Statistical Analysis Plan

A Phase 3 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 Late Preterm and Term Infants (MELODY)

Protocol Number: D5290C00004

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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
CSR	Clinical Study Report
DBL	database lock
DOB	date of birth
eCRF	electronic case report form
ED	emergency department
EU	European Union
GA	gestational age
HRU	healthcare resource utilization
ICU	intensive care unit
IDMC	independent data monitoring committee
IM	intramuscular
IP	Investigational Product
ITT	intent-to-treat
IWRS	interactive web response system
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
NH	Northern Hemisphere
OTC	over-the-counter
PK	pharmacokinetic(s)
PT	Preferred Term
RR	relative risk
RRR	relative risk reduction
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction

Abbreviation or Specialized Term	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SH	Southern Hemisphere
SID	subject identification
SOC	System Organ Class
$t_{1/2}$	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

1 INTRODUCTION

This document describes the statistical analysis plan (SAP) for protocol D5290C00004, a pivotal Phase 3 study to determine if MEDI8897 is safe and efficacious in reducing medically attended respiratory syncytial virus (RSV)-confirmed lower respiratory tract infection (LRTI) in healthy late preterm and term infants entering their first RSV season. The primary efficacy hypothesis of this study is that, compared to placebo, a single intramuscular (IM) MEDI8897 dose, 50 mg if weight < 5 kg or 100 mg if weight ≥ 5 kg, will be efficacious in reducing medically attended LRTI caused by real-time reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed RSV in healthy late preterm and term infants born ≥ 35 weeks 0 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 RT-PCR confirmed RSV, (2) the predicted serum exposure 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 through 150 days post dosing (i.e. over the 5-month RSV season). These hypotheses will be assessed by the incidence of RSV LRTI, RSV hospitalization, ADA, pharmacokinetic (PK) data, 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

To assess the efficacy of MEDI8897 when administered as a single fixed IM dose to infants ≥ 35 weeks 0 days GA and entering their first RSV season, in reducing 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

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

2 To determine anti-RSV neutralizing antibody levels in serum afforded by a single dose of MEDI8897 compared to maternal RSV neutralizing antibody levels and those elicited following infection in the placebo group

3 To evaluate exposure to RSV by measuring seroresponses to different RSV proteins

4 To characterize resistance to MEDI8897 through genotypic and phenotypic analyses

5 To assess the incidence of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo after Day 151 (between Day 152 and Day 361)

2.2 Study Design

The population to be enrolled is healthy late preterm and term infants born ≥ 35 weeks 0 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 approximately 3,000 infants will be randomized in a 2:1 ratio to receive a single 50-mg (if < 5 kg weight at the time of dosing) or 100-mg (if ≥ 5 kg weight at the time of dosing) IM dose of MEDI8897 (N = 2,000) or placebo (N = 1,000). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age group at randomization (ie, ≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months). Enrollment of infants > 6.0 months of

age will be limited to approximately 500. All infants will be followed for approximately 510 days after dosing.

The study will comprise 2 cohorts: a primary cohort (N = ~ 1,500) and a safety cohort (N = ~1,500) for a total of ~ 3000 subjects. The primary cohort will include subjects enrolled from the NH2019, SH2020, and NH2020 enrolment seasons (enrolment was paused after one subject from NH2020 was enrolled due to the impact of the coronavirus disease 2019 [COVID-19] pandemic). The safety cohort will include subjects enrolled after NH2020 enrollment season. Given the largely reduced circulation of RSV due to COVID-19-related measures, the efficacy analyses performed in the primary analysis for the primary cohort will serve the purpose of evaluating the efficacy of MEDI8897 in the study population. Although efficacy data will also be collected for the safety cohort, only descriptive summaries will be provided and there is no intent to pool the efficacy data from safety cohort with that from the primary cohort. Both the primary and the safety cohorts, individually and combined, will serve the purpose of evaluating the safety of MEDI8897. All subjects will be followed for approximately 510 days after dosing. An independent data monitoring committee will review safety data regularly and make recommendations regarding further study conduct.

2.3 Treatment Assignment and Blinding

2.3.1 Methods for Assigning Treatment Groups

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 single fixed IM dose of MEDI8897 (N = 2,000) or placebo (N = 1000). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age group at randomization (ie, ≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months). Enrollment of infants > 6.0 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.

2.3.2 Methods to Ensure Blinding

This is a double-blind study in which sites are using commercially available saline as the placebo. MEDI8897 and placebo are visually indistinguishable once in syringes. Neither the subject/legal representative nor the investigator or any of the site staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9). In the event that treatment allocation for a subject becomes known to the investigator or other blinded study staff involved in the management of study subjects, the sponsor must be notified *immediately*. If the treatment allocation for a subject needs to be known to treat an individual subject for an AE, the investigator must notify the sponsor *immediately*. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

Details of maintaining the double-blind setting until database lock for the primary and safety analyses are provided in Section 3.1.

2.3.3 Methods for Unblinding

2.3.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IWRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

MedImmune retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Site personnel and parents/guardians of the subjects will remain blinded to the treatment assignment until the end of the study.

2.4 Sample Size

This Phase 3 study will enroll approximately 3,000 subjects of whom 2,000 will receive MEDI8897 and 1,000 will receive placebo. The proposed sample size is to ensure a sufficient expected safety database at the time of marketing application submission. The 2,000 subjects to be dosed with MEDI8897 in this Phase 3 study, together with the 968 subjects dosed with MEDI8897 in the Phase 2b study (D5290C00003) and at least 600 subjects to be dosed with MEDI8897 in the palivizumab-controlled Phase 2/3 study (D5290C00005), will contribute to a safety database of at least approximately 3,600 infants exposed to MEDI8897.

For this Phase 3 study, the original sample size of 3,000 was driven by the safety database requirement, and the study had at least 99% power for the primary efficacy endpoint. Reducing the sample size to 1,500 still allows the study to be sufficiently powered. More specifically, the sample size of approximately 1,500 subjects in the primary cohort has at least 99% power to detect 70% relative risk reduction (RRR), 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 versus placebo, with 2-sided, $\alpha = 0.05$.

- The assumption of 8% incidence is supported both by literature (Paramore et al, 2010) and the observed placebo incidence rate [redacted] in the Phase 2b Study D5290C00003.
- The 70% RRR assumption is based on the Phase 2b Study D5290C00003 in which there was 70% RRR in the incidence of medically attended RSV LRTI (9.5% placebo, 2.6% MEDI8897; $p < 0.001$) and [redacted] RRR in the incidence of RSV hospitalization (4.1% placebo, 0.8% MEDI8897; $p < 0.001$) in subjects who received MEDI8897 prophylaxis. In addition, the assumption is supported by a placebo-controlled study in Native American term infants in which there was a [redacted] in infants who received motavizumab prophylaxis (O'Brien et al, 2015O'BrienO'BrienO'BrienO'BrienO'Brien).
- In the event that the incidence rate in the placebo group drops due to the impact of the COVID-19 pandemic (eg, social distancing), the sample size still provides at least 90% power to detect 70% RRR if the placebo incidence rate is 4% or higher.

To evaluate risk, a sample size of 2,000 subjects exposed to MEDI8897 will provide a > 99% probability of observing at least one AE if the true event rate is 0.3%; if no AEs are observed, this study provides 98% confidence that the true event rate is < 0.2%.

3 STATISTICAL METHODS

3.1 General Considerations

There are three planned analyses for this study: the Primary Analysis, Safety Analysis, and Final Analysis. The Primary Analysis will be conducted after all randomized subjects (except for the one subject enrolled in the NH2020 season) from the primary cohort have been followed through Day 361. The subjects enrolled in the NH2020 season will have completed the Day 151 visit. The efficacy of MEDI8897 will be evaluated in the Primary Analysis as intended by the study design. For the Primary Analysis, all efficacy, PK, ADA, and safety data collected for the primary cohort through Day 361 will be analyzed and unless specified otherwise, data collected after Day 361 will only be listed. The Safety Analysis will be conducted when all subjects for the safety cohort have been followed through Day 151. For the Safety Analysis, in addition to the analyses conducted during the Primary Analysis based on the primary cohort, summaries based on data collected for the primary cohort after Day 361 will be generated; all available efficacy, PK, ADA, RSV neutralizing antibody, RSV serology, and safety data collected for the safety cohort will be analyzed (only descriptive summaries will be provided for the efficacy data collected for the safety cohort); unless specified otherwise, data collected for the safety cohort after Day 361 will only be listed. The Final Analysis will be conducted when all subjects have completed the last visit of the study (Day 511) and include all data and planned analyses (including applicable summaries based on data collected for the safety cohort after Day 361). Given the largely reduced circulation of RSV due to COVID-19-related measures, the efficacy analyses performed in the primary analysis for the primary cohort will serve the purpose of evaluating the efficacy of MEDI8897 in the study population. Although efficacy data will also be collected for the safety cohort, only descriptive summaries will be provided and there is no intent to pool the efficacy data from safety cohort with that from the primary cohort. Both the primary and the safety cohorts, individually and combined, will serve the purpose of evaluating the safety of MEDI8897.

The study will maintain a double-blind setting (ie, blind for subjects, Investigators/site staff, and Sponsor/designated clinical research organization) until database lock (DBL) for the primary and safety analyses. More specifically, at the time of the Primary Analysis (where the analyses will be based only on the primary cohort), the data from the primary cohort will be unblinded to Sponsor/designated clinical research organization associated with the analysis, write-up, and regulatory submission. To maintain the double-blind setting for the safety cohort until the Safety Analysis, any data with potential unblinding risk will be split by primary cohort and safety cohort by the corresponding third party data vendors and when the primary DBL occurs, only unblinding data from the primary cohort will be transferred to the Sponsor for analysis. The unblinding data from the safety cohort will not be transferred to the Sponsor until the DBL for Safety Analysis. The site personnel, participants, and the study team members who participate in the advice or decisions involving study subjects and/or day-to-day interactions with the site, will remain blinded until the end of the study (ie, all subjects have

completed Day 511 visit) to ensure the study integrity is maintained. Further details will be specified in the unblinding plan prior to unblinding of the primary cohort data.

For the visit-based summaries for ADA, RSV neutralizing antibody, RSV serology and clinical laboratory data, the summaries will be based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows will be based on the collection schedule listed in the protocol and summaries will be windowed to the closest scheduled visit for those data. Visit windows have been constructed so that every observation collected can be allocated to a particular visit. However, all data will be included in the listings. If multiple readings are recorded within a single analysis-defined visit window, the following rules will apply:

- If there are 2 or more valid, non-missing observations within the same visit window, and
  - if they are on different days, then the non-missing one which is closest to the scheduled visit day will be used in the analysis.
  - if they are on the same day which is closest to the scheduled visit day, then the non-missing one with the later collection time will be used in the analysis.

- If 2 or more valid observations are equidistant from the scheduled visit, and
  - if they are on different days, then the non-missing post-dose observation with the earlier collection date will be used in the analysis for the post-baseline observations, and the non-missing pre-dose observation with the later collection date will be used in the analysis for the screening observations.
  - if they are on the same day, then the non-missing observation with the later collection time will be used in the analysis.

- For LRTI visits or unscheduled visits, if 2 or more valid observations are collected on the same day, then the non-missing observation with the later collection time will be included in the analysis.

- If a visit window does not contain any observations, then the data will remain missing.

- For the visit-based summaries for ADA, if both ADA positive and negative samples are available within a subject's visit, ADA positive will be reported.

For assignment of data to adjusted analysis-defined visit windows, study day will be defined as:

- Screening period: Study day = Date of assessment – date of randomization
- After randomization: Study day = Date of assessment – date of randomization + 1

The adjusted analysis-defined windows for ADA, RSV neutralizing antibody, RSV serology are defined in Appendix 2, and for clinical laboratory data are defined in Appendix 3.

The partial dates imputation are described in Appendix 4.

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.

Data analyses will be conducted using the SAS® System Version 9.4 or higher (SAS Institute Inc., Cary, NC).

3.2 Study Cohorts, Analysis Populations, and Datasets

There are two study cohorts, primary cohort and safety cohort.

- Primary cohort includes all subjects enrolled in the NH2019, SH2020, and NH2020 enrollment seasons.
- Safety cohort includes subjects enrolled after the NH2020 enrollment season.

The primary cohort will serve the purpose of evaluating the efficacy of MEDI8897. Both the primary and the safety cohorts, individually and combined, will serve the purpose of evaluating the safety of MEDI8897.

The analysis populations are defined in Table 1.

Table 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.
Intent-to-treat population 1 (ITT1)	Subjects in the ITT population and from the primary cohort.
Intent-to-treat population 2 (ITT2)	Subjects in the ITT population and from the safety cohort.
As-treated population	Subjects who are randomized and receive any investigational product will be included in the as-treated population; in this population, data will be analyzed according to the treatment they actually receive.
As-treated population 1 (AT1)	Subjects in the as-treated population and from the primary cohort.
As-treated population 2 (AT2)	Subjects in the as-treated population and from the safety cohort.
Per-protocol population	The per-protocol population includes subjects in the ITT1 population who receive the correct dose of randomized treatment and who do not have a serious protocol deviation. Detailed criteria defining this population will be determined and documented prior to performing the Primary Analysis.

Analysis Datasets

- The Primary Dataset contains all efficacy, safety, ADA, and PK data from all randomized subjects from the primary cohort through Day 361, except for the one subject enrolled in the NH2020 enrollment season, for whom the data will be through at least Day 151. The Primary Analysis will be performed on the Primary Dataset.
- The Safety Dataset contains all data (efficacy, safety, ADA, PK, RSV serology and RSV neutralizing antibody) from all randomized subjects from the primary cohort, including data in the Primary Dataset and data from the subjects who were ongoing at the time when the Primary Dataset was locked. The Safety Dataset also contains subjects from the safety cohort that have been followed through Day 151, and all available data as of the data cutoff date. The Safety Analysis will be performed on the Safety Dataset.
- The Final Dataset contains all data collected in this study, including data in the Primary Dataset, Safety Dataset and data from the subjects who were ongoing at the time when the Primary Dataset and Safety Dataset were 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 ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months) 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

(Austria, Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Poland, Republic of Korea, Russia, Spain, Sweden, Turkey, Ukraine, United Kingdom, and United States of America [USA]) and Southern Hemisphere (Argentina, Australia, Brazil, Chile, Colombia, New Zealand, Panama, 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 for each cohort. In addition, disposition of subjects throughout the study and by milestone visit (ie, Day 151, Day 361) will be provided for all screened subjects, screened subjects from the primary cohort, and screened subjects from the safety cohort. These summaries will be presented by treatment group and for all subjects combined. The denominators for these summaries will include all subjects who were randomized into the study or in the corresponding cohorts unless specified otherwise.

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. These summaries will be provided overall and by cohort.

Demographic information related to gender, age at randomization stratum (months) calculated from the CRF, age at randomization stratum determined using the CRF age calculation (age $\leq$ 3.0 months, age > 3.0 to $\leq$ 6.0 months, age > 6.0 months), age at randomization category (age < 9.0 months, age $\geq$ 9.0 months), GA (weeks), ethnicity, race, weight (kg) on Day 1, weight on Day 1 category (weight < 5 kg, weight $\geq$ 5 kg), birth weight (kg), birth weight category (weight $\leq$ 2.5 kg, weight > 2.5 kg), multiple birth (yes/no), siblings enrolled in the study (yes/no), ever breastfed (yes/no), currently breastfed (yes/no), smoking in the household (yes/no), currently in daycare (yes/no), Down syndrome (yes/no), and cystic fibrosis (yes/no) will be summarized by treatment group and for all subjects combined using the overall ITT population, ITT1 and ITT2. 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 at randomization stratum, and by hemisphere.

In addition, family history of atopy (including asthma, hay fever, eczema, wheezing) will be summarized for each treatment group and for all subjects combined overall and by cohort.

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.

3.4.4 Violations and Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

The final list of important protocol deviations will be documented prior to unblinding the study data, and will include but may not be limited to:

- Subjects who did not meet inclusion criteria or met exclusion criteria according to protocol but were enrolled in the study, except for one violation of the exclusion criterion that children of employees of the sponsors, clinical study site, or any other individuals involved with the conduct of the study, or immediate family members of such individuals will not be considered as an important protocol deviation.
- Subjects who reported investigational product (IP) compliance-related deviations. This can be further categorized into IP administration, IP assignment-, and/or IP handling-related deviations.
    - IP administration-related deviations include but are not limited to:
        - Subjects receive incorrect dose, including subjects do not receive full planned dose or are not treated;
        - Subjects receive IP despite withdrawal of consent or not meeting eligibility prior to IP dosing;
        - Subject was administered IP but was not observed for at least 1 hour post dose
    - IP assignment-related deviations include but are not limited to:
        - Inappropriate use of study IP (e.g. giving IP to non-study subjects);
        - Kit dispensed without IWRS transaction
    - Subjects who reported the following IP handling-related deviations:
        - Dispensing of IP that has had an unapproved temperature excursion or is not suitable for use upon inspection for whatever reason to a subject;
        - IP was administered to the subject after 4 hours post preparation.
- Subjects who had no central RT-PCR nasal samples collected at any of the LRTI visits.
- Subjects who received approved or investigational product for RSV prophylaxis prior to Day 151.

- Subjects who reported safety-related deviations:
    - Severe violation in safety follow-up for subject;
    - Serious adverse event not reported in eCRF.

Only important protocol deviations will be tabulated in the clinical study report (CSR). The important protocol deviations will be reviewed and documented by the medical advisors and statisticians prior to the DBL.

Protocol deviations associated with the COVID-19 pandemic will also be summarized and listed separately (see Section 3.10).

In addition, the per-protocol population includes subjects in the ITT1 population who receive the correct dose of randomized treatment and who do not have a serious protocol deviation. The final list of serious protocol deviations will be documented in a separate file reviewed by medical monitor prior to unblinding the study data.

3.5 Efficacy Analyses

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

Efficacy analyses performed on the Primary Dataset will be refreshed in the primary cohort data in Safety Dataset and Final Dataset to make sure statistical inferences on MEDI8897 efficacy made from the Primary Analysis are consistent with those from the Safety and Final Analyses. Although efficacy data will also be collected for the safety cohort, only descriptive summaries will be provided and there is no intent to pool the efficacy data from safety cohort with that from the primary cohort.

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 DBL 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 -7 to 14 days relative to the initial date seen by the healthcare provider (eg, admission/deterioration date associated with the event, urgent care visit, outpatient emergency department [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 ITT1. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary efficacy analysis model to estimate the relative risk (RR) on the incidence of medically attended RSV LRTI between the MEDI8897 and the placebo groups. The full model contains the term of treatment group and age group at randomization based on the calculation detailed in Section 3.3. (ie, age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months) and dichotomous temperate (northern and southern) hemispheres as covariates. The RRR, defined as 1 - 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.

During blinded data review prior to the DBL for Primary Analysis, it was revealed that there was no incidence of medically attended RSV LRTI events through 150 days post dose for SH in primary cohort, which would cause known convergence or estimation issue. Therefore it was decided to drop the stratification factor hemisphere from the full model and a reduced model (including the term of treatment group and age at randomization stratum as covariate) will be used instead. Similar consideration also applies to other analyses for primary efficacy endpoint, where hemisphere will be dropped from the corresponding models.

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 RRR is given by $[(1 - \exp(\hat{\beta})) * 100\%]$. The CI for the percent of RRR 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 3.5.1.3) 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.

Handling of Dropouts and Missing Data

Medically attended 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 factor (age at randomization stratum) 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 drop out (eg, withdrawal by parent/legal representative, lost to follow-up, death not caused by RSV, etc) prior to reaching Day 150 post dose without a medically attended RSV LRTI event will be imputed per stratum determined by the stratification factor (age at randomization stratum) 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 factor [age at randomization stratum]).
- 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 RR on the incidence of medically attended RSV LRTI between MEDI8897 and placebo, with the term of treatment group and stratification factor (age at randomization stratum). 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 RR and the variance. The random seed is 12345.

3.5.1.3 Secondary Analyses of the Primary Efficacy Endpoint

The secondary efficacy analysis of the primary endpoint will be performed on ITT1. A CMH test stratified by age group at randomization (ie, age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 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 RR 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 RRR and the 95% CI will be reported following the relationship of RRR (%) = (1- RR) * 100%. This analysis will be performed without any imputation of event for subjects who dropped out the study prior to Day 150 post dose and did not have a medically attended RSV event. The Breslow-Day test and Zelen's exact test will be used to test the homogeneity of the odds ratios across strata and the corresponding p-values will be judged at the significance level of 0.05.

3.5.1.4 Supplementary Analyses of the Primary Efficacy Endpoint

The following analyses will be conducted on ITT1 as supplementary analyses.

Poisson Regression with Robust Variance Adjusting for Follow-up Time

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. Date of Onset of RSV LRTI is defined as the initial date seen by the healthcare provider for the corresponding AE.
- 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).

For subjects who are ongoing at the time of Primary Analysis, the data cut-off date will be used as their last assessment date.

Kaplan-Meier 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 that for follow-up time (see the section right above). Treatment group differences in time-to-first medically attended RSV LRTI will be compared using the stratified log-rank test with the stratification factor (age at randomization) as the strata. In addition, hazard ratio and the corresponding 95% confidence interval will be obtained from the stratified proportional hazard model with the stratification factor (age at randomization stratum) as the strata.

Primary Endpoint by Visit Setting

In addition, all observed medically attended RSV LRTI events through 150 days post dose 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 ED visits for subjects who did not have a hospitalization due to RSV.

Missing Data Imputation

Five supplementary 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. Count these subjects as having not met the RSV LRTI endpoint within each treatment group
2. Perform multiple imputation using the observed event rate per treatment group for their event status
3. Perform single imputation using observed placebo rate for both groups
4. Impute missing data in MEDI8897 group as an event and missing data in the placebo group as no event
5. Impute missing data in MEDI8897 group as no event and missing data in the placebo group as an event

For supplementary analysis 1, all subjects who do not have an RSV LRTI event and are not followed through 150 days post dose will be assumed having no event. 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 supplementary analysis 2, 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 supplementary analysis 3, the number of medically attended RSV LRTI events for subjects who dropped out prior to Day 150 post dose without the event will be generated using the observed placebo event rates for both treatment groups. With the imputed number of events, the RRR and the 95% CI will be constructed using an exact conditional method without stratum based on the number of RSV LRTIs (Breslow and Day, 1987). The number of events for each treatment group will be used as the response variable and the logarithm of total number of participants for treatment group will be used as an offset variable in the model. This analysis will be implemented using PROC GENMOD with the EXACT statement.

For supplementary analysis 4, for subjects who do not have an RSV LRTI event and are not followed through 150 days post dose, if they are in the placebo group, they will be assumed having no events; if they are in the MEDI8897 group, they will be assumed having events. The remaining part will be the same as that described in supplementary analysis 1.

For supplementary analysis 5, for subjects who do not have an RSV LRTI event and are not followed through 150 days post dose, if they are in the MEDI8897 group, they will be assumed having no events; if they are in the placebo group, they will be assumed having events. The remaining part will be the same as that described in supplementary analysis 1.

In addition, a tipping point analysis will be conducted to assess the robustness of efficacy under a series of assumed event rates for the missing data in both treatment groups, ranging from 10% to 100%, increment by 10%. For the assumed event rates of 10%-90%, the tipping point analysis will be conducted following the steps below:

- Step 1: 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 using the Bernoulli distribution with assumed event rate without involvement of stratification factors.

- Step 2: 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 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, and the stratification factor (age at randomization stratum) as covariates. The point estimate of log-transformed RR and its variance will be produced from the model.
- The steps 1-3 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. The random seed is 12345.

For the assumed event rate of 100%, all subjects who do not have an RSV LRTI and are not followed through 150 days post dose will be imputed as having an event. 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.

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 with the terms of treatment, age group, 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 RRR 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 RRR 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 RRR 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 ITT1:

- Hemisphere

- Age at randomization stratum (age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on Day 1 (weight < 5 kg, weight ≥ 5 kg)
- GA (≥ 35 weeks to < 37 weeks, ≥ 37 weeks)
- Sibling also participating in the study (yes/no)

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

3.5.1.5 Analyses for Medically Attended RSV LRTI Beyond the Primary Endpoint

The following analyses will be conducted on ITT1 and based on observed events, unless stated otherwise.

The incidence of medically attended RSV LRTI that occurred through 360 days post dose and > 360 days post dose will be summarized by treatment group. ITT1 will be used for the summary of the incidence through 360 days post dose, and ITT1 subjects who remained in the study after the Day 361 visit will be used as the denominator to calculate the incidence rate for the summary of the incidence > 360 days post dose.

Age at onset of the first medically attended RSV LRTI through 150 days post dose 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, through 360 days post dose, and > 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 through 150 days post dose, 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 2 for details). A listing will be generated to provide the following information: age at randomization stratum, 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 post dose, through 360 days post dose, and after 360 days post dose.

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 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

Providing information to physicians and parents/legal representatives on the effect of MEDI8897 in reducing the risk of RSV hospitalization is considered important and was the primary endpoint for the approval of palivizumab. Due to its importance, RSV hospitalization was pre-specified as a key secondary endpoint in the Phase 2b Study D5290C00003 and will be again pre-specified as a key secondary endpoint in this Phase 3 study. However, as the management of more serious RSV disease has been shifting to the outpatient setting, there is a risk that the incidence of RSV hospitalization in this Phase 3 study population of healthy late preterm and term infants may be too low (expected to be approximately 1% in the placebo group) for this secondary efficacy analysis to reach statistical significance ($p \leq 0.05$) within this Phase 3 study alone.

The rationale of a pooled analysis, which consists of all ITT subjects from the Phase 2b Study D5290C00003 and ITT1 subjects from the Phase 3 study, is to assess the overall efficacy of

RSV hospitalization in the target population (pre-term and term infants). The pooled analysis consisting of the 860 ITT subjects weighing < 5 kg in the Phase 2b Study D5290C00003 and ITT1 subjects in this Phase 3 study, will be conducted to assess the efficacy in all subjects under the clinically efficacious exposure suggested by PK analysis. Combining these subjects for analysis is justified based on the similar study designs and disease similarity between the infant pediatric study populations.

Given the importance of controlling for multiplicity, a hierarchical testing strategy is proposed as follows. 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. More specifically, after the significance of the primary efficacy endpoint is demonstrated, the secondary efficacy endpoint will first be tested from pooling all ITT subjects from the Phase 2b Study D5290C00003 and ITT1 subjects from the Phase 3 study. If the significance of the pooled efficacy based on pooling all subjects from Phase 2b and ITT1 subjects from Phase 3 is demonstrated (at 2-sided 0.05), the secondary efficacy endpoint will be further tested from pooling the 860 subjects weighing < 5 kg on Day 1 (ie, 290 subjects randomized to placebo and 570 subjects randomized to MEDI8897) in the Phase 2b Study D5290C00003 and ITT1 subjects in this Phase 3 study. If the significance of the pooled efficacy based on pooling the subjects weighing < 5 kg from Phase 2b and Phase 3 ITT1 subjects is again demonstrated (at 2-sided 0.05), the secondary efficacy endpoint will be tested using ITT1 subjects from this Phase 3 study alone. We would test the secondary endpoint in the pooled population before that in this Phase 3 study alone for the reason that the pooling strategy will mimic the efficacy we can expect to see with the dosing scheme we plan to ultimately register and deploy for use in the target population and therefore has a higher importance.

For the pooled analyses, a Poisson regression model with robust variance (Zou, 2004) will be used to assess the treatment effect on the incidence of RSV LRTI hospitalization between MEDI8897 and placebo groups in the pooled ITT population. In addition to the treatment arm, the variable “Study” (which identifies the enrolled study for each subject) will be used as a covariate to adjust for potential differences between the 2 studies. RRR and its corresponding 95% CI will be estimated from the model implemented by PROC GENMOD as detailed in Section 3.5.1.2.

For the analysis using Phase 3 data alone, 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 ITT1 population. RRR and its corresponding 95% CI will be estimated from the model.

Above stated analyses on RSV LRTI hospitalization will also be conducted on the Per-protocol population.

Handling of Dropouts and Missing Data

RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. Subjects who only have outpatient RSV LRTI through 150 days post dose will be regarded as not meeting the RSV LRTI hospitalization endpoint. For subjects who do not have an RSV LRTI and were not followed through 150 days post dose, their event status will be imputed. Due to the expected low event rate, and correspondingly high likelihood of empty cells by strata, the stratification factors will not be used during the repeated imputation step to avoid potential convergence issue.

For the pooled analyses, the event status for subjects requiring imputation will be imputed using the observed placebo RSV LRTI hospitalization rate following the repeated imputation procedure conditional on study, similar to what has been described for imputing missing data for primary endpoint (Section 3.5.1.2) with the exception of using the variable "Study" instead of the stratification factors in SAS PROC MI and the Poisson regression model with robust variance.

For the analysis using Phase 3 data alone, the event status for subjects requiring imputation will be imputed using the observed placebo RSV LRTI hospitalization rate following the repeated imputation procedure without involvement of stratification factors. The computation steps will be conducted following the steps below:

- Step 1: Determine the observed placebo RSV LRTI hospitalization rate through 150 days post dose, which is calculated as the proportion of all randomized placebo subjects with observed RSV LRTI hospitalization.
- 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 group using the Bernoulli distribution with the observed placebo RSV LRTI hospitalization rate.
- Step 3: The subjects with imputed values of RSV LRTI hospitalization status (yes/no) will be combined with the remaining subjects to form a complete dataset.
- Step 4: Analyze the complete dataset using a Poisson regression model with robust variance to compare the incidence of RSV LRTI hospitalization between MEDI8897 and placebo, including the treatment group only. 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. The random seed is 12345.

3.5.2.3 Supplementary Analyses of the Secondary Efficacy Endpoint

The supplementary analyses will be conducted on ITT1.

These analyses including the CMH test stratified by study (for the pooled population) or the CMH test with the only term of treatment (for ITT1 subjects from Phase 3) for the incidence of RSV LRTI hospitalization, and the Kaplan-Meier for time-to-first RSV LRTI hospitalization will be conducted. Treatment group differences in time-to-first RSV LRTI hospitalization will be compared using log-rank test. In addition, hazard ratio and the corresponding 95% confidence interval will be obtained from the proportional hazard model.

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 LRTI hospitalization will also be summarized by RSV subtype (A or B).

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

- Hemisphere
- Age at randomization stratum (age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on Day 1 (weight < 5 kg, weight ≥ 5 kg)
- GA (≥ 35 weeks to < 37 weeks, ≥ 37 weeks)
- Sibling also participating in the study (yes/no)

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

3.5.3 Other Efficacy Analyses

The following analyses will be conducted on ITT1.

An overall summary of subjects with any medically attended LRTI (protocol-defined or not) or hospitalization due to any respiratory illness will be presented by treatment group. In this summary, a subject is reported only once even though he or she might have multiple 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. The rules to define severity among multiple hospitalizations due to any respiratory illness are as follows: LRTI > non-LRTI, RSV > non-RSV. Incidence of all medically attended LRTI will be summarized 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. For subjects who were hospitalized due to any respiratory illness, LRTI and non-LRTI cases will be further reported and broken down by RSV status. In addition, a summary for subjects with at least one medically attended LRTI event (categorized by RSV, non-RSV, hospitalization, outpatient only), regardless of severity, will be presented. In this summary, a subject can be reported in multiple event categories as long as the subject has at least one corresponding event. Correspondingly, a side-by-side bar plot for incidence of all medically attended LRTIs regardless of severity through 150 days post dose will be presented by RSV status (RSV, non-RSV) per treatment group, with the visit setting category (hospitalization, outpatient only) stacked.

Summaries for subjects who met primary efficacy endpoint (ie, protocol-defined medically attended RSV LRTI) will be presented by treatment group for each of the elements used to evaluate for the case definition of medically attended RSV LRTI (Appendix 1). These elements include the following: rhonchi, rales, crackles, wheeze, increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnea, retractions, grunting, dehydration due to respiratory distress requiring IV hydration. In this summary, a subject is reported once even though he or she might have the element multiple times during the reporting period.

For all medically attended LRTI events, RSV status (positive, negative or not done) will be summarized by central 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 LRTI categories (protocol-defined, non-protocol defined) and 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, if a subject has multiple LRTI events, the one with the highest severity will be reported (in the order of protocol-defined > non-protocol defined) 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 medically attended 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 ED 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 through Day 150 post dose (on ITT1), after 150 days post dose (on ITT1 with Day 151 visit), through 360 days post dose (on ITT1), and after 360 days post dose (on ITT1 with Day 361 visit).

For various LRTI events, including the primary endpoint, detailed definitions of new onset of events are defined in the following table, Table 2. For all medically attended LRTI (RSV, non-RSV, protocol-defined, non-protocol defined), the total number of events for each subject and the percentage of each outcome will be summarized by treatment group on 4 time-intervals: Day 150 post dose (on the ITT1), after 150 days post dose (on ITT1 with Day 151 visit), through 360 days post dose (on ITT1), after 360 days post dose (on ITT1 with Day 361 visit). 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 stratum, 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). A similar listing for subjects with more than one medically attended RSV LRTI event (regardless protocol-defined or not) will also be presented.

Table 2 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, through 360 days, and after 360 days post dose on the following populations: ITT1, ITT1 with Day 151 visit, ITT1, and ITT1 with Day 361 visit, respectively.

3.5.4 Additional Efficacy Analyses for the Safety Cohort

The following descriptive analyses will be conducted on ITT2 and based on observed events, unless stated otherwise.

3.5.4.1 Analyses of Incidence of Medically Attended RSV LRTI

The incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose will also be summarized by treatment group using ITT2. For subjects with multiple medically attended RSV LRTI events, only the first occurrence will be used in the summary.

In addition, the same analyses of all observed medically attended RSV LRTI events through 150 days post dose by visit setting as described in Section 3.5.1.4 will be repeated for ITT2.

The incidence of medically attended RSV LRTI will also be summarized by the subgroups and countries as defined in Section 3.5.1.4 for ITT2.

In addition, the incidence of medically attended RSV LRTI that occurred through 360 days post dose and after 360 days post dose will be summarized as described in Section 3.5.1.5 for ITT2.

Age at onset of the first medically attended RSV LRTI through 150 days post dose will be summarized as described in Section 3.5.1.5 for ITT2. 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) will be summarized as described in Section 3.5.1.5 for ITT2.

For multiple medically attended RSV LRTIs, the total number of new onset medically attended RSV LRTIs will be summarized as described in Section 3.5.1.5 for ITT2. A listing will be generated similarly.

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 as described in Section 3.5.1.5 for ITT2.

3.5.4.2 Analyses of Incidence of RSV LRTI Hospitalization

The incidence of RSV hospitalization through 150 post dose days will be summarized by treatment group for each cohort as well as for the ITT2. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis.

For each treatment group, age at onset of the first medically attended RSV LRTI hospitalization will be summarized as described in Section 3.5.2.3 for ITT2. 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 LRTI hospitalization will also be summarized by RSV subtype (A or B).

The incidence of RSV LRTI hospitalization will also be summarized by subgroups and country as described in Section 3.5.2.3 for the ITT2.

3.5.4.3 Other Efficacy Analyses

An overall summary of subjects with any medically attended LRTI (protocol-defined or not) or hospitalization due to any respiratory illness will be presented by treatment group as described in Section 3.5.3 for ITT2.

Summaries will be presented by treatment group for each of the elements used to evaluate for the case definition of medically attended RSV LRTI (Appendix 1) as described in Section 3.5.3 for ITT2.

For all medically attended LRTI events, RSV status (positive, negative or not done) will be summarized by central RT-PCR or local testing results by treatment group as described in Section 3.5.3. In addition, incidence of positive RSV LRTI either by RT-PCR or by local testing results will also be summarized by LRTI categories (protocol-defined, non-protocol defined) and treatment group as described in Section 3.5.3 for ITT2.

In addition, for each treatment group, all medically attended LRTI events will be tabulated by Inpatient (primary hospitalization, nosocomial hospitalization) and Outpatient as described in Section 3.5.3for ITT2.

All above stated summaries will be presented by through Day 150 post dose (on ITT2), after 150 days post dose (on ITT2 with Day 151 visit), through 360 days post dose (on the ITT2), and after 360 days post dose (on ITT2 with Day 361 visit).

For all medically attended LRTI (RSV, non-RSV, protocol-defined, non-protocol defined), the total number of events for each subject and the percentage of each outcome will be summarized by treatment group on 4 time-intervals: Day 150 post dose (on ITT2), after 150 days post dose (on ITT2 with Day 151 visit), through 360 days post dose (on ITT2), and after 360 days post dose (on ITT2 with Day 361 visit). 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 information as described in Section 3.5.3.

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 post dose and after 360 days post dose on the following populations: ITT2, ITT2 with Day 151 visit, ITT2, ITT2 with Day 361 visit, 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 ED, urgent care, outpatient clinic]; will be summarized by treatment group and reported in 3 time periods: through 150 days post dose (on ITT1), after 150 days post dose (on ITT1 with Day 151 visit), and through 360 days post dose (on ITT1).

Specifically, the following summary tables by treatment group will be used to report the magnitudes of overall HRU for all medically-attended LRTI (protocol defined, non-protocol defined, RSV, non-RSV).

- 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 ITT1 for time interval through 150 days post dose, on ITT1 with Day 151 visit for time interval after 150 days post dose, and on ITT1 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 activities.

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, Data Cutoff Date at the time of Analysis}.

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 medically attended RSV LRTI (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 be applied for the respective events and the HRU must occur during the event being summarized. Only the subjects with protocol-defined medically attended RSV LRTI will be included in the summary.

In addition, the number of pre-specified OTC medication (analgesics/antipyretics) use; the number of pre-specified prescription medication (systemic antibacterial agents) use; and the number of anti-wheezing medication use will be summarized by treatment group and reported through 150 days post dose, except for the analgesics/antipyretics use, which will be summarized through one week after dosing. The ATC codes for these medications will be provided in a separate file by the medical monitor prior to the DBL for the Primary Analysis.

The number and percentage of subjects with pre-specified prescription medications (systemic antibacterial agents) use through 150 days post dose will be provided. The number of use per subject (for those with the medication use) will be summarized through 150 days post dose using descriptive statistics (mean, median, SD, minimum, and maximum) by treatment group and for all subjects combined.

The number and percentage of subjects with pre-specified OTC medications (analgesics/antipyretics) use within one week after dosing will be provided. The number of use per subject (for those with the medication use) will be summarized using descriptive statistics (mean, median, SD, minimum, and maximum) by treatment group and for all subjects combined. The same summaries will be repeated for subjects with any co-administered routine childhood vaccination (J07) within one week of dosing.

The number and percentage of subjects with anti-wheezing medications use through 150 days post dose will be provided. The number of use per subject (for those with the medication use) will be summarized through 150 days post dose using descriptive statistics (mean, median, SD, minimum, and maximum) by treatment group and for all subjects combined.

Above summaries will be repeated for ITT2, if data permit.

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 one event in the time-period of reporting. 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 (ie, 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. The summaries for the caregiver burden will be based on ITT1 and ITT2.

3.6.3 Anti-RSV Neutralizing Antibody

RSV neutralizing antibody levels afforded by MEDI8897 will be compared to maternal RSV neutralizing antibody levels and those elicited following infection in the placebo group. RSV exposure as measured by increasing concentrations of serum RSV neutralizing antibody, is defined as ≥ 4-fold rise in concentration of serum RSV neutralizing antibody from the previous timepoint. A subject shows "evidence of exposure" if this criterion is met for any set of consecutive timepoints. The summary will be provided for Placebo at scheduled visits when the serum samples were collected. The summary will be cumulative; that is, if subjects show exposure in a previous timepoint, they should be included in later timepoints as well. At each scheduled timepoint, the denominator will be the number of subjects with a result. The exposure will be examined by results based on serum RSV neutralizing antibodies. These analyses will be conducted for all subjects, as well as subjects with and without RT-PCR confirmed RSV through 360 days post dose.

Individual MEDI8897 and placebo serum RSV neutralizing antibody levels will be tabulated by treatment group along with descriptive statistics. RSV neutralizing antibody levels in serum will be summarized by geometric mean concentration and geometric mean-fold rise from baseline and corresponding 95% Clopper-Pearson exact CIs of the proportion for each treatment group at each visit for all subjects, as well as for subjects with and without RT-PCR confirmed RSV through 360 days post dose. In addition, summaries of geometric mean

concentration will also be provided for all subjects combined at baseline. Box plots of RSV neutralizing antibody levels in logarithm scale with base 10 will be provided by treatment group and by visit.

Anti-RSV neutralizing antibody level $t_{1/2}$ will be estimated using non-compartmental analysis (if data permit), and will be reported outside the CSR. The analysis for the RSV neutralizing antibody will be based on the overall as-treated population, AT1, and AT2. The analysis based on the overall as-treated population will only be conducted at the Final analysis.

3.6.4 RSV serology

RSV seroresponses will be evaluated as a measure of "RSV exposure" in the placebo and MEDI8897 groups. RSV exposure (defined as ≥ 4-fold rise in serum antibody levels to RSV antigens from the previous timepoint) will be examined by results based on anti-RSV pre-F, post-F, Ga, Gb, N, or any of these antigens except Pre-F. Similar summary (as described for anti-RSV neutralizing antibodies in Section 3.6.3) will be provided by treatment group at scheduled visits when the serum samples were collected. As MEDI8897 will interfere with the pre-F result, the exposure based on pre-F will not be examined for the MEDI8897 group. These analyses will be conducted for all subjects, as well as subjects with and without RT-PCR confirmed RSV through 360 days post dose.

Analysis of serum antibody levels to RSV antigens in MEDI8897 and placebo subjects will be summarized by geometric mean concentration and geometric mean-fold rise from baseline for each of the anti-RSV antigens (RSV pre-F, post-F, Ga, Gb and N antigens) and corresponding 95% Clopper-Pearson exact CIs for each treatment group at each visit for all subjects, as well as subjects with and without RT-PCR confirmed RSV through 360 days post dose. In addition, summaries of geometric mean concentration will also be provided for all subjects combined at baseline. Seroresponses in MEDI8897 and placebo subjects will be determined by examining the fold-rise in antibodies to pre-F, post-F, Ga, Gb, and N antigens. By measuring antibodies to pre-F, post-F, Ga, Gb, and N: 1) baseline maternal antibodies and their decay can be measured over time; 2) the exposure to RSV (infection) that results in an increase in RSV-specific antibodies for the infants own immune system can be determined. Box plots of serum antibody levels to RSV antigens in logarithm scale with base 10 will be provided by treatment group and by visit.

The analysis for RSV serology will be based on the overall as-treated population, AT1, and AT2. The analysis based on the overall as-treated population will only be conducted at the Final analysis.

3.6.5 RSV resistance monitoring

Nasal samples collected from study subjects with RT-PCR confirmed RSV will be subtyped, genotyped, and evaluated by genotypic and phenotypic resistance analyses. Genotypic

analyses will report amino acid changes in the mature RSV F protein sequence compared to contemporary reference strains. Phenotypic analyses will report changes in susceptibility of engineered recombinant RSV variants to MEDI8897 and palivizumab neutralization compared to laboratory-derived reference viruses. A detailed description of subjects/samples analyzed, sample collection and testing workflow, performance characteristics of assays and methodologies, analysis plans, and reporting plans have been included in a separate clinical virology analysis plan. The details of genotypic and phenotypic analyses and presentation of these data will be included in a separate virology study report.

3.6.6 Incidence of Medically Attended LRTI Due to RT-PCR-confirmed RSV After Day 151 (Between Day 152 and Day 361)

For summary of this exploratory endpoint, the analysis population will be ITT1 and ITT2, for subjects, who remained in the study at the Day 151 visit. For subjects with multiple medically attended RSV LRTI events after Day 151, only the first occurrence will be used in the summary.

The incidence of medically attended RSV LRTI that occurred > 150 days (from Day 152 to Day 361) post dose will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and will be summarized by treatment group. This endpoint will be further summarized by RSV subtype (RSV A, RSV B) and by treatment group. In addition, AEs associated with this endpoint will be summarized overall, as well as categorized by MedDRA SOC and PT.

3.7 Safety Analyses

All safety analyses will be conducted on overall as-treated population, AT1, and AT2.

3.7.1 Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be coded by MedDRA version 22 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, the total number of AEs will also be provided. 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) and treatment-emergent SAEs (TESAEs) occurring through Day 361 will be summarized overall, as well as categorized by MedDRA SOC and PT. In addition, the TEAEs occurring at 1% or higher in either treatment group will be reported by PT.

Nontreatment-emergent AEs/serious adverse events (SAEs), defined as AEs/SAEs that occur prior to the administration of investigational product or after Day 361, 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 anaphylaxis and other serious hypersensitivity reactions including immune complex disease and AEs of thrombocytopenia. The number and percentage of subjects with AESIs will be summarized by treatment group and by SOC and PT.

Of note, investigators have been requested to identify the AESI in reporting. The primary interpretation of data will be made upon those events with investigator assessment. In addition, a supplementary analysis is conducted which runs the narrow Standardised MedDRA Queries (SMQs) for hypersensitivity, the narrow and broad SMQS for anaphylactic reactions, and a study specific query based on compatible PTs for thrombocytopenia and immune complex disease occurring in the database. Narrow hypersensitivity SMQs include some PTs of immune complex disease. These SMQs and PTs will be provided by the medical monitor in a separate document before DBL for Primary Analysis.

3.7.3 Skin and Hypersensitivity Reactions

The number and percentage of subjects with any skin reactions (including skin hypersensitivity reactions) which are reported on the dedicated eCRF page and judged to be related to IP by the investigator will be summarized by treatment group and by SOC and PT.

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 (including TEAEs, TESAEs, AESIs, IP-related skin reactions [including skin hypersensitivity reactions], NOCDs) will be summarized by age group used as randomization stratum (age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months), and weight on Day 1 (weight < 2.5kg, weight ≥ 2.5 kg and < 5 kg, weight ≥ 5 kg). TEAEs, AESIs, IP-related skin reactions (including skin hypersensitivity reactions), and NOCDs will also be summarized by timing relative to dosing (‘within 1 day,’ ‘within 3 days’, ‘within 7 days’, ‘within 14 days’). In addition, TEAEs occurring within 1 day, 3 days, 7 days, and 14 days post dose by age group at randomization stratum (≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months), weight on Day 1 (weight < 2.5kg, weight ≥ 2.5 kg and < 5 kg, weight ≥ 5 kg) will also be summarized.

3.7.6 Clinical Laboratory Parameters

Laboratory parameters (collected for Japanese subjects only) will be summarized at each visit by treatment group. Frequencies of worst observed Grade 3-4 toxicity, as defined by the

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (available at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables), will be presented for each laboratory parameter below by treatment group:

- CBC: hemoglobin, platelets
- WBC with differential: white blood cell count
- Liver function: bilirubin, AST/ALT
- Chemistry – general: creatinine.

Also, laboratory parameters will be assessed by presenting tables containing information associated with 2-grade (or greater) laboratory shifts from baseline. All other serum chemistry and hematology parameters not listed above will be presented in the data listings.

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

3.7.7 Other Safety Evaluations

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.

Medical history findings and those that are ongoing at the time of signed informed consent will be summarized by treatment group and for all subjects combined using the overall ITT population, ITT1 and ITT2. Data listings will be provided for these data.

In addition, vaccines exposure, including the number of subjects receiving vaccine dose of the six pre-specified vaccine groups (Tuberculosis vaccine; Influenza vaccine; Measles/Mumps/Rubella/Varicella; Rotavirus vaccine; Polyvalent diphtheria-poliomyelitis-tetanus containing vaccine, Pneumococcal vaccine) and the total number of vaccine doses received within ±7 days of IP dosing, will be summarized for each vaccine group. The summaries will be conducted by treatment group and for all subjects combined using the overall as-treated population, AT1 and AT2. The same summary will be repeated within ±14 days of IP dosing for the overall as-treated population, AT1 and AT2, and on the same day of IP dosing for AT2 only.

For subjects with co-administered vaccines doses (on the same day, within ±7 days or ±14 days of IP dosing), TEAEs that occur within 7 or 28 days following vaccine administration will be summarized by SOC and PT and by treatment group. The percentage will be

calculated using subjects who received co-administered vaccine doses (on the same day, within ±7 days or ±14 days of IP dosing) as the denominator. These summaries will be provided for each of the six pre-specified vaccine groups individually. These summaries will only be conducted on AT2. The ATC codes for these vaccines will be provided in a separate file by the medical monitor prior to the DBL for the Primary Analysis.

Subjects flagged as having wheeze during their respiratory illness assessment after Day 361 will be listed.

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 on the overall as-treated population, AT1 and AT2. 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 RSV-neutralizing regions of MEDI8897 will also be summarized.

An additional table will summarize the number and percentage of subjects positive for ADA at baseline and positive at any post-baseline time point. The percentage who were persistent positive and transient positive will also be presented.

1 Persistent positive is defined as negative at baseline and 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 baseline and at the last one post-baseline assessment, and positive at only ≥ 1 post-baseline assessment and not fulfilling the conditions for persistent 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 post-baseline status (ie, at least one post-baseline ADA positive or not through 360 days post dose). The primary and secondary efficacy endpoints will also be summarized by ADA post-baseline status through 150 days post dose. The safety summaries will be based on overall as-treated population, AT1, and AT2. The efficacy summaries will be based on ITT1 and ITT2.

The impact of ADA on PK will be evaluated as described in Section 3.9.

3.9 Pharmacokinetics

Individual MEDI8897 serum concentrations for each nominal sampling time will be listed and summary descriptive statistics will be presented and plotted versus time. Individual MEDI8897 serum concentrations will be graphically illustrated, and summarized, by ADA status. The PK summaries will be based on the as-treated population.

Further, model-based evaluation of PK will be detailed in a separate PK analysis plan and reported outside the CSR.

3.10 Impact on Analyses due to COVID-19 Pandemic

The COVID-19 pandemic has posed challenges in study conduction (including performing scheduled visits, and sample collections etc.).

Efforts are ongoing to collect outstanding data via alternative means where possible, when on-site visits cannot be performed. The following analyses have been added to assess the impact of the pandemic:

- Three sensitivity analyses of primary endpoint will be conducted for ITT1. Details are described in Section 3.10.1.

- Protocol deviations, including sample collections or visits missed due to COVID-19 related protocol deviations will be described separately in the CSR. These deviations will be identifiable in the database with a 'COVID' prefix. This summary will be repeated for ITT1 and ITT2.

- Confirmed or suspected cases of COVID-19 will be summarized and included as AEs as appropriate. This summary will be repeated for the overall as-treated population, AT1, and AT2.

3.10.1 Sensitivity Analyses

Sensitivity analyses 1 and 2 are to assess the robustness of the primary efficacy by exploring different estimands in handling the intercurrent events, defined as COVID-19 related protocol deviations or disruptions which occurs prior to having met the primary efficacy endpoint (and prior to Day 151).

- For sensitivity analysis 1, intercurrent events will be handled using principal stratum strategy. That is, subjects with intercurrent events will be excluded from the analysis. The remaining subjects will be analyzed using the same primary analysis model as described in Section 3.5.1.2.

- For sensitivity analysis 2, intercurrent events will be handled using hypothetical strategy. That is, for subjects with intercurrent events, their event status will be imputed using the standard multiple imputation approach (based on the observed event rate per treatment group). Other than that, the analysis will be conducted using the same primary analysis model as described in Section 3.5.1.2.

Sensitivity analysis 3 is to employ all available positive RT-PCR results (regardless from local or central lab) considering the challenge of obtaining nasal sample for central lab RT-PCR during the pandemic. More specifically, for subjects with intercurrent events, central lab RT-PCR results or local lab results (only if central lab results are not available) obtained after intercurrent events will be evaluated to determine RSV status (subjects will be considered RSV positive with either local or central lab positive RT-PCR result using the same analysis window as described in Section 3.5.1.1). Other than that, the analysis will be conducted using the same analysis model as described in Section 3.5.1.2.

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5 VERSION HISTORY

Version	Date	Description of Change
1.0	22JUL2019	Initial version
2.0	29Jan2021	• Editorial changes for clarification. • Section 2.2 Study Design: added description of the primary and safety cohorts. • Section 2.4 Sample Size: updated study power based on the sample size of the primary cohort, on which the primary efficacy analysis will be based. • Section 3.1 Generation Considerations: updated planned analyses to Primary Analysis, Safety Analysis and Final Analysis; added description of the planned analyses; added general description of unblinding strategy; added visit window definitions. • Section 3.2 Study Cohorts, Analysis Populations and Datasets: added "Study Cohorts" in the section name; added definitions of study cohorts; added the definitions ITT1, ITT2, AT1 and AT2 in Table 1 Analysis Populations; modified the definition of the primary dataset and final dataset, and added the definition of the safety dataset. • Added section 3.4.4 Violations and Deviations • Section 3.5.1.2 Primary Efficacy Analysis: provided the rational of using a reduced model when evaluating the primary endpoint. Dropped hemisphere from the analysis model. • Section 3.5.1.2 Secondary Analyse of the Primary Efficacy Endpoint: dropped hemisphere from the analysis model. • Section 3.5.1.4 Supplementary Analyses of the Primary Efficacy Endpoint: added stratified proportional hazard model to generate hazard ratio and the corresponding 95%

		confidence interval in Kaplan-Meier Analysis. Dropped hemisphere from the analysis model. Used the standard SAS procedure PROC GENMOD with the EXACT statement (rather than StatXact PROC Poisson procedure) in implementing the exact conditional method. Updated subgroup "weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg to < 5 kg, weight ≥ 5 kg)" to "weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)" • Section 3.5.3 Other Efficacy Analyses: in the first paragraph, the summary for subjects who were hospitalized due to any respiratory illness, non-LRTI cases, with at least one medically attended LRTI event will only be categorized by RSV, non-RSV, hospitalization, outpatient only. Categorization by protocol-defined and non-protocol defined were removed. • Added section 3.5.4 Additional Efficacy Analyses for the Safety Cohort. Added descriptive summaries for the safety cohort. • Section 3.6.5 RSV resistance monitoring: revised the RSV resistance monitoring language to improve clarify and to align with clinical virology analysis plan • Section 3.7 Safety Analyses: updated safety summaries by as-treated subjects from the primary and safety cohorts, and the overall as-treated subjects. • Added age at randomization category by ≤ 8 months or > 8 months as a subgroup in Section 3.4.2 Demographics and Baseline Characteristics, and for all AEs summaries in section 3.7.5 Subgroup Analyses • Section 3.7.6 Clinical Laboratory Parameters: removed summary for BUN. • Added section 3.10 Impacted on Analyses due to COVID-19 Pandemic

		• Appendix 2: added analysis window for ADA/RSV Neutralizing Antibody/RSV Serology. • Appendix 3: added analysis window for clinical lab data.
3.0	11Apr2021	• Editorial change for clarity, including updating “3 months”, “6 months” to “3.0 months” , “6.0 months”, respectively. • Section 3.1 General Considerations: clarified that all efficacy, PK, ADA and safety data collected for the primary cohort will be analyzed through Day 361, and data collected after Day 361 will only be listed at Primary Analysis; similarly, data collected after Day 361 for safety cohort will only be listed at the time of the Safety Analysis. • Section 3.4.2 Demographics and Baseline Characteristics: updated age at randomization category from ≤ 8.0 months or > 8.0 months, to < 9.0 months or ≥9.0 months. • Section 3.4.4 Violations and Deviations: updated criteria for IPDs and added criteria for serious PDs. • Section 3.5.1.1 Primary Efficacy Endpoint: defined a RSV sample analysis window [-7, 14] days for medically attended RSV LRTI based on blinded data review. • Section 3.5.2.3 Supplementary Analyses of the Secondary Efficacy Endpoint Point: added hazard ratio and the corresponding 95% CI for time-to-first RSV LRTI hospitalization analysis. • Section 3.5.3 Other Efficacy Analyses: clarified rules to define severity among multiple LRTI events, and among multiple hospitalizations due to any respiratory illness, separately; added a bar plot for incidence of all medically attended LRTI regardless of severity through 150 days post dose; updated summaries for case definition elements to subjects who have at least one medically attended RSV LRIT (protocol-defined).

		• Section 3.6.1 Healthcare Resource Utilization (HRU): updated summaries for pre-specified prescription (systemic antibacterial agents) and over the counter medications (analgesics/antipyretics); added summaries for anti-wheezing medication use; removed medically attended non-RSV LRTI (protocol-defined), medically attended RSV LRTI (non-protocol defined), and medically attended non-RSV LRTI (non-protocol defined) from the HRU summaries. • Section 3.6.2 Caregiver Burden: removed medically attended non-RSV LRTI (protocol-defined), medically attended RSV LRTI (non-protocol defined), and medically attended non-RSV LRTI (non-protocol defined) from the caregiver burden summaries. • Section 3.6.3 Anti-RSV Neutralizing Antibody and Section 3.6.4 RSV Serology: added definition for RSV exposure and summaries for RSV exposure; added summaries of RSV exposure, geometric mean concentration, and geometric mean fold-rise for subjects with and without central RT-PCR positive results through 360 days post dose; added box plot for serum antibody levels for all subjects by treatment group and by visit. Clarified that the analysis based on overall as-treated population will only be conducted during Final Analysis. • Section 3.7.2 Adverse Events of Special Interest: modified wording in summarizing AESIs; added summaries of AESIs based on SMQs and selected MedDRA preferred terms codes. • Section 3.7.3 Skin and Hypersensitivity Reactions: updated the wording to summarize IP-related skin reactions only. • Section 3.7.5 Subgroup Analyses: modified wording for clarification; added “within 3 days” as timing relative to dosing; removed summaries by age at randomization group ≤ 8.0 months or > 8.0 months; added additional summaries examining dose relative to dosing combined with other subgroups of interest.

		• Section 3.7.7 Other Safety Evaluation: added summaries for medical history findings (overall and ongoing); added summaries for vaccines exposure; added summaries for treatment-emergent adverse events onset within 7 or 28 days post co-administered vaccine doses (within ±7 days or ±14 days of IP dosing). • Section 3.8 Anti-drug Antibodies: modified the definition of persistent positive and transient positive. • Section 3.9, serum concentrations and ADA influence on PK will be summarized within the CSR (not in PK report). Removed reference to PK parameters as PK will be evaluated using a model-based approach (described and reported outside the CSR). This change has been made prior to DBL for Primary Analysis. • Added Appendix 4 Imputation Rule of Partial Dates

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

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive by central laboratory RT-PCR assay	**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 due to respiratory distress requiring IV hydration

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.

Appendix 2 Analysis Window for ADA/RSV Neutralizing Antibody/RSV Serology

Protocol	Scheduled Study Day	Analysis Windows
Global/Japan	Day 1	≤ 1
Global/Japan	Day 31	2 - 91
Global/Japan	Day 151	92 - 255
Global/Japan	Day 361	≥ 256
EU	Day 1	≤ 1
EU	Day 151	2 - 255
EU	Day 361	≥ 256

Appendix 3 Analysis Window for Clinical Lab Data

Protocol	Scheduled Study Day	Analysis Windows
Japan	Day 1	≤ 1
Japan	Day 8	2 - 20
Japan	Day 31	21 - 91
Japan	Day 151	≥ 92

Appendix 4 Imputation Rule for Partial Dates

If only a partial date is available is required for imputation, the following rules will be applied.

General Imputation Rule for Partial Date

- 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.

Imputation Rule for Partial AE Start Date

- When AE range is available:

  Step 1: For partial AE start dates, regardless if only the year is known, or only the month and year are known, first use the following rule to impute an AE start date:
  - Assume (dose date + 1 day) if AE started <= 7 days after dosing;
  - Assume (dose date + 7 days) if AE started 8 - 14 days after dosing;
  - Assume (dose date + 14 days) if AE started >14 days after dosing.

  Step 2: After getting an imputed AE start date from Step 1, compare the imputed AE start date with the partial AE start date:
  - If partial AE start date where only the year is known:
    - If the year of partial AE start date is the same as imputed AE start date from Step 1, then use imputed AE start date from Step 1;
    - If the year of partial AE start date is different from the year of imputed AE start date from Step 1, assume partial AE start date as January 1st;
    - If the imputed AE start date is after AE end date, then set AE start date the same as AE end date.
  - If partial AE start date where only the year and month are known:
    - If the year and month of partial AE start date are the same as imputed AE start date from Step 1, then use imputed AE start date from Step 1;
    - Otherwise, assume partial AE start date as the first day of the month.
    - If the imputed AE start date is after AE end date, then set AE start date the same as AE end date.

- When AE range is not available, for any treatment-emergent AEs,
  - If partial AE start date where only the year is known,
    - If the same year as dosing date, and if AE does not occur on the same day of dosing, then AE start date is one day after dosing date; otherwise, AE start date is the same as dosing date.
    - If different year from dosing date, assume January 1st.
  - If partial AE start date where only the year and month are known,
    - If the same year and month as dosing date, and if AE does not occur on the same day of dosing, then AE start date is one day after dosing date; otherwise, AE start date is the same as dosing date.
    - Otherwise, assume the first day of that month.

Imputation Rule for Partial Concomitant Medications Dates

- If a ConMed is not associated with an AE:
  - Apply the general imputation rule wherever fits.

- If a ConMed is associated with an AE:
  - The ConMed start date will be imputed with either observed or imputed AE start date. If there are multiple associated AEs, the earliest AE start date either observed or imputed will be used for imputation.
  - The ConMed end date will be imputed by the general imputation rule for end date whenever fits.

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