion Status table under the summary "Randomized and dosed." No other summary will be reported.

3.5 Efficacy Analyses

An interim analysis for safety and efficacy will be conducted by an independent data monitoring committee (IDMC) after approximately 750 infants have been randomized and followed for at least 150 days post dose. There is no provision to stop early due to an efficacy claim, however 0.001 alpha will be spent at the interim analysis based on advice from the US FDA. The final analysis will be tested at 2-sided alpha 0.049 accordingly.

For the final analysis, the secondary efficacy hypothesis will be assessed only if the primary efficacy hypothesis has been demonstrated. Due to this preplanned sequential testing procedure, the overall Type I error is controlled at 0.049. Therefore, no further multiplicity adjustment is necessary.

3.5.1 Primary Efficacy Endpoint and Analyses

3.5.1.1 Primary Efficacy Endpoint

The primary endpoint is the incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose. For subjects with multiple medically attended RSV LRTI events (inpatient or outpatient), only the first occurrence will be used in the primary analysis.

The analysis of medically attended RSV LRTI will be based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from analyzing the respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A and RSV B performed in a central laboratory. These LRTI events may occur in the inpatient or outpatient visit setting.

Prior to analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as an medically attended RSV LRTI if they occurred in a respiratory sample collected within this window relative to the initial date seen by the healthcare provider (eg, admission/deterioration date associated with the event, urgent care visit, outpatient ED visit, or outpatient clinic visit). The actual window used will be documented prior to unblinding. In addition, deaths which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as primary medically attended RSV LRTI events.

3.5.1.2 Handling of Dropouts and Missing Data

RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo medically attended RSV LRTI rate conditional on stratification factors as described below.

The primary analysis uses Poisson regression with robust variance with stratification factors as covariates, which requires a subject-level dataset. A repeated imputation approach is introduced to impute medically attended RSV LRTI status for missing observations at the subject-level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and confidence interval estimation of the treatment effect is expected through the repeated imputation (Little and Rubin, 2002). To cope with the primary analysis including stratification factors/covariates, the missing values will be imputed at the medically attended RSV LRTI risk level adjusted for subject's stratification value using SAS PROC MI with, e.g., logistic regression method.

The details for the repeated imputation placebo medically attended RSV LRTI rate adjusted for stratification values are provided below. Note that the placebo rate is applied equally to both placebo and MEDI8897 groups in the imputation.

- Step 1: For the subjects in the MEDI8897 arm who do not have an RSV LRTI and are not followed through 150 days post dose, their treatment code of "MEDI8897" will be substituted with "placebo" to ensure the placebo RSV LRTI risk is equally applied in the imputation for both the MEDI8897 and placebo subjects adjusted for their stratification values. The imputation will be executed using SAS PROC MI (e.g., logistic regression with stratification factors).
- Step 2: The original treatment code will be restored after the RSV LRTI event statuses have been imputed. A complete dataset comprises the imputed RSV LRTI status and observed RSV LRTI status.

- Step 3: Analyze the complete dataset using a Poisson regression model with robust variance to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, categorical age at randomization, and dichotomous temperate hemispheres as covariates. The point estimate and variance will be extracted from the model.
- Steps 2-3 will be repeated multiple times. The set of point estimates and variances for the model parameter for each complete dataset will be used to generate statistical inferences using the multiple imputation procedure (eg, SAS MIANALYZE procedure).

3.5.1.3 Primary Efficacy Analysis

The primary (ie, final) efficacy analysis of the primary endpoint will be evaluated using the ITT Population. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary efficacy analysis to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo groups, including treatment group, age at randomization based on CRF calculation (ie, age $\leq$ 3 months, age > 3 to $\leq$ 6 months, age > 6 months) and dichotomous temperate (northern and southern) hemispheres as covariates. If the number of subjects in any stratum is too small and/or convergence cannot be achieved, the covariate(s) may not be included in the model. In addition, the 2-sided p-value and corresponding 2-sided 95.1% CI on the relative risk reduction will be provided from the model. Relative risk reduction is defined as (1 - Pn/Ps) where Pn is the incidence of medically attended RSV LRTI through 150 days post dose in the MEDI8897 group and Ps is the incidence of RSV LRTI through 150 days post dose in the placebo group. Statistical significance will be achieved if the 2-sided p-value is < 0.049.

3.5.1.4 Additional Analyses of the Primary Efficacy Endpoint

Additional analyses will be based on observed events and available follow-up through 150 days, unless stated otherwise.

To allow for differences in follow-up time, the primary analysis using Poisson Regression with robust variance will be repeated, adjusting for the same covariates as well as log(follow-up time) as an offset.

- For subjects who meet the medically attended RSV LRTI endpoint within 150 days postdose, the follow-up time will be calculated as (Date of Onset of RSV LRTI) – (Date of Dosing) +1.
- For subjects who do not experience a medically attended RSV LRTI event within 150 days post dose, the efficacy follow-up will be determined based on the following:
  - If an end of study date occurs within 150 days post dose (or end of study date is missing and last assessment date occurs within 150 days post dose), the efficacy

follow-up will be calculated as (Date of End of Study or Date of Last Assessment, whichever is later) – (Date of Dosing) +1.

- If an end of study date occurs after 150 days post dose (or end of study date is missing and last assessment date is after 150 days post dose), the efficacy follow-up will be set to 150 days.

Medically attended RSV LRTI will be summarized by treatment group for the per-protocol population. Relative risk reduction and its 95.1% CI will be constructed using an exact conditional method based on the number of RSV LRTIs.

A CMH (Cochran-Mantel-Haenszel) test stratified by hemisphere and age at randomization (ie, age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months) will be used to compare between treatment groups through 150 days post dose as a sensitivity analysis for the primary endpoint.A Kaplan-Meier curve for time to first medically attended RSV LRTI will be used as a sensitivity analysis for the primary endpoint. Subjects who have not had a medically attended RSV LRTI through 150 days post dose will be considered censored. For these subjects time will be defined in days from the date of randomization to date of last follow-up (see above for calculation). For subjects experiencing a medically attended RSV LRTI through 150 days post dose, time will be defined from randomization to date of first medically attended RSV LRTI. A plot presenting the Kaplan-Meier curves will be created. Treatment groups will be compared using the stratified log-rank and Wilcoxon tests.

The incidence of medically attended RSV LRTI by subtype (RSV A, RSV B) through 150 days post dose will be summarized for each treatment group using the Poisson regression approach as described for the primary efficacy analysis (Section 3.5.1.3). The analysis will include the relative efficacy, 2-sided p-value and 2-sided 95.1% CI on the relative risk reduction from the model.

The total number of new onset medically attended RSV LRTIs since the previous medically attended RSV LRTI will be calculated for each subject. A new onset medically attended RSV LRTI will be defined as an adverse event (for which at least one healthcare visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV LRTI (see Table 3.5-1). The total number of medically attended RSV LRTIs occurring for each subject through 150 days post dose will be summarized by numbers and percentages of subjects who have X number of medically attended RSV LRTIs (ie, 0, 1, 2, 3... medically attended RSV LRTIs). This summary will be repeated for medically attended RSV LRTIs occurring > 150 days post dose and for ≤ 360 days post dose.

Additional summaries will present the incidence of medically attended RSV LRTI through for ≤ 360 days post dose and occurring > 150 days post dose.

Adverse events associated with medically attended RSV LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days.

Sensitivity Analyses for Subjects who are Not Followed through 150 Days Post Dose

Sensitivity analyses for RSV LRTI through 150 days post dose will be performed to address subjects who do not have an RSV LRTI and are not followed through 150 days post dose. The imputed rates of medically attended RSV LRTI through 150 days post dose will be as follows:

1. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having not met the RSV LRTI endpoint within each treatment group.
2. Impute the missing values in each treatment group using 2-times the placebo RSV LRTI event rate through 150 days post dose (ie, Bernoulli distribution with expected value equal to 2-times placebo RSV LRTI event rate)
3. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 2-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 1 or 2-times placebo RSV LRTI event rate)
4. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 3-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 1 or 3-times placebo RSV LRTI event rate)
5. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having met the RSV LRTI endpoint within each treatment group (ie, clinical failures).
6. Multiple imputation
7. Impute the missing values in each treatment group using 1-times, 2-times, and 3-times the overall placebo event rate.

The sensitivity analyses 2-4 will be carried out following the steps below:

- Step 1: Determine the observed placebo RSV LRTI rate through 150 days post dose, which is calculated as the proportion of all randomized placebo subjects with observed RSV.
- Step 2: Impute the event status for subjects who do not have an RSV LRTI and are not followed through 150 days post dose in each treatment arm or the MEDI8897 arm only

(depending on the sensitivity analysis assumption above) using the Bernoulli distribution with X-times the observed placebo RSV LRTI rate.

- Step 3: The subjects with imputed values of RSV LRTI status will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose, to form a complete dataset.
- Step 4: Analyze the complete dataset using a Poisson regression model with robust variance to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, categorical age at the time of randomization, and dichotomous temperate hemispheres as covariates. The point estimate and variance will be provided from the model.
- The steps 2-4 will be repeated multiple times. The point estimate and variance for the model parameters for each complete dataset will be used to generate statistical inferences using the multiple imputation procedure (eg, SAS MIANALYZE procedure).

For sensitivity analyses 1 and 5, all subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be assumed to either (1) have an RSV LRTI event (sensitivity analysis #5) or (2) not have an RSV LRTI event (sensitivity analysis #1). The subjects with imputed values of RSV LRTI status will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose, to form a complete dataset. The primary efficacy analysis using the Poisson regression model with robust variance adjusting for the same covariates will be run according to this new dataset.

For sensitivity analysis 6, the same missing data imputation steps described above in Section 3.5.1.2 for the primary efficacy analysis will be followed, except step 1 (ie, the "MEDI8897" treatment code will not be substituted with "placebo" prior to the SAS PROC MI imputations); the actual treatment codes will be used.

For sensitivity analysis 7, the missing values will be imputed overall regardless of strata. The relative risk reduction and its 95.1% CI will be constructed using an exact conditional method based on the number of RSV LRTIs.

3.5.1.5 Subgroup Analyses

The following subgroups analysis will be provided including the efficacy of MEDI8897 relative to placebo and corresponding confidence intervals in each subgroup given there are sizable numbers of subjects in each level of the subgroups:

- Hemisphere/Country
- Age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months)

- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg)
- Gestational age (29-32 weeks, > 32 weeks)
- Sibling also participating in the study (yes/no)
- Post-baseline detection of ADA (detected, not detected) – only incidence rates will be provided for this summary

Forest plots may be provided showing the relative risk reduction and 95.1% confidence interval for each level of the subgroup.

Subgroup analysis will be conducted:

- in the ITT population using the same method as for the primary analysis, when applicable;
- in the per-protocol population using the same method as for the per-protocol analysis described in Section 3.5.1.4.

3.5.2 Secondary Efficacy Endpoint and Analyses

3.5.2.1 Secondary Efficacy Endpoint

The secondary efficacy endpoint is the incidence of RSV LRTI hospitalization through 150 days post dose. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis.

The analysis of RSV LRTI hospitalizations will be based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from central laboratory analysis respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A and RSV B.

Prior to analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as an RSV LRTI hospitalization if they occurred in a respiratory sample collected within this window relative to the admission/deterioration date. The actual window used will be documented prior to unblinding. In addition, deaths which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as RSV LRTI hospitalization endpoints.

3.5.2.2 Handling of Dropouts and Missing Data

RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. For subjects who do not have an RSV LRTI hospitalization and were not followed through 150 day post dose, their event status will be imputed assuming the observed placebo RSV LRTI hospitalization rate conditional on stratification factors as described below.

A repeated imputation approach is introduced at the subject-level for the model fitting to impute RSV LRTI hospitalization status for missing observations. The same methods described above for the primary efficacy endpoint will be used (see Section 3.5.1.2). However, the imputation by covariates may not be applicable if the total number of RSV LRTI hospitalization events is not adequate (eg, the anticipated number of RSV LRTI hospitalizations is < 40% of the primary RSV LRTI endpoints). In this case the imputation will be performed using the Bernoulli distribution with the observed placebo RSV LRTI hospitalization rate (see Section 3.5.1.4).

3.5.2.3 Secondary Efficacy Analyses

A Poisson regression model with robust variance (Zou, 2004) will be used to compare the incidence of RSV LRTI hospitalization between MEDI8897 and placebo, including treatment group, age at randomization stratum based on CRF calculation (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months) and dichotomous temperate (northern and southern) hemispheres as covariates (similar analysis as described above for the primary endpoint of medically attended RSV LRTI). In addition, the 2-sided p-value and corresponding 2-sided 95.1% CI on the relative risk reduction will be provided from the model. Relative risk reduction is defined as (1 - Pn/Ps) where Pn is the incidence of RSV LRTI hospitalization through 150 days post dose in the MEDI8897 group and Ps is the incidence of RSV LRTI hospitalization through 150 days post dose in the placebo group. Medically attended RSV LRTI hospitalization will be summarized by treatment group for the per-protocol population. Relative risk reduction and 95.1% CI will be constructed using an exact conditional method based on the number of RSV LRTI hospitalization.

The secondary efficacy hypothesis will be assessed only if the primary efficacy hypothesis has been demonstrated. Statistical significance will be achieved if the 2-sided p-value is < 0.049.

3.5.2.4 Additional Analyses of the Secondary Efficacy Endpoint

The additional analyses (except CMH, Kaplan-Meier, and the sensitivity analyses for subjects who were not followed through 150 days post dose) as described for the primary endpoint will be provided for RSV LRTI hospitalization.

3.5.2.5 Subgroup Analyses

The same subgroups analyses as described for the primary endpoint will be provided for RSV LRTI hospitalization.

3.5.3 Other Efficacy Analyses

An analysis will also include the incidence of all medically attended LRTI, protocol-defined LRTI, non-protocol defined LRTI, and incidence by RSV positive RT-PCR and/or local testing results, and RSV negative LRTI by RT-PCR or local testing. This will be repeated for LRTI hospitalizations and medically attended outpatient LRTI events. The same analysis window as described in above sections for the RT-PCR central tests will be used for the local tests. For subjects with multiple events, only the first occurrence will be used in each incidence summary, respectively. The observed and imputed counts from the primary and secondary endpoint analysis will be presented in this summary. For medically attended RSV outpatient LRTI (Protocol-Defined), if a subject does not have an event prior to discontinuation from participation, their event status will be imputed assuming the observed placebo event rate conditional on stratification value (see Section 3.5.1.2). However, the imputation by covariates may not be applicable if the total number of events is not adequate. In this case the imputation will be performed using the Bernoulli distribution with the observed placebo event rate (see Section 3.5.1.4). All other summaries will be based on observed events and available follow-up through 150 days. . This summary will be presented for the ITT population through 150 days post dose, after 150 days post dose, and through 360 days post dose.

Similar to the primary endpoint (as described in Section 3.5.1.4), the total number of new onset events since previous events will be summarized for the following events:

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset medically attended RSV LRTI	A new onset medically attended RSV LRTI will be defined as an adverse event (for which at least one healthcare visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV LRTI.

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset RSV LRTI **hospitalization**	A new onset medically attended RSV LRTI hospitalization will be defined as an adverse event (for which at least one hospitalization is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV LRTI hospitalization.
New onset medically attended RSV **outpatient** LRTI	A new onset medically attended RSV outpatient LRTI will be defined as an adverse event (for which at least one healthcare outpatient visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV outpatient LRTI.
New onset medically attended LRTI	A new onset medically attended LRTI will be defined as an adverse event of LRTI that occurs after the resolution date of the previous adverse event for a medically attended LRTI.
New onset LRTI **hospitalization**	A new onset medically attended LRTI hospitalization will be defined as an adverse event (with at least one hospitalization associated with LRTI) that occurs after the resolution date of the previous adverse event for a medically attended LRTI hospitalization.
New onset medically attended **outpatient** LRTI	A new onset medically attended outpatient LRTI will be defined as an adverse event (with at least one outpatient healthcare visit associated with LRTI) that occurs after the resolution date of the previous adverse event for a medically attended outpatient LRTI.
New onset medically attended non-RSV LRTI	A new onset medically attended Non-RSV LRTI will be defined as an adverse event (for which at least one healthcare visit is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV LRTI.
New onset non-RSV LRTI **hospitalization**	A new onset medically attended Non-RSV LRTI hospitalization will be defined as an adverse event (for which at least one hospitalization is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV LRTI hospitalization.
New onset medically attended non-RSV **outpatient** LRTI	A new onset medically attended Non-RSV outpatient LRTI will be defined as an adverse event LRTI (for which at least one outpatient healthcare visit is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV outpatient LRTI.

Adverse events associated with medically attended LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days.

3.6 Exploratory Analyses

3.6.1 Healthcare Resource Utilization

The magnitude of HRU (eg, number of admissions to hospitals and ICUs and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and types of outpatient visits, eg, outpatient ED, urgent care, outpatient clinic; and number of prescription and OTC medications and duration of use) will

be summarized by treatment group for all randomized subjects through 150 days post dose, after 150 days post dose, and through 360 days post dose.

Duration of hospitalization will be calculated from the admission or deterioration date to discharge. Durations for the other parameters will be calculated in a similar manner from start date to stop date. The subject's entire experience throughout the study (eg, separate occurrences of mechanical ventilation within a hospitalization or across separate hospitalizations) will be summed together. All randomized subjects will be included in the analysis; therefore, a subject who was not hospitalized or did not utilize the particular parameter (CPAP, supplemental oxygen use, ICU stay, or mechanical ventilation) will have a duration of 0 days. Unlike the other parameters, supplemental oxygen can also be used in the outpatient setting, thus the summary of supplemental oxygen will include use in both hospital and outpatient settings.

Durations will be summarized by total days, mean and standard deviation number of days (mean calculated as total days divided by total number of randomized subjects per group), median days, and minimum/maximum number of days.

For duration of prescription and OTC medication summaries, missing or partial concomitant medication start/stop dates will be imputed as follows:

- Partial dates where only the year is known: For start dates assume January 1st; for stop dates assume December 31st.
- Partial dates where only the month and year are known: For start dates assume the first of the month; for stop dates assume the end of the month.

In addition to the overall HRU summary, the HRU for (1) medically attended RSV LRTI (Protocol-Defined), (2) medically attended non-RSV LRTI (Protocol-Defined), and (3) medically attended LRTI (Non-Protocol Defined) will be summarized for all randomized subjects by treatment group, through 150 days post dose, after 150 days post dose, and through 360 days post dose. The same conventions used for the overall summary will apply for the respective events; however, the HRU must occur during the event being summarized. For example, only supplemental oxygen use during a medically attended RSV LRTI (Protocol-Defined) will be counted for the medically attended RSV LRTI summary. A concomitant medication will be associated with the adverse event associated with the RSV LRTI event if the medication was taken to treat the LRTI (as recorded in the CRF) and the medication overlaps the adverse event being summarized. The duration of medications will be counted as the days of medication use residing within the adverse event associated with the RSV event.

Additional summaries of HRUs will evaluate HRUs among subjects who have an event. The summaries will only include subjects with the event (1) medically attended RSV LRTI (Protocol-Defined), (2) medically attended non-RSV LRTI (Protocol-Defined), and (3) medically attended LRTI (Non-Protocol Defined). These summaries will provide an estimate of the average HRU use among subjects who are experiencing an event.

The average number of prescriptions (and OTC medications) per medically attended non-RSV LRTI (Protocol-Defined) per subject will be summarized for each treatment group through 150 days post dose. The average number of prescriptions per medically attended non-RSV LRTI (Protocol-Defined) will be calculated as the total number of prescriptions provided during the study divided by the total number of medically attended non-RSV LRTI (Protocol-Defined) events. Only subjects with a medically attended non-RSV LRTI (Protocol-Defined) will be included in the analysis. This summary will be provided for subjects with at least one non-RSV LRTI hospitalization and for subjects without any non-RSV LRTI hospitalizations. Similar summaries will be provided for medically attended LRTI (Non-Protocol-Defined).

3.6.2 Caregiver Burden

Caregiver burden (eg, caregiver missed work days, subject absence from day care/babysitting) for subjects with medically attended RSV LRTI (Protocol-Defined) will be summarized by treatment group for all randomized subjects and among subjects who have an event. If at least one healthcare visit occurring during an adverse event is associated with RSV, the caregiver burden collected for that adverse event will be counted in this summary. For example, consider a subject with an LRTI with three healthcare visits: outpatient ER (non-protocol defined LRTI and RSV negative), outpatient clinic (protocol-defined LRTI and RSV negative), and hospitalization (protocol-defined LRTI and RSV positive). Since the hospitalization for this subject meets the protocol definition for LRTI and is associated with RSV, the entire caregiver burden for the adverse event will be included in this summary. Similar summaries will be provided for medically attended non-RSV LRTI (Protocol-Defined) and medically attended LRTI (Non-Protocol-Defined) events. These summaries will be presented through 150 days post dose, after 150 days post dose, and through 360 days post dose.

The average caregiver burden (caregiver missed work days, subject absence from day care/babysitting) per medically attended non-RSV LRTI (Protocol-Defined) per subject will be summarized for each treatment group through 150 days post dose. The average caregiver burden (caregiver missed work days, subject absence from day care/babysitting) per medically attended non-RSV LRTI (Protocol-Defined) will be calculated as the total

caregiver burden divided by the total number of medically attended non-RSV LRTI (Protocol-Defined). Only subjects with a medically attended non-RSV LRTI (Protocol-Defined) will be included in the analysis. This summary will be provided for subjects with at least one non-RSV LRTI hospitalization and for subjects without any non-RSV LRTI hospitalizations. As similar summary will be provided for medically attended LRTI (Non-Protocol-Defined).

3.7 Safety Analyses

3.7.1 Adverse Events and Serious Adverse Events

Adverse events will be coded by Medical Dictionary for Regulatory Activities (MedDRA) version 19 or higher and the type, incidence, severity and relationship to study investigational product will be summarized by treatment group. Specific adverse events (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 will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT).

Additional summaries will present treatment-emergent AEs by SOC and high-level term and by SOC and high-level group term. Nontreatment-emergent AEs/serious adverse events (SAEs) will be presented in the listings.

3.7.2 Adverse Events of Special Interest

Adverse events of special interest will include targeted AEs of hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA. Additional groupings may be added by the Medical Monitor if warranted.

3.7.3 Skin and Hypersensitivity Reactions

All skin reactions and skin reactions identified as hypersensitivity/allergic reactions and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA.

3.7.4 New Onset Chronic Disease

New onset chronic diseases include but are not limited to diabetes, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy) and the type, incidence,

and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA.

3.7.5 Subgroup Analyses

All adverse events will be summarized by age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months), and weight on day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg).

3.7.6 Other Safety Evaluations

Adverse events, adverse events of special interest, skin reactions and skin hypersensitivity reactions will also be summarized by timing relative to dosing ('within 1 day'/'greater than 1 day', 'within 7 days/greater than 7 days').

Additional data collected throughout the study include screen failure data, significant findings in medical history and physical exam, vital signs, and concomitant medications through Day 361. 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.

3.8 Anti-drug Antibodies

The number and percentage of subjects who develop anti-MEDI8897 antibodies will be summarized at each visit by treatment group. For those with a positive assessment, the ADA titer results will also be summarized.

An additional table will summarize 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 summarized by SOC and PT based on MedDRA for subjects with ADA to MEDI8897 at any time post-baseline.

The impact of ADA on PK will be included in the PK report as mentioned in Section 3.9.

3.9 Pharmacokinetics

Following a single dose of MEDI8897, individual MEDI8897 serum concentrations data will be tabulated by treatment group along with description statistics. Terminal-phase half-life ($t_{1/2}$) will be estimated using non-compartmental analysis, if data permit. The details of the analyses and presentation of these data will be included in a separate PK report.

4 INTERIM ANALYSIS

An interim analysis for safety and efficacy will be conducted by an IDMC after approximately 750 infants have been randomized and followed for 150 days post dose. This analysis is being conducted to address the US FDA request that the benefit risk assessment should be performed after 500 infants have received MEDI8897 before moving forward into Phase 3 in infants > 35 wGA. There is no provision to stop the study early due to an efficacy claim; however 0.001 alpha will be spent at this interim analysis based on advice from the US FDA. The final analysis will be tested at 2-sided alpha 0.049 accordingly. Additional details will be provided in the IDMC charter.

Given an IDMC recommendation that the risk/benefit is favorable and a Phase 3 study may be initiated, a limited and controlled internal review of the unblinded interim results will be initiated in order to design the Phase 3 trial and prepare materials for further discussion with regulatory agencies. The site investigators, subjects' parent(s)/legal representative, site monitors, and all study team members at MedImmune having direct contact with the site or involved in the data collection and cleaning process will remain blinded to individual treatment allocation so that blinded follow-up can continue through Day 361. Details will be documented in a separate unblinding plan.

A final analysis is planned after all subjects have completed the 360-day safety follow-up period.

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Appendix 1 Elements to Evaluate for Case Definition of Medically Attended RSV LRTI

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive RT-PCR	**Documented PE findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration • Prescription medications (only for children with underlying lung disease)

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = real time reverse transcriptase-polymerase chain reaction;

Note: One item from each column is required to meet the case definition of RSV LRTI.

Statistical Analysis Plan

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

Protocol Number: D5290C00003

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Abbreviation or Specialized Term	Definition
AAP	American Academy of Pediatrics
AE	adverse event
AESI	adverse event of special interest
CE	*Conformité Européenne* or European Conformity
CI	confidence interval
eCRF	electronic case report form
ER	emergency room
EU	European Union
hMPV	human metapneumovirus
HRU	healthcare resource utilization
ICU	intensive care unit
IDMC	independent data monitoring committee
IM	intramuscular
ITT	intent-to-treat
IWRS	interactive web response system
LRTI	lower respiratory tract infection
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOCD	new onset chronic disease
OTC	over-the-counter
PK	pharmacokinetics
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SID	subject identification
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
US FDA	United States Food and Drug Administration
USA	United States of America
wGA	weeks gestational age

1 INTRODUCTION

This document describes the statistical analysis for protocol D5290C00003, a pivotal Phase 2b study to determine if MEDI8897 is efficacious in reducing medically attended respiratory syncytial virus (RSV)-confirmed lower respiratory tract infection (LRTI) in healthy preterm infants entering their first RSV season. The primary efficacy hypothesis of

this study is that, compared to placebo, a single 50-mg intramuscular (IM) dose of MEDI8897 will be efficacious in reducing medically attended LRTI caused by RT-PCR-confirmed RSV in healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable. The secondary hypotheses are that (1) there will be a reduction in the incidence of hospitalizations attributable to RSV, (2) the predicted extended $t_{1/2}$ will be adequate for the duration of the RSV season, and (3) ADA to MEDI8897 will not significantly impact the serum concentrations or safety of MEDI8897 over the 5-month RSV season. These hypotheses will be assessed by the incidence of RSV LRTI, RSV hospitalization, ADA, pharmacokinetics parameters, and descriptive statistics from safety data. 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(s)

To assess the efficacy of MEDI8897 when administered as a single 50 mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo.

2.1.2 Secondary Study Objectives

1. To assess the efficacy of MEDI8897 for the reduction of hospitalizations due to RT-PCR-confirmed RSV, compared to placebo
2. To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared to placebo
3. To evaluate single-dose serum concentrations of MEDI8897
4. To evaluate ADA responses to MEDI8897 in serum

2.1.3 Exploratory Study Objectives

To assess healthcare resource utilization (HRU) and caregiver burden for MEDI8897 recipients compared to placebo recipients.

2.2 Study Design

The population to be enrolled is healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who would not receive RSV prophylaxis based on the AAP or other local or national guidelines. These infants will not be receiving palivizumab, allowing for a placebo comparator group for the determination of efficacy and the safety profile. A total of 1,500 infants will be randomized 2:1 to receive a 50 mg IM dose of MEDI8897 (N = 1000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age group at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. All infants will be followed for approximately 360 days after dosing.

2.3 Treatment Assignment and Blinding

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized at a 2:1 ratio to receive a 50 mg IM dose of MEDI8897 (N = 1,000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age group at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500.

The procedure for using IWRS is as follows:

- The investigator or designee contacts the IWRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject
- Placebo (provided by site) or a vial from a MEDI8897 kit will be assigned to the subject
- Confirmation of this information is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log

Investigational product (MEDI8897 or placebo) must be administered the same day the investigational product is assigned. Total in-use storage time from needle puncture of the investigational product vial to administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used. If there is a delay in the administration of investigational product such that it will not be administered within the

specified timeframe, the unblinded investigational product monitor must be notified immediately.

2.4 Sample Size

The sample size of 1,500 is necessary based on advice from the US FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size has approximately > 99% power to detect 70% relative risk reduction, assuming a placebo group medically attended RSV LRTI incidence of 8%. Power calculations are based on Poisson regression model with robust variance (Zou, 2004) comparing MEDI8897 50 mg versus placebo, with 2-sided, $\alpha = 0.05$.

- The 70% relative risk reduction assumption is based on a placebo-controlled study in Native American infants in which there was 87% relative reduction in the incidence of RSV hospitalization (11.3% placebo; 1.5% motavizumab; $p < 0.001$) and 71% relative reduction in the incidence of outpatient RSV LRTI (10.0% placebo; 2.9% motavizumab; $p < 0.001$) in infants who received motavizumab prophylaxis (O'Brien et al, 2015)

In order to evaluate risk, a sample size of 1,000 subjects exposed to MEDI8897 will provide a 90% probability of observing at least one AE if the true event rate is 0.2%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.3%.

3 STATISTICAL METHODS

3.1 General Considerations

Summary statistics will be tabulated by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by mean, median, standard deviation, minimum and maximum. In general, unless stated otherwise, baseline will be defined as the last non-missing value prior to dosing.

There are two planned analyses for this study: the Primary Analysis and the Final Analysis. The Primary Analysis will be conducted after all randomized subjects have completed the Day 151 visit. At the time of this primary analysis, approximately half of all subjects enrolled (722 subjects) will have completed the Day 361 visit. The remaining 731 subjects will have completed approximately 8 months of the study. MEDI8897'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 and Datasets

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	Subjects who are randomized will be included in the ITT population; in this population data will be analyzed according to their randomized treatment group.
As-treated population	Subjects who are randomized and receive any study investigational product will be included in the as-treated population; in this population, data will be analyzed according to the treatment they actually receive.
Per-protocol population	The per-protocol population includes subjects in the ITT population who receive the correct dose of randomized treatment and who do not have a serious protocol violation. Detailed criteria defining this population will be determined and documented prior to performing the Primary Analysis.

Analysis Datasets

- The Primary Dataset contains all data (efficacy, safety, ADA, PK) from all randomized subjects through the Day 151visit 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 Stratification Factors

Two stratification factors are used in study design as well as in data analysis, and these are: age group at randomization [age ≤ 3 months (ie, age ≤ 91 days), age > 3 to ≤ 6 months (ie, age > 91 to ≤ 183 days), age > 6 months (ie, age > 183 days)] and hemisphere (northern hemisphere, southern hemisphere). For subjects who were assigned to an incorrect age stratum at randomization, the age stratum as calculated from the electronic case report form (eCRF) will differ from the stratum recorded for the subject in the IWRS database. Unless stated otherwise, the age stratum based on the CRF calculation will be used.

CRF calculation for age when full DOB is available:

- Age at randomization (months) = (randomization date – date of birth) / (365.25/12)

When full DOB is unavailable, age at screening will be used. Since screening may be collected in terms of days, weeks, or months, it will be first converted in terms of months as follows:

- Age at screening (days) / (365.25/12) = Age at screening (months)
- Age at screening (weeks) / (52/12) = Age at screening (months)

Once Age at screening is converted to months,

- Age at randomization (months)= Age at screening (months) + [(randomization date – screening date) / (365.25/12)]

Determination of hemisphere in stratification and analysis is as follows. The sites have been grouped together by country into the following two hemispheres: Northern Hemisphere (Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Hungary, Italy, Latvia, Lithuania, Poland, Spain, Sweden, Turkey, United Kingdom, and USA) and Southern Hemisphere (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa).

3.4 Study Subjects

3.4.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment received (including summary of subjects randomized but not treated) will be provided. In addition, disposition of subjects throughout the study and by visit will be provided. This summary will be presented by treatment group and for all subjects combined. The denominators for this summary will include all subjects who were randomized into the study.

3.4.2 Demographics and Baseline Characteristics

Enrollment will be summarised by hemisphere, country and site, and by hemisphere, country, and age at randomization stratum for each treatment group and for all subjects combined. The total number of subjects randomized into each treatment group will be used as the denominator. For the summary of hemisphere, country, and age at randomization stratum, the number of mis-stratified subjects (ie, age stratum as calculated from the eCRF does not match the IWRS database) will be summarized.

Demographic information related to gender, age at randomization (months) calculated from the CRF, age at randomization category determined using the CRF age calculation (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months), gestational age (weeks), gestational age category (29-32 weeks, > 32 weeks), ethnicity, race, weight (kg) on day 1, weight on day 1 category (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg), birth weight (kg), birth weight category (weight ≤ 2.5 kg, weight > 2.5 kg), multiple birth (yes/no), and siblings enrolled in the study (yes/no) will be summarized by treatment group and for all subjects combined using the ITT population. Subjects will be excluded from the summary (eg, means and percentages) of an individual parameter if data are missing. This will be done for all subjects, each age category at randomization, country, and by hemisphere.

3.4.3 Study Drug Exposure

Due to the simplicity of dosing for this study, exposure is summarized in the Subject Disposition and Completion Status table under "Randomized and dosed." No other summary will be reported.

3.5 Efficacy Analyses

The analyses of the primary efficacy endpoint, the medically attended RSV LRTI through 150 days post dose, and the secondary efficacy endpoint, RSV hospitalization through 150 days post dose, will be performed on the Primary Dataset.

The Final Dataset will include the events that occurred 150 days post dose, either medically attended RSV LRTI or RSV hospitalization, therefore will be used to summarize these events that occurred after Day 151 or up to Day 361. Efficacy analyses performed on the Primary Dataset will be refreshed in the Final Dataset to make sure statistical inferences on MEDI8897 efficacy made from the Primary Analysis are consistent with those from the Final Dataset.

3.5.1 Primary Efficacy Endpoint and Analyses

3.5.1.1 Primary Efficacy Endpoint

The primary endpoint is the incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose. For subjects with multiple medically attended RSV LRTI events (inpatient or outpatient), only the first occurrence will be used in the primary analysis.

The determination of medically attended RSV LRTI will be based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results

obtained from analyzing the respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A or RSV B performed in a central laboratory. These LRTI events may occur in the inpatient or outpatient visit setting.

Prior to database lock for the primary analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as a medically attended RSV LRTI if they occurred in a respiratory sample collected within this window relative to the initial date seen by the healthcare provider (eg, admission/deterioration date associated with the event, urgent care visit, outpatient ED visit, or outpatient clinic visit). The actual window used will be documented prior to unblinding. In addition, deaths which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as primary medically attended RSV LRTI events.

3.5.1.2 Primary Efficacy Analysis

The primary efficacy analysis of the primary endpoint will be performed on the ITT Population. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary efficacy analysis model to estimate the relative risk on the incidence of medically attended RSV LRTI between MEDI8897 and placebo groups. The model contains the term of treatment group and age group at randomization based on the calculation detailed in Section 3.3. (ie, age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months) and dichotomous temperate (northern and southern) hemispheres as covariates. If the number of subjects in any stratum is too small and/or convergence cannot be achieved, the covariate(s) will be excluded from the model. The relative risk reduction, defined as 1- Relative Risk (RR), and its corresponding 2-sided 95% CI, will be estimated from the model. In addition, the 2-sided p-value testing null hypothesis that the incidence of medically attended RSV LRTI between MEDI8897 and placebo groups are the same will be obtained from the model. Statistical significance will be achieved if the 2-sided p-value is ≤ 0.05.

The Poisson regression with robust variance analysis will be implemented by using the SAS PROC GENMOD procedure with the REPEATED statement for subject ID and logarithm link. The estimated parameter $\hat{\beta}$ [i.e., log($\widehat{RR}$)], 2-sided 95% confidence interval for $\hat{\beta}$, and the 2-sided p-value will be obtained from the SAS outputs. The estimated relative risk (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 Per Protocol population.

3.5.1.3 Handling of Dropouts and Missing Data

RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo medically attended RSV LRTI rate conditional on stratification factors using multiple imputation techniques as described below.

The primary analysis uses Poisson regression with robust variance requires a subject-level dataset. A repeated imputation approach is introduced to impute medically attended RSV LRTI status for missing observations at the subject-level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and confidence interval estimation of the treatment effect is expected through the repeated imputation (Little and Rubin, 2002). To cope with the primary analysis including stratification factors/covariates, the missing values will be imputed at the medically attended RSV LRTI risk level adjusted for subject's stratification value using SAS PROC MI with, e.g., logistic regression method.

The details for the repeated imputation placebo medically attended RSV LRTI rate adjusted for stratification values are provided below. Note that the placebo rate is applied equally to both placebo and MEDI8897 groups in the imputation.

- Step 1: For the subjects in the MEDI8897 arm who do not have an RSV LRTI and are not followed through 150 days post dose, their treatment code of "MEDI8897" will be substituted with "placebo" to ensure the placebo RSV LRTI risk is equally applied in the imputation for both the MEDI8897 and placebo subjects adjusted for their stratification values. The imputation will be executed using SAS PROC MI (e.g., logistic regression with stratification factors).
- Step 2: The original treatment code will be restored after the RSV LRTI event statuses have been imputed. A complete dataset comprises the imputed RSV LRTI status and observed RSV LRTI status.
- Step 3: Analyze the complete dataset using a Poisson regression model with robust variance to estimate the relative risk on the incidence of medically attended RSV LRTI between MEDI8897 and placebo, with the term of treatment group. The point estimate and variance will be extracted from the model.
- Steps 2-3 will be repeated multiple times. The set of point estimates and variances for the model parameter for each complete dataset will be used to generate statistical inferences using the multiple imputation procedure (eg, SAS MIANALYZE procedure).

3.5.1.4 Additional Analyses of the Primary Efficacy Endpoint

The following analyses will be conducted on the ITT population.

To allow for differences in follow-up time, the primary analysis using Poisson Regression with robust variance will be repeated, adjusting for the same covariates as well as log(follow-up time) as an offset. Since the follow-up time is adjusted in the model, there is no missing imputation for this analysis. Calculation of follow-up are detailed below.

- For subjects who meet the medically attended RSV LRTI endpoint within 150 days post dose, the follow-up time will be calculated as (Date of Onset of RSV LRTI) – (Date of Dosing) +1.
- For subjects who do not experience a medically attended RSV LRTI event within 150 days post dose, the efficacy follow-up will be determined based on the following:
  - If an end of study date occurs within 150 days post dose (or end of study date is missing and last assessment date occurs within 150 days post dose), the efficacy follow-up will be calculated as (Date of End of Study or Date of Last Assessment, whichever is later) – (Date of Dosing) +1.
  - If an end of study date occurs after 150 days post dose (or end of study date is missing and last assessment date is after 150 days post dose), the efficacy follow-up will be set to 150 days.

A CMH (Cochran-Mantel-Haenszel) test stratified by hemisphere and age group at randomization (ie, age $\leq$ 3 months, age > 3 to $\leq$ 6 months, age > 6 months) will be used to compare between treatment groups through 150 days post dose as the key secondary analysis for the primary endpoint. Same missing data imputation procedures as applied to the primary analysis (Section 3.5.1.3) will be applied in this analysis.

A Kaplan-Meier curve for time to first medically attended RSV LRTI will be generated based on observed events. The algorithm for time-to-event calculation is the same as to that for follow-up time (see above). Treatment group differences in time-to-first medically attended RSV LRTI will be compared using the stratified log-rank test with two stratification factors as the stratum and the Wilcoxon tests.

In addition, all observed medically attended RSV LRTI events and the corresponding incidence rates will be tabulated by Inpatient (i.e., Hospitalization) and Outpatient, for the latter category, further presentation will be made by different medical settings: outpatient

clinic, urgent care clinic, and emergency department visits for subjects who did not have a hospitalization due to RSV.

3.5.1.5. Analyses for Medically Attended RSV LRTI beyond the Primary Endpoint

The following analyses will be conducted on the ITT population and based on observed events, unless stated otherwise.

The incidence of medically attended RSV LRTI that occurred > 150 days post dose and ≤ 360 days post dose will be summarized by treatment group. Subjects who remained in the study at the Day 151 visit will be used as the denominator to calculate the incidence rate.

To capture and summarize multiple medically attended RSV LRTIs, the total number of new onset medically attended RSV LRTIs since the previous medically attended RSV LRTI will be calculated for each subject. A new onset medically attended RSV LRTI is defined as an adverse event meeting protocol specified medically attended RSV LRTI that occurred at least 14 days after the resolution date of the previous adverse event for a medically attended RSV LRTI. Similar definition is applied with a 30 days interval between the resolution of the previous event and a new onset of event (see Table 3.5-1 for details). The total number of medically attended RSV LRTIs occurring for each subject through 150 days post dose will be summarized by numbers and percentages of subjects who have X number of medically attended RSV LRTIs (ie, 0, 1, 2, 3... medically attended RSV LRTIs). This summary will be repeated for medically attended RSV LRTIs occurring > 150 days post dose and for ≤ 360 days post dose.

Adverse events associated with medically attended RSV LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days.

Sensitivity Analyses for Subjects who are Not Followed through 150 Days Post Dose

Sensitivity analyses for RSV LRTI through 150 days post dose will be performed to address subjects who do not have an RSV LRTI and are not followed through 150 days post dose. The imputed rates of medically attended RSV LRTI through 150 days post dose will be as follows:

1. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having not met the RSV LRTI endpoint within each treatment group.

2. Impute the missing values in each treatment group using 2-times the placebo RSV LRTI event rate through 150 days post dose (ie, Bernoulli distribution with expected value equal to 2-times placebo RSV LRTI event rate)
3. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 2-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 1 or 2-times placebo RSV LRTI event rate)
4. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 3-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 1 or 3-times placebo RSV LRTI event rate)
5. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having met the RSV LRTI endpoint within each treatment group (ie, clinical failures).
6. Multiple imputation
7. Impute the missing values in each treatment group using 1-times, 2-times, and 3-times the overall placebo event rate.

The sensitivity analyses 2-4 will be carried out following the steps below:

- Step 1: Determine the observed placebo RSV LRTI rate through 150 days post dose, which is calculated as the proportion of all randomized placebo subjects with observed RSV.
- Step 2: Impute the event status for subjects who do not have an RSV LRTI and are not followed through 150 days post dose in each treatment arm or the MEDI8897 arm only (depending on the sensitivity analysis assumption above) using the Bernoulli distribution with X-times the observed placebo RSV LRTI rate.
- Step 3: The subjects with imputed values of RSV LRTI status will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose, to form a complete dataset.
- Step 4: Analyze the complete dataset using a Poisson regression model with robust variance to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, categorical age at the time of randomization, and dichotomous temperate hemispheres as covariates. The point estimate and variance will be provided from the model.
- The steps 2-4 will be repeated multiple times. The point estimate and variance for the model parameters for each complete dataset will be used to generate statistical inferences using the multiple imputation procedure (eg, SAS MIANALYZE procedure).

For sensitivity analyses 1 and 5, all subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be assumed to either (1) have an RSV LRTI event (sensitivity analysis #5) or (2) not have an RSV LRTI event (sensitivity analysis #1). The

subjects with imputed values of RSV LRTI status will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose, to form a complete dataset. The primary efficacy analysis using the Poisson regression model with robust variance adjusting for the same covariates will be run according to this new dataset.

For sensitivity analysis 6, the same missing data imputation steps described above in Section 3.5.1.3 for the primary efficacy analysis will be followed, except step 1 (ie, the "MEDI8897" treatment code will not be substituted with "placebo" prior to the SAS PROC MI imputations); the actual treatment codes will be used.

For sensitivity analysis 7, the missing values will be imputed overall regardless of strata. The relative risk reduction and its 95% CI will be constructed using an exact conditional method based on the number of RSV LRTIs.

3.5.1.5 Subgroup Analyses

Subgroup analysis will be performed for the primary efficacy endpoint, the incidence of medically attended RSV LRTI. Treatment-by-subgroup interaction will be tested using the Poisson regression with robust variance model, which will be implemented using Pro GENMOD procedure. Significant treatment-by-subgroup interaction is judged at the significance level of 0.10. The relative risk reduction and its corresponding 95% CI will be estimated using a Poisson regression with robust variance with the term of treatment. A forest plot of the relative risk reduction and the 95% CI will be presented.

The subgroup analysis will be conducted for the following subgroups, provided there are sizable numbers of subjects in each level of the subgroups:

- RSV A and B subtypes
- Hemisphere/Country
- Age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg)
- Gestational age (29-32 weeks, > 32 weeks)
- Sibling also participating in the study (yes/no)

- Post-baseline detection of ADA (detected, not detected) – only incidence rates will be provided for this summary

Subgroup analysis will be conducted on the ITT population.

3.5.2 Secondary Efficacy Endpoint and Analyses

3.5.2.1 Secondary Efficacy Endpoint

The secondary efficacy endpoint is the incidence of RSV LRTI hospitalization through 150 days post dose. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis.

The events of "RSV hospitalization" are a subset of "medically attended RSV LRTI", which are determined based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from central laboratory analysis respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A or RSV B.

Prior to analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as an RSV LRTI hospitalization if they occurred in a respiratory sample collected within this window relative to the admission/deterioration date. The actual window used will be documented prior to unblinding. In addition, deaths which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as RSV LRTI hospitalization endpoints.

3.5.2.2 Secondary Efficacy Analyses

A Poisson regression model with robust variance (Zou, 2004) using only the treatment term will be used to assess the treatment effect on the incidence of RSV LRTI hospitalization between MEDI8897 and placebo groups in the ITT population. Relative risk reduction and its corresponding 95% CI are estimated from the model implemented by Proc GENMOD as detailed in Section 3.5.1.2.

Statistical testing of the null hypothesis that the incidence of RSV LRTI hospitalization between MEDI8897 and placebo groups is the same will only be performed if the primary efficacy analysis has achieved a p-value that is ≤0.05. In that event, statistically significant treatment effect on this secondary efficacy endpoint will be claimed if the 2-sided p-value is ≤ 0.05. In this approach, the family-wise Type I error rate of testing the first and the secondary hypotheses is controlled under the significance level of $\alpha \leq 0.05$.

Above stated analysis on RSV LRTI hospitalization will also be conducted on the per-protocol population.

3.5.2.3 Handling of Dropouts and Missing Data

RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. For subjects who do not have an RSV LRTI hospitalization and were not followed through 150 days post dose, their event status will be imputed assuming the observed placebo RSV LRTI hospitalization rate conditional on stratification factors as described below.

A repeated imputation approach is introduced at the subject-level for the model fitting to impute RSV LRTI hospitalization status for missing observations. The same methods described above for the primary efficacy endpoint will be used (see Section 3.5.1.3). However, the imputation by covariates may not be applicable since the total number of RSV LRTI hospitalization events could be much lower than that for medically attended RSV LRTI. In this case the imputation will be performed using the Bernoulli distribution with the observed placebo RSV LRTI hospitalization rate (see Section 3.5.1.4) without consideration of stratification factors.

3.5.2.4 Additional Analyses of the Secondary Efficacy Endpoint

The additional analyses, including stratified CMH, Kaplan-Meier, and the sensitivity analyses for subjects who were not followed through 150 days post dose using observed placebo rate imputation as described for the primary endpoint (Section 3.1.5.3) will be conducted for RSV LRTI hospitalization.

3.5.2.5 Subgroup Analyses

The same subgroups analysis as described for the primary endpoint will be provided for RSV LRTI hospitalization.

3.5.3 Other Efficacy Analyses

An analysis will also include the incidence of all medically attended LRTI, protocol-defined LRTI, non-protocol defined LRTI, and incidence by RSV positive RT-PCR and/or local testing results, and RSV negative by RT-PCR or local testing. This will be repeated for LRTI hospitalizations and medically attended outpatient LRTI events. The same analysis window as described in above sections for the RT-PCR central tests will be used for the local tests. For subjects with multiple events, only the first occurrence will be used in each incidence summary, respectively. The observed and imputed counts from the primary and secondary endpoint analysis will be presented in this summary. For medically attended RSV outpatient

LRTI (Protocol-Defined), if a subject does not have an event prior to discontinuation from participation, their event status will be imputed assuming the observed placebo event rate conditional on stratification value (see Section **3.5.1.3**). However, the imputation by covariates may not be applicable if the total number of events is not adequate. In this case the imputation will be performed using the Bernoulli distribution with the observed placebo event rate (see Section 3.5.1.4). All other summaries will be based on observed events and available follow-up through 150 days. This summary will be presented for the ITT population through 150 days post dose, after 150 days post dose, and through 360 days post dose.

Similar to the primary endpoint (as described in Section 3.5.1.4), the total number of new onset events since previous events will be summarized for the following events:

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset medically attended RSV LRTI	A new onset medically attended RSV LRTI will be defined as an adverse event (for which at least one healthcare visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV LRTI.
New onset RSV LRTI **hospitalization**	A new onset medically attended RSV LRTI hospitalization will be defined as an adverse event (for which at least one hospitalization is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV LRTI hospitalization.
New onset medically attended RSV **outpatient** LRTI	A new onset medically attended RSV outpatient LRTI will be defined as an adverse event (for which at least one healthcare outpatient visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous adverse event for a medically attended RSV outpatient LRTI.
New onset medically attended LRTI	A new onset medically attended LRTI will be defined as an adverse event of LRTI that occurs after the resolution date of the previous adverse event for a medically attended LRTI.
New onset LRTI **hospitalization**	A new onset medically attended LRTI hospitalization will be defined as an adverse event (with at least one hospitalization associated with LRTI) that occurs after the resolution date of the previous adverse event for a medically attended LRTI hospitalization.
New onset medically attended **outpatient** LRTI	A new onset medically attended outpatient LRTI will be defined as an adverse event (with at least one outpatient healthcare visit associated with LRTI) that occurs after the resolution date of the previous adverse event for a medically attended outpatient LRTI.
New onset medically attended non-RSV LRTI	A new onset medically attended Non-RSV LRTI will be defined as an adverse event (for which at least one healthcare visit is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV LRTI.
New onset non-RSV LRTI **hospitalization**	A new onset medically attended Non-RSV LRTI hospitalization will be defined as an adverse event (for which at least one hospitalization is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV LRTI hospitalization.

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset medically attended non-RSV **outpatient** LRTI	A new onset medically attended Non-RSV outpatient LRTI will be defined as an adverse event LRTI (for which at least one outpatient healthcare visit is associated with LRTI, but not associated with RSV) that occurs after the resolution date of the previous adverse event for a medically attended Non-RSV outpatient LRTI.

Adverse events associated with medically attended LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days.

3.6 Exploratory Analyses

3.6.1 Healthcare Resource Utilization

The magnitude of HRU (eg, number of admissions to hospitals and ICUs and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and types of outpatient visits, eg, outpatient ED, urgent care, outpatient clinic; and number of prescription and OTC medications and duration of use) will be summarized by treatment group for all randomized subjects through 150 days post dose, after 150 days post dose, and through 360 days post dose.

Duration of hospitalization will be calculated from the admission or deterioration date to discharge. Durations for the other parameters will be calculated in a similar manner from start date to stop date. The subject's entire experience throughout the study (eg, separate occurrences of mechanical ventilation within a hospitalization or across separate hospitalizations) will be summed together. All randomized subjects will be included in the analysis; therefore, a subject who was not hospitalized or did not utilize the particular parameter (CPAP, supplemental oxygen use, ICU stay, or mechanical ventilation) will have a duration of 0 days. Unlike the other parameters, supplemental oxygen can also be used in the outpatient setting, thus the summary of supplemental oxygen will include use in both hospital and outpatient settings.

Durations will be summarized by total days, mean and standard deviation number of days (mean calculated as total days divided by total number of randomized subjects per group), median days, and minimum/maximum number of days.

For duration of prescription and OTC medication summaries, missing or partial concomitant medication start/stop dates will be imputed as follows:

- Partial dates where only the year is known: For start dates assume January 1st; for stop dates assume December 31st.
- Partial dates where only the month and year are known: For start dates assume the first of the month; for stop dates assume the end of the month.

In addition to the overall HRU summary, the HRU for (1) medically attended RSV LRTI (Protocol-Defined), (2) medically attended non-RSV LRTI (Protocol-Defined), and (3) medically attended LRTI (Non-Protocol Defined) will be summarized for all randomized subjects by treatment group, through 150 days post dose, after 150 days post dose, and through 360 days post dose. The same conventions used for the overall summary will apply for the respective events; however, the HRU must occur during the event being summarized. For example, only supplemental oxygen use during a medically attended RSV LRTI (Protocol-Defined) will be counted for the medically attended RSV LRTI summary. A concomitant medication will be associated with the adverse event associated with the RSV LRTI event if the medication was taken to treat the LRTI (as recorded in the CRF) and the medication overlaps the adverse event being summarized. The duration of medications will be counted as the days of medication use residing within the adverse event associated with the RSV event.

Additional summaries of HRUs will evaluate HRUs among subjects who have an event. The summaries will only include subjects with the event (1) medically attended RSV LRTI (Protocol-Defined), (2) medically attended non-RSV LRTI (Protocol-Defined), and (3) medically attended LRTI (Non-Protocol Defined). These summaries will provide an estimate of the average HRU use among subjects who are experiencing an event.

The average number of prescriptions (and OTC medications) per medically attended non-RSV LRTI (Protocol-Defined) per subject will be summarized for each treatment group through 150 days post dose. The average number of prescriptions per medically attended non-RSV LRTI (Protocol-Defined) will be calculated as the total number of prescriptions provided during the study divided by the total number of medically attended non-RSV LRTI (Protocol-Defined) events. Only subjects with a medically attended non-RSV LRTI (Protocol-Defined) will be included in the analysis. This summary will be provided for subjects with at least one non-RSV LRTI hospitalization and for subjects without any non-RSV LRTI hospitalizations. Similar summaries will be provided for medically attended LRTI (Non-Protocol-Defined).

3.6.2 Caregiver Burden

Caregiver burden (eg, caregiver missed work days, subject absence from day care/babysitting) for subjects with medically attended RSV LRTI (Protocol-Defined) will be summarized by treatment group for all randomized subjects and among subjects who have an event. If at least one healthcare visit occurring during an adverse event is associated with RSV, the caregiver burden collected for that adverse event will be counted in this summary. For example, consider a subject with an LRTI with three healthcare visits: outpatient ER (non-protocol defined LRTI and RSV negative), outpatient clinic (protocol-defined LRTI and RSV negative), and hospitalization (protocol-defined LRTI and RSV positive). Since the hospitalization for this subject meets the protocol definition for LRTI and is associated with RSV, the entire caregiver burden for the adverse event will be included in this summary. Similar summaries will be provided for medically attended non-RSV LRTI (Protocol-Defined) and medically attended LRTI (Non-Protocol-Defined) events. These summaries will be presented through 150 days post dose, after 150 days post dose, and through 360 days post dose.

The average caregiver burden (caregiver missed work days, subject absence from day care/babysitting) per medically attended non-RSV LRTI (Protocol-Defined) per subject will be summarized for each treatment group through 150 days post dose. The average caregiver burden (caregiver missed work days, subject absence from day care/babysitting) per medically attended non-RSV LRTI (Protocol-Defined) will be calculated as the total caregiver burden divided by the total number of medically attended non-RSV LRTI (Protocol-Defined). Only subjects with a medically attended non-RSV LRTI (Protocol-Defined) will be included in the analysis. This summary will be provided for subjects with at least one non-RSV LRTI hospitalization and for subjects without any non-RSV LRTI hospitalizations. As similar summary will be provided for medically attended LRTI (Non-Protocol-Defined).

3.7 Safety Analyses

3.7.1 Adverse Events and Serious Adverse Events

Adverse events will be coded by Medical Dictionary for Regulatory Activities (MedDRA) version 19 or higher and the type, incidence, severity and relationship to study investigational product will be summarized by treatment group. Specific adverse events (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 will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT).

Additional summaries will present treatment-emergent AEs by SOC and high-level term and by SOC and high-level group term. Nontreatment-emergent AEs/serious adverse events (SAEs) will be presented in the listings.

3.7.2 Adverse Events of Special Interest

Adverse events of special interest will include targeted AEs of hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA. Additional groupings may be added by the Medical Monitor if warranted.

3.7.3 Skin and Hypersensitivity Reactions

All skin reactions and skin reactions identified as hypersensitivity/allergic reactions and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA.

3.7.4 New Onset Chronic Disease

New onset chronic diseases include but are not limited to diabetes, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy) and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA.

3.7.5 Subgroup Analyses

All adverse events will be summarized by age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months), and weight on day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg).

3.7.6 Other Safety Evaluations

Adverse events, adverse events of special interest, skin reactions and skin hypersensitivity reactions will also be summarized by timing relative to dosing (‘within 1 day/greater than 1 day’, ‘within 7 days/greater than 7 days’).

Additional data collected throughout the study include screen failure data, significant findings in medical history and physical exam, vital signs, and concomitant medications through Day 361. 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.

3.8 Anti-drug Antibodies

The number and percentage of subjects who develop anti-MEDI8897 antibodies will be summarized at each visit by treatment group. For those with a positive assessment, the ADA titer results will also be summarized.

An additional table will summarize 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 summarized by SOC and PT based on MedDRA for subjects with ADA to MEDI8897 at any time post-baseline.

The impact of ADA on PK will be included in the PK report as mentioned in Section 3.9.

3.9 Pharmacokinetics

Following a single dose of MEDI8897, individual MEDI8897 serum concentrations data will be tabulated by treatment group along with description statistics. Terminal-phase half-life ($t_{1/2}$) will be estimated using non-compartmental analysis, if data permit. The details of the analyses and presentation of these data will be included in a separate PK report.

4 REFERENCES

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Little, R. J. A. and Rubin, D. B. Statistical Analysis with Missing Data, 2nd Edition, Hoboken, NJ: John Wiley & Sons 2002; 257.

O'Brien KL, Chandran A, Weatherholtz R, Jafri HS, Griffin MP, Bellamy T, et al. Respiratory Syncytial Virus Prevention study group. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase

3 randomized double-blind placebo-controlled trial. Lancet Infect Dis. 2015;15(12):1398-408.

Appendix 1 Elements to Evaluate for Case Definition of Medically Attended RSV LRTI

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive RT-PCR	**Documented PE findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration • Prescription medications (only for children with underlying lung disease)

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = real time reverse transcriptase-polymerase chain reaction;

Note: One item from each column is required to meet the case definition of RSV LRTI.

Statistical Analysis Plan

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

Protocol Number: D5290C00003

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List of Abbreviations

Abbreviation or Specialized Term	Definition
AAP	American Academy of Pediatrics
ADA	Anti-drug antibody (ies)
AE(s)	adverse event(s)
AESI	adverse event of special interest
CE	*Conformité Européenne* or European Conformity
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPAP	Continuous Positive Airway Pressure
DOB	date of birth
eCRF	electronic case report form
ED	Emergency Department
ER	emergency room
EU	European Union
GA	gestational age
HRU	healthcare resource utilization
ICU	intensive care unit
IDMC	independent data monitoring committee
IM	intramuscular
ITT	intent-to-treat
IWRS	interactive web response system
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PK	pharmacokinetic(s)
PT	Preferred Term
RR	relative risk
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SID	subject identification
SOC	System Organ Class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event

Abbreviation or Specialized Term	Definition
US FDA	United States Food and Drug Administration
USA	United States of America

1 INTRODUCTION

This document describes the statistical analysis plan (SAP) for protocol D5290C00003, a pivotal Phase 2b study to determine if MEDI8897 is efficacious in reducing medically attended respiratory syncytial virus (RSV)-confirmed lower respiratory tract infection (LRTI) in healthy preterm infants entering their first RSV season. The primary efficacy hypothesis of this study is that, compared with placebo, a single 50-mg intramuscular (IM) dose of MEDI8897 will be efficacious in reducing medically attended LRTI caused by reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed RSV in healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable. The secondary hypotheses are that (1) there will be a reduction in the incidence of hospitalizations attributable to RSV, (2) the predicted extended terminal half-life ($t_{1/2}$) will be adequate for the duration of the RSV season, and (3) anti-drug antibodies (ADA) to MEDI8897 will not significantly impact the serum concentrations or safety of MEDI8897 over the 5-month RSV season. These hypotheses will be assessed by the incidence of RSV LRTI, RSV hospitalization, ADA, pharmacokinetic (PK) parameters, and descriptive statistics from safety data. 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(s)

To assess the efficacy of MEDI8897 when administered as a single 50 mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared with placebo.

2.1.2 Secondary Study Objectives

1. To assess the efficacy of MEDI8897 for the reduction of hospitalizations due to RT-PCR-confirmed RSV, compared with placebo
2. To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared with placebo
3. To evaluate single-dose serum concentrations of MEDI8897
4. To evaluate ADA responses to MEDI8897 in serum

2.1.3 Exploratory Study Objectives

To assess healthcare resource utilization (HRU) and caregiver burden for MEDI8897 recipients compared with placebo recipients.

2.2 Study Design

The population to be enrolled is healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who would not receive RSV prophylaxis based on the American Academy of Pediatrics (AAP) or other local or national guidelines. These infants will not be receiving palivizumab, allowing for a placebo comparator group for the determination of efficacy and the safety profile. A total of 1,500 infants will be randomized in a 2:1 ratio to receive a 50 mg IM dose of MEDI8897 (N = 1000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age group at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. All infants will be followed for approximately 360 days after dosing.

2.3 Treatment Assignment and Blinding

An interactive web response system (IWRS) will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized at a 2:1 ratio to receive a 50 mg IM dose of MEDI8897 (N = 1,000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age group at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500.

The procedure for using IWRS is as follows:

- The investigator or designee contacts the IWRS and provides the subject identification (SID) number and subject's baseline characteristic(s) used to verify that it is the same subject
- Placebo (provided by site) or a vial from a MEDI8897 kit will be assigned to the subject
- Confirmation of this information is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log

Investigational product (MEDI8897 or placebo) must be administered the same day the investigational product is assigned. Total in-use storage time from needle puncture of the investigational product vial to administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used. If there is a delay in the administration of investigational product such that it will not be administered within the specified time frame, the unblinded investigational product monitor must be notified immediately.

2.4 Sample Size

The sample size of 1,500 subjects is necessary based on advice from the United States Food and Drug Administration US FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size has approximately > 99% power to detect 70% relative-risk reduction, assuming a placebo group medically attended RSV LRTI incidence of 8%. Power calculations are based on a Poisson regression model with robust variance (Zou, 2004) comparing MEDI8897 50 mg versus placebo, with 2-sided, $\alpha = 0.05$.

- The 70% relative-risk reduction assumption is based on a placebo-controlled study in Native American infants in which there was 87% relative reduction in the incidence of RSV hospitalization (11.3% placebo; 1.5% motavizumab; $p < 0.001$) and 71% relative reduction in the incidence of outpatient RSV LRTI (10.0% placebo; 2.9% motavizumab; $p < 0.001$) in infants who received motavizumab prophylaxis (O'Brien et al, 2015)

In order to evaluate risk, a sample size of 1,000 subjects exposed to MEDI8897 will provide a 90% probability of observing at least one AE if the true event rate is 0.2%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.3%.

3 STATISTICAL METHODS

3.1 General Considerations

Summary statistics will be tabulated by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by mean, median, standard deviation, minimum, and maximum. In general, unless stated otherwise, baseline will be defined as the last non-missing value prior to dosing.

There are two planned analyses for this study: the Primary Analysis and the Final Analysis. The Primary Analysis will be conducted after all randomized subjects have completed the Day 151 visit. At the time of this primary analysis, approximately half of all subjects enrolled (722 subjects) will have completed the Day 361 visit. The remaining 731 subjects will have completed approximately 8 months of the study. MEDI8897'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 and Datasets

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	Subjects who are randomized will be included in the ITT population; in this population data will be analyzed according to their randomized treatment group.
As-treated population	Subjects who are randomized and receive any study investigational product will be included in the as-treated population; in this population, data will be analyzed according to the treatment they actually receive.
Per-protocol population	The per-protocol population includes subjects in the ITT population who receive the correct dose of randomized treatment and who do not have a serious protocol violation. Detailed criteria defining this population will be determined and documented prior to performing the Primary Analysis.

Analysis Datasets

- The Primary Dataset contains all data (efficacy, safety, ADA, PK) from all randomized subjects through the Day 151visit 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 Stratification Factors

Two stratification factors are used in study design as well as in data analysis, and these are: age group at randomization [age ≤ 3 months (ie, age ≤ 91 days), age > 3 to ≤ 6 months (ie, age > 91 to ≤ 183 days), age > 6 months (ie, age > 183 days)] and hemisphere (northern hemisphere, southern hemisphere). For subjects who were assigned to an incorrect age stratum at randomization, the age stratum as calculated from the electronic case report form (eCRF) will differ from the stratum recorded for the subject in the IWRS database. Unless stated otherwise, the age stratum based on the CRF calculation will be used.

CRF calculation for age when full date of birth (DOB) is available:

- Age at randomization (months) = (randomization date – DOB) / (365.25/12)

When full DOB is unavailable, age at screening will be used. Since screening may be collected in terms of days, weeks, or months, it will be first converted in terms of months as follows:

- Age at screening (days) / (365.25/12) = Age at screening (months)
- Age at screening (weeks) / (52/12) = Age at screening (months)

Once age at screening is converted to months,

- Age at randomization (months)= Age at screening (months) + [(randomization date – screening date) / (365.25/12)]

Determination of hemisphere in stratification and analysis is as follows: The sites have been grouped together by country into the following two hemispheres: Northern Hemisphere (Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Hungary, Italy,

Latvia, Lithuania, Poland, Spain, Sweden, Turkey, United Kingdom, and United States of America [USA]) and Southern Hemisphere (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa).

3.4 Study Subjects

3.4.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment received (including summary of subjects randomized but not treated) will be provided. In addition, disposition of subjects throughout the study and by visit will be provided. This summary will be presented by treatment group and for all subjects combined. The denominators for this summary will include all subjects who were randomized into the study.

3.4.2 Demographics and Baseline Characteristics

Enrolment will be summarized by hemisphere, country, site, and by hemisphere, country, and age at randomization stratum for each treatment group and for all subjects combined. The total number of subjects randomized into each treatment group will be used as the denominator. For the summary of hemisphere, country, and age at randomization stratum, the number of mis-stratified subjects (ie, age stratum as calculated from the eCRF does not match the IWRS database) will be summarized.

Demographic information related to gender, age at randomization (months) calculated from the CRF, age at randomization category determined using the CRF age calculation (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months), GA (weeks), GA category (29-32 weeks, > 32 weeks), ethnicity, race, weight (kg) on day 1, weight on day 1 category (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg), birth weight (kg), birth weight category (weight ≤ 2.5 kg, weight > 2.5 kg), multiple birth (yes/no), and siblings enrolled in the study (yes/no) will be summarized by treatment group and for all subjects combined using the ITT population. Subjects will be excluded from the summary (eg, means and percentages) of an individual parameter if data are missing. This will be done for all subjects, each age category at randomization, country, and by hemisphere.

3.4.3 Study Drug Exposure

Due to the simplicity of dosing for this study, exposure is summarized in the Subject Disposition and Completion Status table under “Randomized and dosed.” No other summary will be reported.

3.5 Efficacy Analyses

The analyses of the primary efficacy endpoint, the protocol-defined medically attended RSV LRTI through 150 days post dose (also described as the medically attended RSV LRTI through 150 days post dose in Section 3.5.1., Primary Efficacy Endpoint and Analyses), and the secondary efficacy endpoint, the protocol-defined RSV hospitalization through 150 days post dose (also described as the RSV LRTI hospitalization in Section 3.5.2., Secondary Efficacy Endpoint and Analyses), will be performed on the Primary Dataset.

The Final Dataset will include the events that occurred 150 days post dose, either medically attended RSV LRTI or RSV hospitalization, therefore will be used to summarize these events that occurred after Day 151 or up to Day 361. Efficacy analyses performed on the Primary Dataset will be refreshed in the Final Dataset to make sure statistical inferences on MEDI8897 efficacy made from the Primary Analysis are consistent with those from the Final Dataset.

3.5.1 Primary Efficacy Endpoint and Analyses

3.5.1.1 Primary Efficacy Endpoint

The primary endpoint is the incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose. For subjects with multiple medically attended RSV LRTI events (inpatient or outpatient), only the first occurrence will be used in the primary analysis.

The determination of medically attended RSV LRTI will be based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from analyzing the respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A or RSV B performed in a central laboratory. These LRTI events may occur in the inpatient or outpatient visit setting.

Prior to database lock for the primary analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as a medically attended RSV LRTI if they occurred in a respiratory sample collected within this window relative to the initial date seen by the healthcare provider (eg, admission/deterioration date associated with the event, urgent care visit, outpatient ED visit, or outpatient clinic visit). The actual window used will be documented prior to unblinding. In addition, deaths that can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as primary medically attended RSV LRTI events.

3.5.1.2 Primary Efficacy Analysis

The primary efficacy analysis of the primary endpoint will be performed on the ITT Population. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary efficacy analysis model to estimate the relative risk on the incidence of medically attended RSV LRTI between the MEDI8897 and the placebo groups. The model contains the term of treatment group and age group at randomization based on the calculation detailed in Section 3.3. (ie, age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months) and dichotomous temperate (northern and southern) hemispheres as covariates. The relative risk reduction, defined as 1- Relative Risk (RR), and its corresponding 2-sided 95% CI, will be estimated from the model. In addition, the 2-sided p-value testing null hypothesis that the incidence of medically attended RSV LRTI between MEDI8897 and placebo groups are the same will be obtained from the model. Statistical significance will be achieved if the 2-sided p-value is ≤ 0.05.

The Poisson regression with robust variance analysis will be implemented by 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 95% confidence interval (CI) for $\hat{\beta}$, and the 2-sided p-value will be obtained from the SAS outputs. The estimated RR and corresponding CI for the RR is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of RR reduction is given by [(1 – exp($\hat{\beta}$)) * 100%]. The CI for the percent of RR reduction is given by ([1 – exp(upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp(lower confidence limit for $\hat{\beta}$) * 100%]).

If the number of subjects in any stratum is too small and/or convergence cannot be achieved with the Poisson regression analysis model, the stratified Cochran-Mantel-Haenszel (CMH) test (detailed in Section 3.5.1.4) will be used as the primary analysis model to test the treatment effect on medically attended RSV LRTI between MEDI8897 and placebo groups.

The above described analysis on the primary efficacy endpoint will also be conducted on the Per-protocol population.

3.5.1.3 Handling of Dropouts and Missing Data

RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo medically attended RSV LRTI rate conditional on stratification factors using multiple imputation techniques as described in the following paragraphs.

The primary analysis uses Poisson regression with robust variance requires a subject-level dataset. A repeated imputation approach is introduced to impute medically attended RSV LRTI status for missing observations at the subject-level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and CI estimation of the treatment effect is expected through the repeated imputation (Little and Rubin, 2002). In the primary analysis the missing outcome for subjects who dropped out prior to reaching Day 150 post dose without a medically attended RSV LRTI event will be imputed per stratum determined by the two stratification factors using placebo event rate. The imputation and subsequent analysis will be carried out using SAS PROC MI (Monotone Logistic Regression Method) and SAS PROC MIANALYZE. The detailed imputation steps are described as follows.

- Step 1: For the subjects in the MEDI8897 arm who do not have an RSV LRTI and are not followed through 150 days post dose, their treatment code of "MEDI8897" will be substituted with "placebo" to ensure the placebo RSV LRTI rate is applied in the imputation for the MEDI8897 dropouts adjusted for their stratification values. The imputation will be executed using SAS Proc MI (eg, logistic regression with the recoded treatment term and stratification factors).
- Step 2: The original treatment code will be restored after the RSV LRTI event statuses have been imputed. A complete dataset comprises the imputed RSV LRTI status and observed RSV LRTI status.
- Step 3: Analyze the complete dataset using a Poisson regression model with robust variance to estimate the relative risk on the incidence of medically attended RSV LRTI between MEDI8897 and placebo, with the term of treatment group and two stratification factors. The point estimate of log-transformed RR and its variance will be extracted from the model.
- Steps 2-3 will be repeated 20 times. SAS procedure PROC MIANALYZE will be used to combine inferences from the 20 completed datasets, that will result in a combined point estimate of log-transformed relative risk and the variance. The random seed is 12345.

3.5.1.4 Additional Analyses of the Primary Efficacy Endpoint

The following analyses will be conducted on the ITT population.

To allow for differences in follow-up time, the primary analysis using a Poisson Regression with robust variance will be repeated, adjusting for the same covariates as well as log (follow-up time) as an offset. Since the follow-up time is adjusted in the model, there is no missing imputation for this analysis. Calculation of follow-up are detailed as follows:

- For subjects who meet the medically attended RSV LRTI endpoint within 150 days post dose, the follow-up time will be calculated as (Date of Onset of RSV LRTI) – (Date of Dosing) +1.
- For subjects who do not experience a medically attended RSV LRTI event within 150 days post dose, the efficacy follow-up will be determined based on the following:
  - If an end of study date occurs within 150 days post dose (or end of study date is missing and last assessment date occurs within 150 days post dose), the efficacy follow-up will be calculated as (Date of End of Study or Date of Last Assessment, whichever is later) – (Date of Dosing) +1.
  - If an end of study date occurs after 150 days post dose (or end of study date is missing and last assessment date is after 150 days post dose), the efficacy follow-up will be censored (at 151 days).

A CMH test stratified by hemisphere and age group at randomization (ie, age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months) will be used to compare between treatment groups through 150 days post dose as the key secondary analysis for the primary endpoint. SAS procedure of PROC FREQ with CMH option will be used to perform the analysis. The relative risk of MEDI8897 over placebo for the incidence of medically attended RSV LRTI events and the 95% CI will be obtained from the SAS procedure. The percent of RR reduction and the 95% CI will be reported following the relationship of RR reduction (%) = (1- relative risk)*100%. Similar to the data imputation plan for the Poisson regression model with robust variance, repeated imputation algorithm will be applied and placebo event rate per stratum will be used to impute the event status for MEDI9987 subjects who dropped out the study prior to Day 150 post dose and did not have a medically attended RSV event in the stratified CMH test. Detailed steps from data imputation to generate a pooled statistical inference from imputed completed datasets for CMH test are described in O'Kelly et al. (2014). The key steps are: 1) for each imputed complete dataset, the log-transformed relative risk of MEDI8897 over placebo for the incidence of medically attended RSV LRTI events and standard error derived from the CMH output will be used as the input for PROC MIANALYZE to obtain combined relative risk and the 95% CI; 2) for each imputed complete dataset, the Wilson-Hilferty transformed CMH statistic will be used as the input for PROC MIANALYZE to obtain a combined p-value (Wilson and Hilferty, 1931).

A Kaplan-Meier curve for time to first medically attended RSV LRTI will be generated based on observed events. The algorithm for time-to-event calculation is the same as to that for follow-up time (see previous). Treatment group differences in time-to-first medically

attended RSV LRTI will be compared using the stratified log-rank test and Wilcoxon test with two stratification factors as the strata.

In addition, all observed medically attended RSV LRTI events and the corresponding incidence rates will be tabulated by Inpatient (primary hospitalization, nosocomial hospitalization) and Outpatient, for the latter category, further presentation will be made by different medical settings: outpatient clinic, urgent care clinic, and emergency department visits for subjects who did not have a hospitalization due to RSV.

3.5.1.5. Analyses for Medically Attended RSV LRTI beyond the Primary Endpoint

The following analyses will be conducted on the ITT population and based on observed events, unless stated otherwise.

The incidence of medically attended RSV LRTI that occurred > 150 days post dose and ≤ 360 days post dose will be summarized by treatment group. ITT subjects who remained in the study at the Day 151 visit will be used as the denominator to calculate the incidence rate for the summary of the incidence > 150 days post dose, and the ITT population will be used for the summary of the incidence ≤ 360 days post dose.

Age at onset of the first medically attended RSV LRTI will be tabulated by age group used for randomization stratification by treatment group. In addition, time-to-first medically attended RSV LRTI will be plotted at subject's level along the axis of age at birth.

The incidence of medically attended RSV LRTI by subtype (RSV A, RSV B) through 150 days post dose, > 150 Days and through 360 days post dose will be summarized by treatment group. The populations that the summary will be based on will be similar to what had been used for the analysis of medically attended RSV LRTI at each corresponding time period.

To capture and summarize multiple medically attended RSV LRTIs, the total number of new onset medically attended RSV LRTIs since the previous medically attended RSV LRTI will be calculated for each subject. A new onset medically attended RSV LRTI is defined as an adverse event (AE) meeting protocol specified medically attended RSV LRTI that occurred at least 14 days after the resolution date of the previous AE for a medically attended RSV LRTI. Similar definition is applied with a 30 days interval between the resolution of the previous event and a new onset of event (see Table 3.5-1 for details). A listing will be generated to provide the following information: age at randomization, hemisphere, total number of events (at least 14 days apart), total number of events (at least 30 days apart), days to event, adverse event (AE) verbatim term, Date of AE onset/stop, Days from previous

event, Visit setting, and RSV subtype. AEs associated with medically attended RSV LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days.

3.5.1.6. Sensitivity Analyses for Subjects who are Not Followed through 150 Days Post Dose

Sensitivity analyses for RSV LRTI through 150 days post dose will be performed to address subjects who do not have an RSV LRTI and are not followed through 150 days post dose through various approaches of missing data imputation are described as follows:

1. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having not met the RSV LRTI endpoint.
2. Impute the missing values in each treatment group using 2-times the placebo RSV LRTI event rate through 150 days post dose (ie, Bernoulli distribution with expected value equal to 2-times placebo RSV LRTI event rate).
3. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 2-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 2 or 1-times placebo RSV LRTI event rate).
4. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 3-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 3 or 1-times placebo RSV LRTI event rate)
5. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having met the RSV LRTI endpoint.
6. Multiple imputations
7. Impute the missing values in each treatment group using 1-time, 2-time, and 3-time the overall placebo event rate in single imputation approach.

The sensitivity analyses 2-4 will be conducted following the steps below:

- Step 1: Determine the observed placebo RSV LRTI rate through 150 days post dose, which is calculated as the proportion of all randomized placebo subjects with observed RSV.
- Step 2: Impute the event status for subjects who do not have an RSV LRTI and are not followed through 150 days post dose in each treatment arm or the MEDI8897 arm only

(depending on the sensitivity analysis planed above) using the Bernoulli distribution with X-times the observed placebo RSV LRTI rate without involvement of stratification factors.

- Step 3: The subjects with imputed values of RSV LRTI status (Yes/No) will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose without an RSV LRTI, to form a complete dataset.
- Step 4: Analyze the complete dataset using a Poisson regression model with robust variance to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, and two stratification factors (age group and hemispheres) as covariates. The point estimate of log-transformed RR and its variance will be produced from the model.
- The steps 2-4 will be repeated 20 times with seed 1-20, respectively. SAS procedure PROC MIANALYZE will be used to combine inferences from the 20 completed datasets, which will result in a combined point estimate of log-transformed RR and the variance.

For sensitivity analyses 1 and 5, all subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be assumed to either (1) have an RSV LRTI event (sensitivity analysis #5) or (2) not have an RSV LRTI event (sensitivity analysis #1). The subjects with imputed values of RSV LRTI status will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose without the event to form a complete dataset. The primary efficacy analysis model will be used to analyse the completed datasets via the specified imputation method.

For sensitivity analysis 6, the medically attended RST LRTI event status for the subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be imputed by the observed event rate per treatment group. That is, following the standard Multiple Imputation procedure and carried by Proc MI (Monotone Logistic Regression Method) and PROC MIANALYZE.

For sensitivity analysis 7, the number of medically attended RSV LRTI events for those MEDI8897-treated subjects who dropped out prior to Day 150 post dose without the event will be generated using a binomial distribution with 1-time, 2-time, or 3-time observed placebo event rates, respectively. While placebo-treated subjects who dropped out prior to Day 150 post dose without the event will be imputed using a 1-time observed placebo rate. With the imputed number of events, the RR reduction and the 95% CI will be constructed using

an exact conditional method based on the number of RSV LRTIs (Breslow and Day, 1987). This analysis will be carried out by StatXact PROC Poisson procedure.

3.5.1.7. Subgroup Analyses for the Primary Efficacy Endpoint

Subgroup analysis will be performed for the primary efficacy endpoint, the incidence of medically attended RSV LRTI. Treatment-by-subgroup interaction will be tested using the Poisson regression with robust variance model with the terms of treatment, age group, hemisphere, subgroup, and treatment-by-subgroup interaction, which will be implemented using PROC GENMOD procedure. If this full model does not achieve convergence, a reduced model of treatment, subgroup, and treatment-by-subgroup interaction will be used. Significant treatment-by-subgroup interaction is judged at the significance level of 0.10. Within each level of a subgroup, the RR reduction and its corresponding 95% CI will be estimated using a Poisson regression model with robust variance with the term of treatment. A forest plot of the RR reduction and the 95% CI will be presented. In the event that the Poisson regression model does not converge for any stratum of a subgroup, the exact conditional method based on the number of RSV LRTIs (Breslow and Day, 1987) will be used as the analytical model to generate the relative risk reduction and its corresponding CI for all subgroup strata. This model will be implemented by StatXact PROC Poisson procedure and the point estimate and mid-p adjusted 95% CI will be reported.

The subgroup analysis will be conducted for the following subgroups on the ITT population:

- Hemisphere
- Age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on Day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg)
- GA (29-32 weeks, > 32 weeks)
- Sibling also participating in the study (yes/no)

In addition, incidence of medically attended RSV LRTI will be summarized by Country.

3.5.2 Secondary Efficacy Endpoint and Analyses

3.5.2.1 Secondary Efficacy Endpoint

The secondary efficacy endpoint is the incidence of RSV LRTI hospitalization through 150 days post dose. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis.

The events of "RSV hospitalization" are a subset of "medically attended RSV LRTI," which are determined based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from central laboratory analysis respiratory secretions using a validated RSV reverse transcriptase -polymerase chain reaction (RT-PCR) assay for the detection of RSV A or RSV B.

Prior to analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as an RSV LRTI hospitalization if they occurred in a respiratory sample collected within this window relative to the admission/deterioration date. The actual window used will be documented prior to unblinding. In addition, deaths that can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as RSV LRTI hospitalization endpoints.

3.5.2.2 Secondary Efficacy Analyses

A Poisson regression model with robust variance (Zou, 2004) using only the treatment term will be used to assess the treatment effect on the incidence of RSV LRTI hospitalization between MEDI8897 and placebo groups in the ITT population. Relative risk reduction and its corresponding 95% CI are estimated from the model implemented by PROC GENMOD as detailed in Section 3.5.1.2.

Statistical testing of the null hypothesis that the incidence of RSV LRTI hospitalization between MEDI8897 and placebo groups is the same will only be performed if the primary efficacy analysis has achieved a p-value that is ≤ 0.05. In that event, statistically significant treatment effect on this secondary efficacy endpoint will be claimed if the 2-sided p-value is ≤ 0.05. In this approach, the family-wise Type I error rate of testing the first and the secondary efficacy hypotheses is controlled under the significance level of $\alpha \leq 0.05$.

Above stated analysis on RSV LRTI hospitalization will also be conducted on the per-protocol population.

3.5.2.3 Handling of Dropouts and Missing Data

RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. For subjects who do not have an RSV LRTI and were not followed through 150 days post dose, their event status will be imputed using the observed placebo RSV LRTI hospitalization rate following the repeated imputation procedure without involvement of stratification factors. The computation steps are similar to what has been described in the Sensitivity analysis 2 for the primary efficacy endpoint (Section 3.5.1.6).

3.5.2.4 Additional Analyses of the Secondary Efficacy Endpoint

The additional analyses, including the CMH test with the only term of treatment for the incidence of RSV LRTI hospitalization, and the Kaplan-Meier for time-to-first RSV LRTI hospitalization will be conducted. Treatment effect for time-to-first RSV hospitalization will be tested by a log-rank test. For the CHM test, the procedures for missing data imputation and the statistical inference from imputed datasets will follow what been described in Section 3.5.1.4, except for the fact that no stratification factors are involved in the steps.

For each treatment group, age at onset of the first medically attended RSV LRTI hospitalization will be tabulated by age group used for randomization stratification by treatment group. In addition, time-to-first medically attended RSV LRTI hospitalization will be plotted at subject's level along the axis of age at birth. RSV hospitalization will also be summarized by RSV subtype (A or B).

3.5.2.5 Subgroup Analyses for the Secondary Efficacy Endpoint

The incidence of RSV LRTI hospitalization will be summarized by the following subgroups.

- Hemisphere
- Country
- Age at randomization stratum (age $\leq$ 3 months, age > 3 to $\leq$ 6 months, age > 6 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight $\leq$ 2.5 kg, weight > 2.5 kg)
- Weight on Day 1 (weight $\leq$ 2.5 kg, weight > 2.5 to $\leq$ 5 kg, weight > 5 kg)
- GA (29-32 weeks, > 32 weeks)
- Sibling also participating in the study (yes/no)

3.5.3 Other Efficacy Analyses

Summary of incidence for all medically attended LRTI, breaking done by protocol-defined LRTI (RSV or non-RSV) and non-protocol defined LRTI (RSV or non-RSV) with each further breaking done by hospitalization status, will be presented by treatment group.
For all medically attended LRTI, the incidence of RSV status (positive, negative or not done) will be summarized by RT-PCR or local testing results. Incidence of positive RSV either by RT-PCR or by local testing results will also be summarized by treatment group. The same analysis window as described in above sections for the RT-PCR central tests will be used for the local tests.

In addition, all LRTI hospitalizations (primary or nosocomial hospitalization) and medically attended outpatient LRTI events by different outpatient settings, such as outpatient clinics, urgent care clinics, or emergency department visits will be summarized by treatment group.

All above stated summaries will be based on observed events and data summary will be presented by Day 150 post dose (on the ITT population), after 150 days post dose (on the ITT population with Day 151 visit), and through 360 days post dose (on ITT population). For subjects with multiple events, only the first occurrence will be used in each relevant incidence summary.

For various medical events, including the primary endpoint, detailed definitions of new onset of events are defined in the following table, Table 3.5-1. For medically attended LRTI (regardless RSV Yes or No, or Protocol-defined Yes or No) the total number of event occurrences for each subject and the percentage of each outcome will be summarized by treatment group on 3 time-intervals: Day 150 post dose (on the ITT population), after 150 days post dose (on the ITT population with Day 151 visit), and through 360 days post dose (on ITT population). In addition, a listing that provides relevant information for subjects with more than one medically attended LRTI event throughout the study will be generated. The listing contains the following information: Age at randomization, Hemisphere, Total number of events, Days post dose, AE verbatim term, Date of AE onset/stop, Days from previous event, Visit setting, Protocol-defined (Y/N), RSV (Y/N), and RSV subtype (when applicable).

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset medically attended RSV LRTI	A new onset medically attended RSV LRTI will be defined as an adverse event (AE) (for which at least one healthcare visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous AE for a medically attended RSV LRTI.
New onset RSV LRTI **hospitalization**	A new onset medically attended RSV LRTI hospitalization will be defined as an AE (for which at least one hospitalization is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous AE for a medically attended RSV LRTI hospitalization.
New onset medically attended RSV **outpatient** LRTI	A new onset medically attended RSV outpatient LRTI will be defined as an AE (for which at least one healthcare outpatient visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous AE for a medically attended RSV outpatient LRTI.
New onset medically attended LRTI	A new onset medically attended LRTI will be defined as an AE of LRTI that occurs after the resolution date of the previous AE for a medically attended LRTI.
New onset LRTI **hospitalization**	A new onset medically attended LRTI hospitalization will be defined as an AE (with at least one hospitalization associated with LRTI) that occurs after the resolution date of the previous AE for a medically attended LRTI hospitalization.
New onset medically attended **outpatient** LRTI	A new onset medically attended outpatient LRTI will be defined as an AE (with at least one outpatient healthcare visit associated with LRTI) that occurs after the resolution date of the previous AE for a medically attended outpatient LRTI.

AEs associated with all medically attended LRTI will be summarized overall, as well as categorized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days on the ITT, ITT with Day 151 visit and ITT populations, respectively.

3.6 Exploratory Analyses

3.6.1 Healthcare Resource Utilization (HRU)

The magnitude of Healthcare Resource Utilization (HRU) (measured by number of admissions to hospitals and duration of stay; number of admissions to the Intensive Care Unit (ICU) and duration of stay, number requiring respiratory support (using Continuous Positive Airway Pressure [CPAP] or mechanical ventilation) and the duration of use, and the number of supplemental oxygen and the duration of use; number of visiting out-patient facilities (outpatient Emergency Department [ED], urgent care, outpatient clinic); and number of prescription or over the counter [OTC] medications and duration of use) will be summarized by treatment group and reported in 3 time period: through 150 days post dose

(on ITT population), after 150 days post dose (on ITT population with Day 151 visit), and through 360 days post dose (on ITT population).

Specifically, following summary tables by treatment group will be used to report the magnitudes of HRU (overall for any reason).

- The number and percent of subjects who have had at least one of the following: hospitalization, ICU admission, requiring respiratory support, requiring supplemental oxygen, or visiting an outpatient facility (for any type of the outpatient facility). Similar summaries will also be provided by respiratory support subtype (CPAP or mechanical ventilation) and the type of outpatient facility. The percentage will be calculated based on ITT population for time interval through 150 days post dose, on ITT population with Day 151 visit for time interval after 150 days post dose, and on ITT population for time interval through 360 days post dose.

- For each of the medical activities listed above, the total number of the activity for a subject who has had at least one respective event in the reporting time-period will be calculated and summarized by treatment group using descriptive statistics (mean, median, standard deviation [SD], minimum, and maximum).

- The total duration of each of the following (in days) will be calculated accumulatively throughout the reporting time-period and summarized by descriptive statistics (mean, median, SD, minimum, and maximum): hospital stay, ICU stay, use of respiratory support, or use of supplemental oxygen for the subjects who has had at least one of the corresponding activity.

Duration of each hospitalization will be calculated from the admission or deterioration date to discharge date. If the discharge date is missing because of the reason that the subject died in the hospital, the duration of that hospital stay will be calculated by from admission to the minimum of {Death Date, End-of-Study Date}. Total duration of hospitalization is the cumulated days of each hospital stay throughout the reporting time-period.

Similarly, duration of each ICU admission, use of respiratory support, or use of supplemental oxygen will be calculated from start date to stop date or the end date, and the total duration of each medical intervention for a subject is calculated by summing the duration of all occurrences in the time interval of interest.

In addition to the overall HRU summary, the HRU for (1) medically attended RSV LRTI (Protocol-Defined), (2) medically attended non-RSV LRTI (Protocol-Defined), (3) medically

attended RSV LRTI (Non-protocol Defined) and (4) medically attended non-RSV LRTI (Non-protocol Defined) will be summarized through 150 days post dose, after 150 days post dose, and through 360 days post dose. The same conventions used for the overall summary (eg, patient population included in a specific summary) will apply for the respective events and the HRU must occur during the event being summarized.

The total number and duration of prescriptions (or OTC medications) related to each of the 4 previously mentioned events per subject through Day 150 post dose will be summarized using descriptive statistics (mean, median, SD, minimum, and maximum) by treatment group. For each treatment group, the average number of prescriptions and duration per event of interest will also be reported. The average number of prescriptions is calculated by dividing the total number of prescriptions across subjects who have had at least one prescription for the event over the total number of such events over the time interval of interest. The average duration will be calculated similarly. Only subjects with the respective event will be included in the above analysis. Similar summaries will be provided for subjects by RSV hospitalization or non-RSV LRTI hospitalization status (has had at least one or none).

3.6.2 Caregiver Burden

Caregiver burden (measured by days of work the caregiver missed, days of daycare/babysitting the subject missed) will be summarized for subjects with medically attended RSV LRTI (Protocol-defined) by treatment group for subjects who have had at least an event in the time-period of reporting. Similar summaries will be provided for medically attended non-RSV LRTI (Protocol-defined), medically attended RSV LRTI (Non-protocol Defined) and medically attended non-RSV LRTI (Non-protocol Defined), respectively. These summaries will be presented through 150 days post dose, after 150 days post dose, and through 360 days post dose using similar reporting convention as described previously.

For each of the events mentioned above and each time-period of reporting, the accumulated total days of work the caregiver missed and the accumulated total days of daycare/babysitting the subject missed will be calculated for each subject and presented using descriptive statistics (mean, median, SD, minimum, and maximum) by treatment group. For each treatment group, the average caregiver burden (i.e., the average number of days of work the caregiver missed, the average number of days of daycare/babysitting the subject missed) for a respective event will be calculated as the total caregiver burden across subjects who has had at least one of the events divided by the total number of the events among these subjects in the time interval of interest. Similar summary will also be provided by the status of hospitalization (at least one or none) that is caused by a respective event mentioned above.

3.7 Safety Analyses

All safety analyses will be conducted on As-treated population.

3.7.1 Adverse Events and Serious Adverse Events

Adverse events will be coded by MedDRA version 19 or higher and the type, incidence, severity and relationship to study investigational product will be summarized by treatment group. 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 (TEAEs) will be summarized overall, as well as categorized by MedDRA SOC and PT.

Additional summaries will present TEAEs by SOC, high-level term, SOC, and high-level group term. Nontreatment-emergent AEs/serious adverse events (SAEs) will be presented in the listings.

3.7.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will include targeted AEs of hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA. Additional groupings may be added by the Medical Monitor, if warranted.

3.7.3 Skin and Hypersensitivity Reactions

All skin reactions and skin reactions identified as hypersensitivity/allergic reactions and the type, incidence, and relationship to study investigational product will be summarized by treatment group, and by SOC and PT based on MedDRA.

3.7.4 New Onset Chronic Disease

New onset chronic diseases include, but are not limited to diabetes, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy) and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA.

3.7.5 Subgroup Analyses

All AEs will be summarized by age group used as randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months), weight on Day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg), and age at randomization by ≤ 8 months or > 8 months.

3.7.6 Other Safety Evaluations

TEAEs, AESIs, skin reactions, and skin hypersensitivity reactions will also be summarized by timing relative to dosing ('within 1 day/greater than 1 day,' 'within 7 days/greater than 7 days').

Additional data collected throughout the study include screen failure data, significant findings in medical history and physical exam, vital signs, and concomitant medications through Day 361. 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.

3.8 Anti-drug Antibodies

The number and percentage of subjects who develop anti-MEDI8897 antibodies will be summarized at each visit by treatment group. For those with a positive assessment, the ADA titer results will also be summarized. The number and percentage of ADA positive samples with specificity to the YTE or neutralizing regions of MEDI8897 will also be summarized.

An additional table will summarize 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 one 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)

To evaluate the impact of ADA on efficacy and safety, the primary and the secondary efficacy endpoints, as well as TEAE and SAE by SOC and PT based on MedDRA will be summarized by ADA status in three ways: 1) ADA post-baseline status (ie, at least one post-baseline ADA positive or not); 2) ADA persistent positive status (Yes or No); 3) ADA transient positive status (Yes or No).

The impact of ADA on PK will be included in the PK report as mentioned in Section 3.9.

3.9 Pharmacokinetics (PK)

Individual and mean MEDI8897 serum concentrations for each nominal sampling time will be listed, summarized and plotted versus time. Pharmacokinetic parameters will be listed for each subject and summary descriptive statistics will be presented. Individual and mean Tmax, Cmax, C150, AUC_0-150, and AUC_0-last will be graphically illustrated by ADA status and MA-LRTI outcome. The details of the analyses and presentation of these data will be included in a separate PK report.

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Appendix 1 Elements to Evaluate for Case Definition of Medically Attended RSV LRTI (Protocol defined)

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive RT-PCR	**Documented PE findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration • Prescription medications (only for children with underlying lung disease)

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = real time reverse transcriptase-polymerase chain reaction;

Note: One item from each column is required to meet the case definition of RSV LRTI.

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Statistical Analysis Plan

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

Protocol Number: D5290C00003

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List of Abbreviations

Abbreviation or Specialized Term	Definition
AAP	American Academy of Pediatrics
ADA	Anti-drug antibody (ies)
AE(s)	adverse event(s)
AESI	adverse event of special interest
CE	*Conformité Européenne* or European Conformity
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPAP	Continuous Positive Airway Pressure
DOB	date of birth
eCRF	electronic case report form
ED	Emergency Department
ER	emergency room
EU	European Union
GA	gestational age
HRU	healthcare resource utilization
ICU	intensive care unit
IDMC	independent data monitoring committee
IM	intramuscular
ITT	intent-to-treat
IWRS	interactive web response system
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PK	pharmacokinetic(s)
PT	Preferred Term
RR	relative risk
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SID	subject identification
SOC	System Organ Class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
US FDA	United States Food and Drug Administration
USA	United States of America

1 INTRODUCTION

This document describes the statistical analysis plan (SAP) for protocol D5290C00003, a pivotal Phase 2b study to determine if MEDI8897 is efficacious in reducing medically attended respiratory syncytial virus (RSV)-confirmed lower respiratory tract infection (LRTI) in healthy preterm infants entering their first RSV season. The primary efficacy hypothesis of this study is that, compared with placebo, a single 50-mg intramuscular (IM) dose of MEDI8897 will be efficacious in reducing medically attended LRTI caused by reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed RSV in healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable. The secondary hypotheses are that (1) there will be a reduction in the incidence of hospitalizations attributable to RSV, (2) the predicted extended terminal half-life ($t_{1/2}$) will be adequate for the duration of the RSV season, and (3) anti-drug antibodies (ADA) to MEDI8897 will not significantly impact the serum concentrations or safety of MEDI8897 over the 5-month RSV season. These hypotheses will be assessed by the incidence of RSV LRTI, RSV hospitalization, ADA, pharmacokinetic (PK) parameters, and descriptive statistics from safety data. 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(s)

To assess the efficacy of MEDI8897 when administered as a single 50 mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared with placebo.

2.1.2 Secondary Study Objectives

1. To assess the efficacy of MEDI8897 for the reduction of hospitalizations due to RT-PCR-confirmed RSV, compared with placebo
2. To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared with placebo
3. To evaluate single-dose serum concentrations of MEDI8897

4. To evaluate ADA responses to MEDI8897 in serum

2.1.3 Exploratory Study Objectives

To assess healthcare resource utilization (HRU) and caregiver burden for MEDI8897 recipients compared with placebo recipients.

2.2 Study Design

The population to be enrolled is healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who would not receive RSV prophylaxis based on the American Academy of Pediatrics (AAP) or other local or national guidelines. These infants will not be receiving palivizumab, allowing for a placebo comparator group for the determination of efficacy and the safety profile. A total of 1,500 infants will be randomized in a 2:1 ratio to receive a 50 mg IM dose of MEDI8897 (N = 1000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age group at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. All infants will be followed for approximately 360 days after dosing.

2.3 Treatment Assignment and Blinding

An interactive web response system (IWRS) will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized at a 2:1 ratio to receive a 50 mg IM dose of MEDI8897 (N = 1,000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age group at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500.

The procedure for using IWRS is as follows:

- The investigator or designee contacts the IWRS and provides the subject identification (SID) number and subject's baseline characteristic(s) used to verify that it is the same subject
- Placebo (provided by site) or a vial from a MEDI8897 kit will be assigned to the subject

- Confirmation of this information is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log

Investigational product (MEDI8897 or placebo) must be administered the same day the investigational product is assigned. Total in-use storage time from needle puncture of the investigational product vial to administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used. If there is a delay in the administration of investigational product such that it will not be administered within the specified time frame, the unblinded investigational product monitor must be notified immediately.

2.4 Sample Size

The sample size of 1,500 subjects is necessary based on advice from the United States Food and Drug Administration US FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size has approximately > 99% power to detect 70% relative-risk reduction, assuming a placebo group medically attended RSV LRTI incidence of 8%. Power calculations are based on a Poisson regression model with robust variance (Zou, 2004) comparing MEDI8897 50 mg versus placebo, with 2-sided, $\alpha = 0.05$.

- The 70% relative-risk reduction assumption is based on a placebo-controlled study in Native American infants in which there was 87% relative reduction in the incidence of RSV hospitalization (11.3% placebo; 1.5% motavizumab; $p < 0.001$) and 71% relative reduction in the incidence of outpatient RSV LRTI (10.0% placebo; 2.9% motavizumab; $p < 0.001$) in infants who received motavizumab prophylaxis (O'Brien et al, 2015)

In order to evaluate risk, a sample size of 1,000 subjects exposed to MEDI8897 will provide a 90% probability of observing at least one AE if the true event rate is 0.2%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.3%.

3 STATISTICAL METHODS

3.1 General Considerations

Summary statistics will be tabulated by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by mean, median, standard deviation, minimum, and maximum. In general, unless stated otherwise, baseline will be defined as the last non-missing value prior to dosing.

There are two planned analyses for this study: the Primary Analysis and the Final Analysis. The Primary Analysis will be conducted after all randomized subjects have completed the Day 151 visit. At the time of this primary analysis, approximately half of all subjects enrolled (722 subjects) will have completed the Day 361 visit. The remaining 731 subjects will have completed approximately 8 months of the study. MEDI8897'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 and Datasets

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	Subjects who are randomized will be included in the ITT population; in this population data will be analyzed according to their randomized treatment group.
As-treated population	Subjects who are randomized and receive any study investigational product will be included in the as-treated population; in this population, data will be analyzed according to the treatment they actually receive.
Per-protocol population	The per-protocol population includes subjects in the ITT population who receive the correct dose of randomized treatment and who do not have a serious protocol violation. Detailed criteria defining this population will be determined and documented prior to performing the Primary Analysis.

Analysis Datasets

- The Primary Dataset contains all data (efficacy, safety, ADA, PK) from all randomized subjects through the Day 151visit 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 Stratification Factors

Two stratification factors are used in study design as well as in data analysis, and these are: age group at randomization [age ≤ 3 months (ie, age ≤ 91 days), age > 3 to ≤ 6 months (ie, age > 91 to ≤ 183 days), age > 6 months (ie, age > 183 days)] and hemisphere (northern hemisphere, southern hemisphere). For subjects who were assigned to an incorrect age stratum at randomization, the age stratum as calculated from the electronic case report form (eCRF) will differ from the stratum recorded for the subject in the IWRS database. Unless stated otherwise, the age stratum based on the CRF calculation will be used.

CRF calculation for age when full date of birth (DOB) is available:

- Age at randomization (months) = (randomization date – DOB) / (365.25/12)

When full DOB is unavailable, age at screening will be used. Since screening may be collected in terms of days, weeks, or months, it will be first converted in terms of months as follows:

- Age at screening (days) / (365.25/12) = Age at screening (months)
- Age at screening (weeks) / (52/12) = Age at screening (months)

Once age at screening is converted to months,

- Age at randomization (months)= Age at screening (months) + [(randomization date – screening date) / (365.25/12)]

Determination of hemisphere in stratification and analysis is as follows: The sites have been grouped together by country into the following two hemispheres: Northern Hemisphere (Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Hungary, Italy, Latvia, Lithuania, Poland, Spain, Sweden, Turkey, United Kingdom, and United States of America [USA]) and Southern Hemisphere (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa).

3.4 Study Subjects

3.4.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment received (including summary of subjects randomized but not treated) will be provided. In addition, disposition of subjects throughout the study and by visit will be provided. This summary will be presented

by treatment group and for all subjects combined. The denominators for this summary will include all subjects who were randomized into the study.

3.4.2 Demographics and Baseline Characteristics

Enrolment will be summarized by hemisphere, country, site, and by hemisphere, country, and age at randomization stratum for each treatment group and for all subjects combined. The total number of subjects randomized into each treatment group will be used as the denominator. For the summary of hemisphere, country, and age at randomization stratum, the number of mis-stratified subjects (ie, age stratum as calculated from the eCRF does not match the IWRS database) will be summarized.

Demographic information related to gender, age at randomization (months) calculated from the CRF, age at randomization category determined using the CRF age calculation (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months), GA (weeks), GA category (29-32 weeks, > 32 weeks), ethnicity, race, weight (kg) on day 1, weight on day 1 category (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg), birth weight (kg), birth weight category (weight ≤ 2.5 kg, weight > 2.5 kg), multiple birth (yes/no), and siblings enrolled in the study (yes/no) will be summarized by treatment group and for all subjects combined using the ITT population. Subjects will be excluded from the summary (eg, means and percentages) of an individual parameter if data are missing. This will be done for all subjects, each age category at randomization, country, and by hemisphere.

3.4.3 Study Drug Exposure

Due to the simplicity of dosing for this study, exposure is summarized in the Subject Disposition and Completion Status table under “Randomized and dosed.” No other summary will be reported.

3.5 Efficacy Analyses

The analyses of the primary efficacy endpoint, the protocol-defined medically attended RSV LRTI through 150 days post dose (also described as the medically attended RSV LRTI through 150 days post dose in Section 3.5.1., Primary Efficacy Endpoint and Analyses), and the secondary efficacy endpoint, the protocol-defined RSV hospitalization through 150 days post dose (also described as the RSV LRTI hospitalization in Section 3.5.2., Secondary Efficacy Endpoint and Analyses), will be performed on the Primary Dataset.

The Final Dataset will include the events that occurred 150 days post dose, either medically attended RSV LRTI or RSV hospitalization, therefore will be used to summarize these events

that occurred after Day 151 or up to Day 361. Efficacy analyses performed on the Primary Dataset will be refreshed in the Final Dataset to make sure statistical inferences on MEDI8897 efficacy made from the Primary Analysis are consistent with those from the Final Dataset.

3.5.1 Primary Efficacy Endpoint and Analyses

3.5.1.1 Primary Efficacy Endpoint

The primary endpoint is the incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose. For subjects with multiple medically attended RSV LRTI events (inpatient or outpatient), only the first occurrence will be used in the primary analysis.

The determination of medically attended RSV LRTI will be based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from analyzing the respiratory secretions using a validated RSV RT-PCR assay for the detection of RSV A or RSV B performed in a central laboratory. These LRTI events may occur in the inpatient or outpatient visit setting.

Prior to database lock for the primary analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as a medically attended RSV LRTI if they occurred in a respiratory sample collected within this window relative to the initial date seen by the healthcare provider (eg, admission/deterioration date associated with the event, urgent care visit, outpatient ED visit, or outpatient clinic visit). The actual window used will be documented prior to unblinding. In addition, deaths that can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as primary medically attended RSV LRTI events.

3.5.1.2 Primary Efficacy Analysis

The primary efficacy analysis of the primary endpoint will be performed on the ITT Population. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary efficacy analysis model to estimate the relative risk on the incidence of medically attended RSV LRTI between the MEDI8897 and the placebo groups. The model contains the term of treatment group and age group at randomization based on the calculation detailed in Section 3.3. (ie, age $\leq$ 3 months, age > 3 to $\leq$ 6 months, age > 6 months) and dichotomous temperate (northern and southern) hemispheres as covariates. The relative risk reduction, defined as 1- Relative Risk (RR), and its corresponding 2-sided 95% CI, will be estimated from the model. In addition, the 2-sided p-value testing null hypothesis that the incidence of

medically attended RSV LRTI between MEDI8897 and placebo groups are the same will be obtained from the model. Statistical significance will be achieved if the 2-sided p-value is ≤ 0.05.

The Poisson regression with robust variance analysis will be implemented by 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 95% confidence interval (CI) for $\hat{\beta}$, and the 2-sided p-value will be obtained from the SAS outputs. The estimated RR and corresponding CI for the RR is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of RR reduction is given by [$(1 - \exp(\hat{\beta})) * 100\%$]. The CI for the percent of RR reduction is given by ([1 – exp(upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp(lower confidence limit for $\hat{\beta}$) * 100%]).

If the number of subjects in any stratum is too small and/or convergence cannot be achieved with the Poisson regression analysis model, the stratified Cochran-Mantel-Haenszel (CMH) test (detailed in Section 3.5.1.4) will be used as the primary analysis model to test the treatment effect on medically attended RSV LRTI between MEDI8897 and placebo groups.

The above described analysis on the primary efficacy endpoint will also be conducted on the Per-protocol population.

3.5.1.3 Handling of Dropouts and Missing Data

RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo medically attended RSV LRTI rate conditional on stratification factors using multiple imputation techniques as described in the following paragraphs.

The primary analysis uses Poisson regression with robust variance requires a subject-level dataset. A repeated imputation approach is introduced to impute medically attended RSV LRTI status for missing observations at the subject-level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and CI estimation of the treatment effect is expected through the repeated imputation (Little and Rubin, 2002). In the primary analysis the missing outcome for subjects who dropped out prior to reaching Day 150 post dose without a medically attended RSV LRTI event will be imputed per stratum determined by the two stratification factors using placebo event rate. The imputation and subsequent analysis will be carried out using SAS PROC MI (Monotone Logistic Regression Method) and SAS PROC MIANALYZE. The detailed imputation steps are described as follows.

- Step 1: For the subjects in the MEDI8897 arm who do not have an RSV LRTI and are not followed through 150 days post dose, their treatment code of "MEDI8897" will be substituted with "placebo" to ensure the placebo RSV LRTI rate is applied in the imputation for the MEDI8897 dropouts adjusted for their stratification values. The imputation will be executed using SAS Proc MI (eg, logistic regression with the recoded treatment term and stratification factors).
- Step 2: The original treatment code will be restored after the RSV LRTI event statuses have been imputed. A complete dataset comprises the imputed RSV LRTI status and observed RSV LRTI status.
- Step 3: Analyze the complete dataset using a Poisson regression model with robust variance to estimate the relative risk on the incidence of medically attended RSV LRTI between MEDI8897 and placebo, with the term of treatment group and two stratification factors. The point estimate of log-transformed RR and its variance will be extracted from the model.
- Steps 2-3 will be repeated 20 times. SAS procedure PROC MIANALYZE will be used to combine inferences from the 20 completed datasets, that will result in a combined point estimate of log-transformed relative risk and the variance. The random seed is 12345.

3.5.1.4 Additional Analyses of the Primary Efficacy Endpoint

The following analyses will be conducted on the ITT population.

To allow for differences in follow-up time, the primary analysis using a Poisson Regression with robust variance will be repeated, adjusting for the same covariates as well as log (follow-up time) as an offset. Since the follow-up time is adjusted in the model, there is no missing imputation for this analysis. Calculation of follow-up are detailed as follows:

- For subjects who meet the medically attended RSV LRTI endpoint within 150 days post dose, the follow-up time will be calculated as (Date of Onset of RSV LRTI) – (Date of Dosing) +1.
- For subjects who do not experience a medically attended RSV LRTI event within 150 days post dose, the efficacy follow-up will be determined based on the following:
  - If an end of study date occurs within 150 days post dose (or end of study date is missing and last assessment date occurs within 150 days post dose), the efficacy follow-up will be calculated as (Date of End of Study or Date of Last Assessment, whichever is later) – (Date of Dosing) +1.

- If an end of study date occurs after 150 days post dose (or end of study date is missing and last assessment date is after 150 days post dose), the efficacy follow-up will be censored (at 151 days).

A CMH test stratified by hemisphere and age group at randomization (ie, age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months) will be used to compare between treatment groups through 150 days post dose as the key secondary analysis for the primary endpoint. SAS procedure of PROC FREQ with CMH option will be used to perform the analysis. The relative risk of MEDI8897 over placebo for the incidence of medically attended RSV LRTI events and the 95% CI will be obtained from the SAS procedure. The percent of RR reduction and the 95% CI will be reported following the relationship of RR reduction (%) = (1- relative risk)*100%. This analysis will be performed without any imputation of event for MEDI9987 subjects who dropped out the study prior to Day 150 post dose and did not have a medically attended RSV event.

A Kaplan-Meier curve for time to first medically attended RSV LRTI will be generated based on observed events. The algorithm for time-to-event calculation is the same as to that for follow-up time (see previous). Treatment group differences in time-to-first medically attended RSV LRTI will be compared using the stratified log-rank test and Wilcoxon test with two stratification factors as the strata.

In addition, all observed medically attended RSV LRTI events and the corresponding incidence rates will be tabulated by Inpatient (primary hospitalization, nosocomial hospitalization) and Outpatient, for the latter category, further presentation will be made by different medical settings: outpatient clinic, urgent care clinic, and emergency department visits for subjects who did not have a hospitalization due to RSV.

3.5.1.5. Analyses for Medically Attended RSV LRTI beyond the Primary Endpoint

The following analyses will be conducted on the ITT population and based on observed events, unless stated otherwise.

The incidence of medically attended RSV LRTI that occurred > 150 days post dose and ≤ 360 days post dose will be summarized by treatment group. ITT subjects who remained in the study at the Day 151 visit will be used as the denominator to calculate the incidence rate for the summary of the incidence > 150 days post dose, and the ITT population will be used for the summary of the incidence ≤ 360 days post dose.

Age at onset of the first medically attended RSV LRTI will be tabulated by age group used for randomization stratification by treatment group. In addition, time-to-first medically attended RSV LRTI will be plotted at subject's level along the axis of age at birth.

The incidence of medically attended RSV LRTI by subtype (RSV A, RSV B) through 150 days post dose, > 150 Days and through 360 days post dose will be summarized by treatment group. The populations that the summary will be based on will be similar to what had been used for the analysis of medically attended RSV LRTI at each corresponding time period.

To capture and summarize multiple medically attended RSV LRTIs, the total number of new onset medically attended RSV LRTIs since the previous medically attended RSV LRTI will be calculated for each subject. A new onset medically attended RSV LRTI is defined as an adverse event (AE) meeting protocol specified medically attended RSV LRTI that occurred at least 14 days after the resolution date of the previous AE for a medically attended RSV LRTI. Similar definition is applied with a 30 days interval between the resolution of the previous event and a new onset of event (see Table 3.5-1 for details). A listing will be generated to provide the following information: age at randomization, hemisphere, total number of events (at least 14 days apart), total number of events (at least 30 days apart), days to event, adverse event (AE) verbatim term, Date of AE onset/stop, Days from previous event, Visit setting, and RSV subtype. AEs associated with medically attended RSV LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days.

3.5.1.6. Sensitivity Analyses for Subjects who are Not Followed through 150 Days Post Dose

Sensitivity analyses for RSV LRTI through 150 days post dose will be performed to address subjects who do not have an RSV LRTI and are not followed through 150 days post dose through various approaches of missing data imputation are described as follows:

1. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having not met the RSV LRTI endpoint.
2. Impute the missing values in each treatment group using 2-times the placebo RSV LRTI event rate through 150 days post dose (ie, Bernoulli distribution with expected value equal to 2-times placebo RSV LRTI event rate).
3. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 2-times the placebo event rate through 150 days post dose and imputing the missing

values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 2 or 1-times placebo RSV LRTI event rate).

4. Tipping point analysis by imputing the missing values in the MEDI8897 arm using 3-times the placebo event rate through 150 days post dose and imputing the missing values in the placebo arm with the placebo rate (ie, Bernoulli distribution with expected value equal to 3 or 1-times placebo RSV LRTI event rate)
5. Subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be counted as having met the RSV LRTI endpoint.
6. Multiple imputations
7. Impute the missing values in each treatment group using 1-time, 2-time, and 3-time the overall placebo event rate in single imputation approach.

The sensitivity analyses 2-4 will be conducted following the steps below:

- Step 1: Determine the observed placebo RSV LRTI rate through 150 days post dose, which is calculated as the proportion of all randomized placebo subjects with observed RSV.
- Step 2: Impute the event status for subjects who do not have an RSV LRTI and are not followed through 150 days post dose in each treatment arm or the MEDI8897 arm only (depending on the sensitivity analysis planed above) using the Bernoulli distribution with X-times the observed placebo RSV LRTI rate without involvement of stratification factors.
- Step 3: The subjects with imputed values of RSV LRTI status (Yes/No) will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose without an RSV LRTI, to form a complete dataset.
- Step 4: Analyze the complete dataset using a Poisson regression model with robust variance to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, and two stratification factors (age group and hemispheres) as covariates. The point estimate of log-transformed RR and its variance will be produced from the model.
- The steps 2-4 will be repeated 20 times with seed 1-20, respectively. SAS procedure PROC MIANALYZE will be used to combine inferences from the 20 completed datasets, which will result in a combined point estimate of log-transformed RR and the variance.

For sensitivity analyses 1 and 5, all subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be assumed to either (1) have an RSV LRTI event

(sensitivity analysis #5) or (2) not have an RSV LRTI event (sensitivity analysis #1). The subjects with imputed values of RSV LRTI status will be combined with the remaining subjects who either have an RSV LRTI prior to 150 days post dose or who were followed through 150 days post dose without the event to form a complete dataset. The primary efficacy analysis model will be used to analyse the completed datasets via the specified imputation method.

For sensitivity analysis 6, the medically attended RST LRTI event status for the subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be imputed by the observed event rate per treatment group. That is, following the standard Multiple Imputation procedure and carried by Proc MI (Monotone Logistic Regression Method) and PROC MIANALYZE.

For sensitivity analysis 7, the number of medically attended RSV LRTI events for those MEDI8897-treated subjects who dropped out prior to Day 150 post dose without the event will be generated using a binomial distribution with 1-time, 2-time, or 3-time observed placebo event rates, respectively. While placebo-treated subjects who dropped out prior to Day 150 post dose without the event will be imputed using a 1-time observed placebo rate. With the imputed number of events, the RR reduction and the 95% CI will be constructed using an exact conditional method based on the number of RSV LRTIs (Breslow and Day, 1987). This analysis will be carried out by StatXact PROC Poisson procedure.

3.5.1.7. Subgroup Analyses for the Primary Efficacy Endpoint

Subgroup analysis will be performed for the primary efficacy endpoint, the incidence of medically attended RSV LRTI. Treatment-by-subgroup interaction will be tested using the Poisson regression with robust variance model with the terms of treatment, age group, hemisphere, subgroup, and treatment-by-subgroup interaction, which will be implemented using PROC GENMOD procedure. If this full model does not achieve convergence, a reduced model of treatment, subgroup, and treatment-by-subgroup interaction will be used. Significant treatment-by-subgroup interaction is judged at the significance level of 0.10. Within each level of a subgroup, the RR reduction and its corresponding 95% CI will be estimated using a Poisson regression model with robust variance with the term of treatment. A forest plot of the RR reduction and the 95% CI will be presented. In the event that the Poisson regression model does not converge for any stratum of a subgroup, the exact conditional method based on the number of RSV LRTIs (Breslow and Day, 1987) will be used as the analytical model to generate the relative risk reduction and its corresponding CI for all subgroup strata. This model will be implemented by StatXact PROC Poisson procedure and the point estimate and mid-p adjusted 95% CI will be reported.

The subgroup analysis will be conducted for the following subgroups on the ITT population:

- Hemisphere
- Age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on Day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg)
- GA (29-32 weeks, > 32 weeks)
- Sibling also participating in the study (yes/no)

In addition, incidence of medically attended RSV LRTI will be summarized by Country.

3.5.2 Secondary Efficacy Endpoint and Analyses

3.5.2.1 Secondary Efficacy Endpoint

The secondary efficacy endpoint is the incidence of RSV LRTI hospitalization through 150 days post dose. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis.

The events of "RSV hospitalization" are a subset of "medically attended RSV LRTI," which are determined based on objective clinical LRTI criteria (described in the Protocol Section 4.3.1.1 and SAP Appendix 1) and RSV test results obtained from central laboratory analysis respiratory secretions using a validated RSV reverse transcriptase -polymerase chain reaction (RT-PCR) assay for the detection of RSV A or RSV B.

Prior to analysis, a blinded review of data will be undertaken to determine an analysis window such that all positive results will be counted as an RSV LRTI hospitalization if they occurred in a respiratory sample collected within this window relative to the admission/deterioration date. The actual window used will be documented prior to unblinding. In addition, deaths that can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as RSV LRTI hospitalization endpoints.

3.5.2.2 Secondary Efficacy Analyses

A Poisson regression model with robust variance (Zou, 2004) using only the treatment term will be used to assess the treatment effect on the incidence of RSV LRTI hospitalization

between MEDI8897 and placebo groups in the ITT population. Relative risk reduction and its corresponding 95% CI are estimated from the model implemented by PROC GENMOD as detailed in Section 3.5.1.2.

Statistical testing of the null hypothesis that the incidence of RSV LRTI hospitalization between MEDI8897 and placebo groups is the same will only be performed if the primary efficacy analysis has achieved a p-value that is ≤ 0.05. In that event, statistically significant treatment effect on this secondary efficacy endpoint will be claimed if the 2-sided p-value is ≤ 0.05. In this approach, the family-wise Type I error rate of testing the first and the secondary efficacy hypotheses is controlled under the significance level of $\alpha \leq 0.05$.

Above stated analysis on RSV LRTI hospitalization will also be conducted on the per-protocol population.

3.5.2.3 Handling of Dropouts and Missing Data

RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. For subjects who do not have an RSV LRTI and were not followed through 150 days post dose, their event status will be imputed using the observed placebo RSV LRTI hospitalization rate following the repeated imputation procedure without involvement of stratification factors. The computation steps are similar to what has been described in the Sensitivity analysis 2 for the primary efficacy endpoint (Section 3.5.1.6).

3.5.2.4 Additional Analyses of the Secondary Efficacy Endpoint

The additional analyses, including the CMH test with the only term of treatment for the incidence of RSV LRTI hospitalization, and the Kaplan-Meier for time-to-first RSV LRTI hospitalization will be conducted. Treatment effect for time-to-first RSV hospitalization will be tested by a log-rank test.

For each treatment group, age at onset of the first medically attended RSV LRTI hospitalization will be tabulated by age group used for randomization stratification by treatment group. In addition, time-to-first medically attended RSV LRTI hospitalization will be plotted at subject's level along the axis of age at birth. RSV hospitalization will also be summarized by RSV subtype (A or B).

3.5.2.5 Subgroup Analyses for the Secondary Efficacy Endpoint

The incidence of RSV LRTI hospitalization will be summarized by the following subgroups.

- Hemisphere
- Country
- Age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on Day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg)
- GA (29-32 weeks, > 32 weeks)
- Sibling also participating in the study (yes/no)

3.5.3 Other Efficacy Analyses

An overall summary of subjects with any medically attended LRTI or hospitalization due to any respiratory illness will be presented by treatment group. Summary of medically attended LRTI, breaking done by protocol-defined LRTI (RSV or non-RSV) and non-protocol defined LRTI (RSV or non-RSV) with each further breaking done by hospitalization status, will be presented. In this summary, a subject is reported only once even he or she might have multiple LRTI events in the time interval of reporting. In that occasion, the event with the highest severity level will be reported. The rules to define severity among multiple LRTI events for a subject are as follows: Protocol-defined > Non-protocol defined, RSV > non-RSV, and Hospitalization > non-Hospitalization. For subjects who were hospitalized due to any respiratory illness, non-LRTI cases will be further reported and broken done by RSV status. A subject is reported only once even he or she might have multiple non-LRTI events in the time interval of reporting. In that occasion the rule to report is RSV > non-RSV.

For all medically attended LRTI, RSV status (positive, negative or not done) will be summarized by RT-PCR or local testing results by treatment group. The proportion of each category will be calculated based on the total number of LRTI events for the respective treatment group. In addition, incidence of positive RSV LRTI either by RT-PCR or by local testing results will also be summarized by treatment group. The same analysis window as described in above sections for the RT-PCR central tests will be used for the local tests. In this summary, only first occurrence of RSV LRTI event either by PT-PCR or local testing will be reported and the incidence of the event will be calculated based on the number of randomized subjects for the respective treatment group.

In addition, for each treatment group, all LRTI events will be tabulated by Inpatient (primary hospitalization, nosocomial hospitalization) and Outpatient, for the latter category, further presentation will be made by different medical settings: outpatient clinic, urgent care clinic, and emergency department visits. The proportion of each category will be calculated based on the total number of LRTI events for the respective treatment group.

All above stated summaries will be based on observed events and data summary will be presented by Day 150 post dose (on the ITT population), after 150 days post dose (on the ITT population with Day 151 visit), and through 360 days post dose (on ITT population). For subjects with multiple events, only the first occurrence will be used in each relevant incidence summary.

For various medical events, including the primary endpoint, detailed definitions of new onset of events are defined in the following table, Table 3.5-1. For medically attended LRTI (regardless RSV Yes or No, or Protocol-defined Yes or No) the total number of event occurrences for each subject and the percentage of each outcome will be summarized by treatment group on 3 time-intervals: Day 150 post dose (on the ITT population), after 150 days post dose (on the ITT population with Day 151 visit), and through 360 days post dose (on ITT population). In addition, a listing that provides relevant information for subjects with more than one medically attended LRTI event throughout the study will be generated. The listing contains the following information: Age at randomization, Hemisphere, Total number of events, Days post dose, AE verbatim term, Date of AE onset/stop, Days from previous event, Visit setting, Protocol-defined (Y/N), RSV (Y/N), and RSV subtype (when applicable).

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset medically attended RSV LRTI	A new onset medically attended RSV LRTI will be defined as an adverse event (AE) (for which at least one healthcare visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous AE for a medically attended RSV LRTI.
New onset RSV LRTI **hospitalization**	A new onset medically attended RSV LRTI hospitalization will be defined as an AE (for which at least one hospitalization is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous AE for a medically attended RSV LRTI hospitalization.
New onset medically attended RSV **outpatient** LRTI	A new onset medically attended RSV outpatient LRTI will be defined as an AE (for which at least one healthcare outpatient visit is associated with RSV LRTI) and occurs at least 14 days (and similarly using 30 days) after the resolution date of the previous AE for a medically attended RSV outpatient LRTI.

Table 3.5-1 Definition for New Onset of Events

Event	Description
New onset medically attended LRTI	A new onset medically attended LRTI will be defined as an AE of LRTI that occurs after the resolution date of the previous AE for a medically attended LRTI.
New onset LRTI **hospitalization**	A new onset medically attended LRTI hospitalization will be defined as an AE (with at least one hospitalization associated with LRTI) that occurs after the resolution date of the previous AE for a medically attended LRTI hospitalization.
New onset medically attended **outpatient** LRTI	A new onset medically attended outpatient LRTI will be defined as an AE (with at least one outpatient healthcare visit associated with LRTI) that occurs after the resolution date of the previous AE for a medically attended outpatient LRTI.

AEs associated with all medically attended LRTI will be summarized overall, as well as categorized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days, after 150 days, and through 360 days on the ITT, ITT with Day 151 visit and ITT populations, respectively.

3.6 Exploratory Analyses

3.6.1 Healthcare Resource Utilization (HRU)

The magnitude of Healthcare Resource Utilization (HRU) (measured by number of admissions to hospitals and duration of stay; number of admissions to the Intensive Care Unit (ICU) and duration of stay, number requiring respiratory support (using Continuous Positive Airway Pressure [CPAP] or mechanical ventilation) and the duration of use, and the number of supplemental oxygen and the duration of use; number of visiting out-patient facilities (outpatient Emergency Department [ED], urgent care, outpatient clinic); and number of prescription or over the counter [OTC] medications and duration of use) will be summarized by treatment group and reported in 3 time period: through 150 days post dose (on ITT population), after 150 days post dose (on ITT population with Day 151 visit), and through 360 days post dose (on ITT population).

Specifically, following summary tables by treatment group will be used to report the magnitudes of HRU (overall for any reason).

- The number and percent of subjects who have had at least one of the following: hospitalization, ICU admission, requiring respiratory support, requiring supplemental oxygen, or visiting an outpatient facility (for any type of the outpatient facility). Similar summaries will also be provided by respiratory support subtype (CPAP or

mechanical ventilation) and the type of outpatient facility. The percentage will be calculated based on ITT population for time interval through 150 days post dose, on ITT population with Day 151 visit for time interval after 150 days post dose, and on ITT population for time interval through 360 days post dose.

- For each of the medical activities listed above, the total number of the activity for a subject who has had at least one respective event in the reporting time-period will be calculated and summarized by treatment group using descriptive statistics (mean, median, standard deviation [SD], minimum, and maximum).

- The total duration of each of the following (in days) will be calculated accumulatively throughout the reporting time-period and summarized by descriptive statistics (mean, median, SD, minimum, and maximum): hospital stay, ICU stay, use of respiratory support, or use of supplemental oxygen for the subjects who has had at least one of the corresponding activity.

Duration of each hospitalization will be calculated from the admission or deterioration date to discharge date. If the discharge date is missing because of the reason that the subject died in the hospital, the duration of that hospital stay will be calculated by from admission to the minimum of {Death Date, End-of-Study Date}. Total duration of hospitalization is the cumulated days of each hospital stay throughout the reporting time-period.

Similarly, duration of each ICU admission, use of respiratory support, or use of supplemental oxygen will be calculated from start date to stop date or the end date, and the total duration of each medical intervention for a subject is calculated by summing the duration of all occurrences in the time interval of interest.

In addition to the overall HRU summary, the HRU for (1) medically attended RSV LRTI (Protocol-Defined), (2) medically attended non-RSV LRTI (Protocol-Defined), (3) medically attended RSV LRTI (Non-protocol Defined) and (4) medically attended non-RSV LRTI (Non-protocol Defined) will be summarized through 150 days post dose, after 150 days post dose, and through 360 days post dose. The same conventions used for the overall summary (eg, patient population included in a specific summary) will apply for the respective events and the HRU must occur during the event being summarized.

The total number and duration of prescriptions (or OTC medications) related to each of the 4 previously mentioned events per subject through Day 150 post dose will be summarized using descriptive statistics (mean, median, SD, minimum, and maximum) by treatment group. For each treatment group, the average number of prescriptions and duration per event

of interest will also be reported. The average number of prescriptions is calculated by dividing the total number of prescriptions across subjects who have had at least one prescription for the event over the total number of such events over the time interval of interest. The average duration will be calculated similarly. Only subjects with the respective event will be included in the above analysis. Similar summaries will be provided for subjects by RSV hospitalization or non-RSV LRTI hospitalization status (has had at least one or none).

3.6.2 Caregiver Burden

Caregiver burden (measured by days of work the caregiver missed, days of daycare/babysitting the subject missed) will be summarized for subjects with medically attended RSV LRTI (Protocol-defined) by treatment group for subjects who have had at least an event in the time-period of reporting. Similar summaries will be provided for medically attended non-RSV LRTI (Protocol-defined), medically attended RSV LRTI (Non-protocol Defined) and medically attended non-RSV LRTI (Non-protocol Defined), respectively. These summaries will be presented through 150 days post dose, after 150 days post dose, and through 360 days post dose using similar reporting convention as described previously.

For each of the events mentioned above and each time-period of reporting, the accumulated total days of work the caregiver missed and the accumulated total days of daycare/babysitting the subject missed will be calculated for each subject and presented using descriptive statistics (mean, median, SD, minimum, and maximum) by treatment group. For each treatment group, the average caregiver burden (i.e., the average number of days of work the caregiver missed, the average number of days of daycare/babysitting the subject missed) for a respective event will be calculated as the total caregiver burden across subjects who has had at least one of the events divided by the total number of the events among these subjects in the time interval of interest. Similar summary will also be provided by the status of hospitalization (at least one or none) that is caused by a respective event mentioned above.

3.7 Safety Analyses

All safety analyses will be conducted on As-treated population.

3.7.1 Adverse Events and Serious Adverse Events

Adverse events will be coded by MedDRA version 19 or higher and the type, incidence, severity and relationship to study investigational product will be summarized by treatment group. 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 (TEAEs) will be summarized overall, as well as categorized by MedDRA SOC and PT.

Additional summaries will present TEAEs by SOC, high-level term, SOC, and high-level group term. Nontreatment-emergent AEs/serious adverse events (SAEs) will be presented in the listings.

3.7.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will include targeted AEs of hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA. Additional groupings may be added by the Medical Monitor, if warranted.

3.7.3 Skin and Hypersensitivity Reactions

All skin reactions and skin reactions identified as hypersensitivity/allergic reactions and the type, incidence, and relationship to study investigational product will be summarized by treatment group, and by SOC and PT based on MedDRA.

3.7.4 New Onset Chronic Disease

New onset chronic diseases include, but are not limited to diabetes, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy) and the type, incidence, and relationship to study investigational product will be summarized by treatment group and by SOC and PT based on MedDRA.

3.7.5 Subgroup Analyses

All AEs will be summarized by age group used as randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months), weight on Day 1 (weight ≤ 2.5 kg, weight > 2.5 to ≤ 5 kg, weight > 5 kg), and age at randomization by ≤ 8 months or > 8 months. In addition, TEAEs occurring within 1-day and 7-day post dose by age at randomization (≤ 3 Months, >3 to ≤ 6 Months, > 6 Months) will also be summarized, respectively.

3.7.6 Other Safety Evaluations

TEAEs, AESIs, skin reactions, and skin hypersensitivity reactions will also be summarized by timing relative to dosing (‘within 1 day/greater than 1 day,’ ‘within 7 days/greater than 7 days’).

Additional data collected throughout the study include screen failure data, significant findings in medical history and physical exam, vital signs, and concomitant medications through Day 361. 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.

3.8 Anti-drug Antibodies

The number and percentage of subjects who develop anti-MEDI8897 antibodies will be summarized at each visit by treatment group. For those with a positive assessment, the ADA titer results will also be summarized. The number and percentage of ADA positive samples with specificity to the YTE or neutralizing regions of MEDI8897 will also be summarized.

An additional table will summarize 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 one 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)

To evaluate the impact of ADA on efficacy and safety, the primary and the secondary efficacy endpoints, as well as TEAE and SAE by SOC and PT based on MedDRA will be summarized by ADA status in three ways: 1) ADA post-baseline status (ie, at least one post-baseline ADA positive or not); 2) ADA persistent positive status (Yes or No); 3) ADA transient positive status (Yes or No).

The impact of ADA on PK will be included in the PK report as mentioned in Section 3.9.

3.9 Pharmacokinetics (PK)

Individual and mean MEDI8897 serum concentrations for each nominal sampling time will be listed, summarized and plotted versus time. Pharmacokinetic parameters will be listed for each subject and summary descriptive statistics will be presented. Individual and mean Tmax, Cmax, C150, AUC_0-150, and AUC_0-last will be graphically illustrated by ADA status and MA-LRTI outcome. The details of the analyses and presentation of these data will be included in a separate PK report.

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Appendix 1 Elements to Evaluate for Case Definition of Medically Attended RSV LRTI (Protocol defined)

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive RT-PCR	**Documented PE findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration • Prescription medications (only for children with underlying lung disease)

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = real time reverse transcriptase-polymerase chain reaction;

Note: One item from each column is required to meet the case definition of RSV LRTI.

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