Statistical Analysis Plan

A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (MEDLEY)

Protocol Number: D5290C00005

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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
ATC	Anatomical Therapeutic Chemical
CE	*Conformité Européenne* or European Conformity
CHD	congenital heart disease
CI	confidence interval
CLD	chronic lung disease
CMH	Cochran-Mantel-Haenszel
CPAP	Continuous Positive Airway Pressure
C_{max}	Maximum observed concentration
COVID-19	Coronavirus Disease 2019
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
IM	intramuscular
IP	investigational product
ITT	intent-to-treat
IWRS	interactive web response system
LRTI	lower respiratory tract infection
mAB	Monoclonal antibody
MEDLEY	Study D5290C00005
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PK	pharmacokinetic(s)

Abbreviation or Specialized Term	Definition
PT	Preferred Term
RR	relative risk
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis System
SD	standard deviation
SID	subject identification
SMQ	Standardised MedDRA Query
SOC	System Organ Class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UK	United Kingdom
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 D5290C00005, a pivotal Phase 2/3 randomized, double-blind, palivizumab-controlled study to evaluate the safety, PK, ADA response, and descriptive efficacy for MEDI8897 in high-risk infants eligible to receive palivizumab when entering their first or second RSV season (Season 1 or Season 2, respectively).

The primary objective of this study is to evaluate the safety and tolerability of MEDI8897 compared to palivizumab when administered to preterm infants entering their first RSV season and children with CLD or CHD entering their first and second RSV season. The secondary objectives are: (1) to evaluate serum concentrations of MEDI8897 and palivizumab, (2) to evaluate ADA responses to MEDI8897 and to palivizumab in serum, (3) to assess the descriptive efficacy of MEDI8897 when administered as a single IM dose of 50 mg to infants < 5 kg or 100 mg to infants ≥ 5 kg in the first RSV season or a single 200-mg IM dose administered in the second RSV season, in reducing medically attended LRTI (inpatient and outpatient) and hospitalization due to RT-PCR-confirmed RSV, compared to palivizumab

These objectives will be assessed by descriptive statistics from safety data, pharmacokinetic (PK) parameters, ADA, and the incidence of RSV LRTI and RSV hospitalization. This document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used. Although formal hypothesis testing (for either safety or efficacy) will not be performed whereas only numerical summaries will be provided, an extrapolation study is planned to support extending the efficacy and safety data from the Phase 2b (D5290C00003) and Phase 3 (D5290C00004) studies in healthy preterm and term infants (ie, the palivizumab-ineligible population) to the target palivizumab-eligible population. The detail of the extrapolation will be provided in a separate PK extrapolation plan.

In addition, a set of templates and specifications for the tables, figures and listings is planned to be created in a statistical programming plan to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

To evaluate the safety and tolerability of MEDI8897 compared to palivizumab when administered to preterm infants entering their first RSV season and children with CLD or CHD entering their first and second RSV season.

2.1.2 Secondary Study Objectives

1 To evaluate serum concentrations of MEDI8897 and palivizumab

2 To evaluate ADA responses to MEDI8897 and to palivizumab in serum

3 To assess the descriptive efficacy of MEDI8897 when administered as a single IM dose of 50 mg to infants < 5 kg or 100 mg to infants ≥ 5 kg in the first RSV season or a single 200 mg IM dose administered in the second RSV season, in reducing medically attended LRTI (inpatient and outpatient) and hospitalization due to RT-PCR-confirmed RSV, compared to palivizumab.

2.1.3 Exploratory Study Objectives

4 To assess HRU and caregiver burden for MEDI8897 recipients compared to palivizumab recipients

5 To determine anti-RSV neutralizing antibody levels in serum afforded by a single dose of MEDI8897 compared to 5 monthly doses of palivizumab

6 To evaluate exposure to RSV by measuring seroresponses to different RSV proteins in MEDI8897 and palivizumab recipients and to evaluate the levels of maternal RSV-specific antibody in MEDI8897 and palivizumab recipients

7 To characterize resistance to MEDI8897 through genotypic and phenotypic analyses

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

2.2 Study Design

This is a randomized, double-blind, palivizumab-controlled study in which approximately 900 palivizumab-eligible infants entering their first RSV season will be enrolled into one of 2 cohorts (Figure 1): (1) preterm cohort, including approximately 600 preterm infants (≤ 35 weeks gestational age [GA]) without CLD/CHD, or (2) CLD/CHD cohort, including approximately 300 infants with CLD of prematurity or hemodynamically significant CHD. A minimum of 100 infants with hemodynamically significant CHD will be enrolled. Within each cohort, randomization will be stratified by hemisphere (northern, southern) and subject age at the time of Season 1 randomization (≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months).

Season 1, Preterm and CLD/CHD Cohorts

All subjects will be randomized 2:1 to either the MEDI8897 group (approximately 600 subjects, including approximately 400 subjects in the preterm cohort and approximately 200 subjects in the CLD/CHD cohort) or palivizumab group (approximately 300 subjects, including approximately 200 subjects in the preterm cohort and 100 subjects in the CLD/CHD cohort). Subjects in the MEDI8897 group will receive a single fixed IM dose of MEDI8897 followed by 4 once-monthly IM doses of placebo. The MEDI8897 dose level will be stratified by weight band, ie, 50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg. Subjects in the palivizumab group will receive 5 once-monthly IM doses of 15 mg/kg palivizumab.

Season 2, CLD/CHD Cohort Only

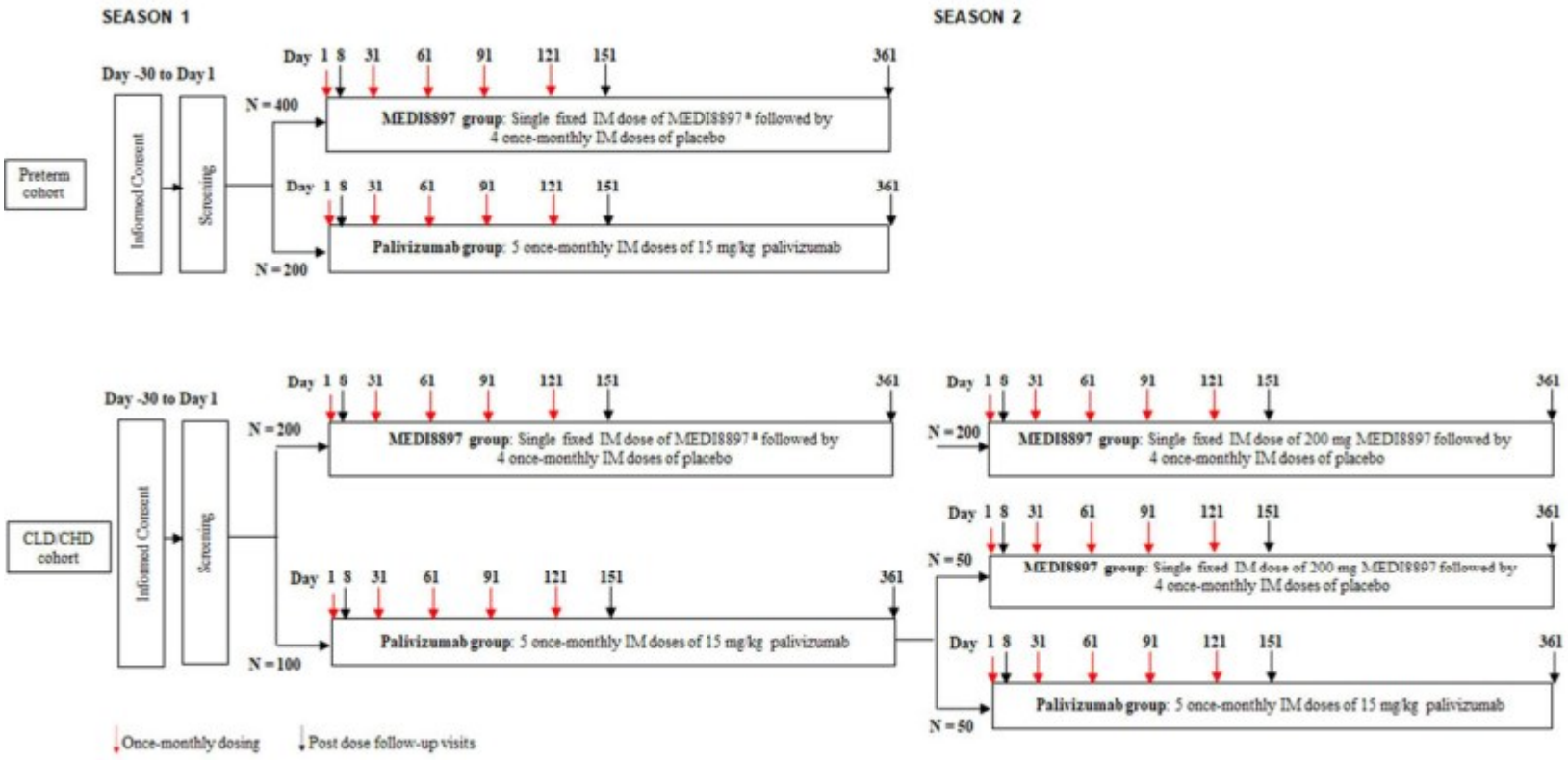
- Subjects with CLD/CHD ≤ 24 months of age who were randomized to the MEDI8897 group for Season 1 will receive a single fixed IM dose of 200 mg MEDI8897 followed by 4 once-monthly IM doses of placebo (approximately 200 subjects).
- Subjects with CLD/CHD ≤ 24 months of age who were randomized to the palivizumab group for Season 1 will be re randomized 1:1 to either the MEDI8897 group or the palivizumab group. Subjects in the MEDI8897 group will receive a single fixed IM dose of 200 mg MEDI8897 followed by 4 once monthly IM doses of placebo (approximately 50 subjects). Subjects in the palivizumab group will receive 5 once monthly IM doses of 15 mg/kg palivizumab (approximately 50 subjects).

In Season 1 or Season 2, subjects in the CLD/CHD cohort who undergo cardiac surgery with cardiopulmonary bypass after receipt of Dose 1 but prior to receipt of Dose 5 will receive a replacement dose of the study drug they received for Dose 1 immediately following the

surgery when determined by the physician to be medically stable for an IM injection. Any subsequent doses of study drug will continue to be given according to the protocol specified dosing schedule.

Subjects in the preterm cohort will be followed through 1 year after Season 1/Dose 1, and subjects in the CLD/CHD cohort will be followed through 1 year after Season 2/Dose 1. Subjects in the CLD/CHD cohort who receive a replacement dose in Season 2 will be followed through 1 year after the last replacement dose.

Figure 1: Study Design



2.3 Treatment Assignment and Blinding

2.3.1 Methods for Assigning Treatment Groups

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

In Season 1, subjects in the preterm and CLD/CHD cohorts will be randomized using a 2:1 ratio to either the MEDI8897 group or palivizumab group. Within each cohort, the randomization will be stratified by hemisphere (northern, southern) and subject age at the time of Season 1 randomization (≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months).

In Season 2, subjects in the CLD/CHD cohort only will be randomized. Subjects who were randomized to the MEDI8897 group in Season 1 will remain in the MEDI8897 group. Subjects who were randomized to the palivizumab group in Season 1 will be re-randomized using a 1:1 ratio to either the MEDI8897 or palivizumab group. For simplicity, the following notations will be used to describe the treatment groups in Season 2.

- MEDI8897/MEDI8897: CHD/CLD subjects who were randomized to MEDI8897 group in Season 1 and remained in MEDI8897 group in Season 2.
- Palivizumab/MEDI8897: CHD/CLD subjects who were randomized to Palivizumab group in Season 1 and re-randomized to MEDI8897 group in Season 2.
- Palivizumab/Palivizumab: CHD/CLD subjects who were randomized to Palivizumab group in Season 1 and re-randomized to Palivizumab group in Season 2.

Study drug (MEDI8897, placebo, or palivizumab) must be administered the same day the study drug is assigned. If there is a delay in the administration of study drug such that it will not be administered within the specified timeframe, the unblinded investigational product monitor must be notified immediately.

2.3.2 Methods to Ensure Blinding

This is a double-blind study in which MedImmune will provide sites with MEDI8897 and palivizumab. Sites will use commercially available saline as the placebo. Syringe barrels will be covered by the unblinded investigational product manager. 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.

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 study drug 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 study drug. In the majority of cases, the management of a medical emergency would be the same whether or not study drug was received by the subject. If this was the case, the study drug allocation should not be unblinded. In the event there is unblinding, the investigator should promptly document and explain to MedImmune the reason for any premature unblinding.

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

If a subject's study drug allocation is unblinded to the blinded staff or blinded MedImmune/contract research organization study team, the subject should be discontinued from study drug.

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

With respect to safety, 600 subjects exposed to MEDI8897 in Season 1 will provide a 95% probability of observing at least one AE if the true event rate is 0.5%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.5%. The sample size is for safety consideration.

With respect to the descriptive efficacy, 600 subjects will be exposed to MEDI8897 and 300 subjects will be exposed to palivizumab in Season 1 to observe numerically similar efficacy for both mAbs. Using an assumption of a 6% medically attended RSV LRTI rate in palivizumab recipients, approximately 18 events will be observed in that group. The 6% RSV

LRTI rate (1.9% RSV hospitalizations and 3.9% outpatient RSV illness) was based on a prior study in preterm infants with and without CLD who received palivizumab (Carbonell-Estrany X, 2010). Assuming a 6% rate of medically attended RSV LRTI in MEDI8897 recipients, 600 MEDI8897 subjects in Season 1 will provide approximately 36 events in that group. However, because of the largely reduced RSV circulation due to COVID-19 pandemic related measures, the observed event rates could be much lower.

3 STATISTICAL METHODS

3.1 General Considerations

There are 3 planned analyses for this study: the primary analysis, the Season 2 analysis and the final analysis. The primary analysis will be conducted after all randomized subjects have completed follow-up through the first 5-month RSV season (ie, Season 1 Day 151 visit) and include all available Season 1 safety, efficacy, PK, and ADA data at the time of the data cutoff. The Season 2 analysis will be conducted after all CLD/CHD subjects have completed follow-up through the second 5-month RSV season (ie, Season 2 Day 151 visit) and include all available Season 1 data and Season 2 safety, efficacy, PK, and ADA data at the time of the data cutoff. The final analysis will be conducted when all subjects have completed the last visit of the study and include all data collected in the study.

At the time of the primary analysis, the Season 1 data will be unblinded to Sponsor/designated clinical research organization associated with the analysis, write-up and submission. To ensure the blinding of Season 2 treatment assignment for CHD/CLD subjects who were randomized to palivizumab arm in Season 1, any data with potential unblinding risk will be split by Season 1 and Season 2 by the corresponding third party data vendors and when the primary database lock (DBL) occurs, only unblinding data from Season 1 will be transferred to the Sponsor for 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 to ensure the trial integrity is maintained. Details of the unblinding process will be documented in a separated file of unblinding plan.

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 observation with the earlier collection date will be used in the analysis for the post-baseline observations, and the non-missing 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 earlier 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, and RSV serology are defined in Appendix 2, and for clinical laboratory data are defined in Appendix 3.

The partial dates imputation rules are described in Appendix 4 and Appendix 5.

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 of each season will be defined as the last non-missing value within 30 days prior to the 1st dosing of the season. Baseline of Season 1 + Season 2 will be the same as baseline of Season 1.Data analyses will be conducted using the SAS® System Version 9.4 or higher (SAS Institute Inc., Cary, NC).

3.2 Analysis Populations

The analysis populations are defined in Table 1.

Table 1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population (Season 1)	The ITT population (Season 1) includes all subjects randomized in Season 1. In this population, subjects will be analyzed according to their randomized treatment group in Season 1. The analysis for baseline/demographic characteristics, efficacy and HRU for Season 1 will be performed on this population.
Intent-to-treat (ITT) population (Season 2)	The ITT population (Season 2) includes all CHD/CLD subjects enrolled in Season 2. In this population, subjects will be analyzed according to their randomized treatment group through the two seasons (ie, in Season 1 and in Season 2). The analysis for baseline/demographic characteristics, efficacy, and HRU for Season 2 and/or through the two seasons (Season 1 + Season 2), will be performed on this population.
As-treated population (Season 1)	The As-treated population (Season 1) includes subjects who receive any investigational product in Season 1. In this population, subjects will be analyzed according to the actual treatment received in Season 1. The analysis for safety, PK, ADA, serology, and RSV neutralizing antibody for Season 1 will be performed on this population. For subjects who accidentally receive both MEDI8897 and palivizumab in Season 1: - For summaries on safety, subjects who receive any amount of MEDI8897 will be included in the MEDI8897 group. - For summaries on PK, ADA, serology, and RSV neutralizing antibody, subjects will be analyzed according to the first dose they receive. The data collected up to the point of dose switch will be included in the summaries. All the data collected afterwards will be presented in the listing.
As-treated population (Season 2)	The As-treated population (Season 2) includes subjects who receive any study investigational product in Season 2. In this population, subjects will be analyzed according to the actual treatment received through the two seasons (ie, in Season 1 and in Season 2). The analysis for safety, PK, ADA, serology, and RSV neutralizing antibody for Season 2 and/or through the two seasons (Season 1 + Season 2), will be performed on this population. For subjects who received mixed doses of investigational product, similar rules as described above for Season 1 will be applied for Season 2.

3.3 Stratification Factors

Two stratification factors are used in study design as well as in data analysis, and these are: age group at Season 1 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 eCRF calculation will be used.

eCRF 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 to 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, then age at randomization will be obtained as follows:

- 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

Summaries will be presented by treatment group (as-randomized) for each season:

- Season 1: summary of subject eligibility and randomization as well as treatment received (including summary of subjects randomized but not treated, subjects who discontinued treatment) will be provided for all screened subjects. In addition, disposition of subjects throughout the study and by milestone visit (ie, Day 151, Day 361) will be provided.

These summaries will be provided for each cohort (pre-term, CHD/CLD) as well as for all subjects combined.

- Season 2: Similar summary as described above for Season 1 will be provided for all subjects enrolled in Season 2, with the exception of subject eligibility, which is not applicable for Season 2.

3.4.2 Demographics and Baseline Characteristics

Enrollment will be summarized by treatment group for each season using the respective ITT population.

- Season 1: Enrollment will be summarized by hemisphere, country, site, and by hemisphere, country, and age at randomization stratum. 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, subjects whose age stratum as calculated from the eCRF do not match the IWRS database) will also be summarized. These summaries will be provided for each cohort (pre-term, CHD/CLD) as well as for all subjects combined.
- Season 2: Similar summary as described above for Season 1 will be provided for all subjects enrolled in Season 2.

Demographic characteristics will be summarized by treatment group using the respective ITT population:

- Season 1: Summary of demographic characteristics including gender, age at randomization (months) calculated from the CRF, age at randomization category determined using the CRF age calculation (age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months), GA (weeks), GA category (< 29 weeks, ≥ 29 weeks to < 32 weeks, ≥ 32 weeks to < 35 weeks, ≥ 35 weeks), ethnicity, race, weight (kg) on Day 1, weight on Day 1 category (weight < 5 kg, weight ≥ 5 kg), birth weight (kg), birth weight category (≤ 2.5 kg, > 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), underlying lung disease (yes/no), CHD (yes/no), CLD (yes/no), Down syndrome (yes/no), family history of atopy (including asthma, hay fever, eczema, wheezing) will be provided for each cohort (pre-term, CHD/CLD) and for all subjects. Subjects will be excluded from the summary (eg, means and percentages) of an individual parameter if data are missing. The summaries will also be provided for each age at randomization category and by hemisphere category.
- Season 2: Similar summary as described above for Season 1 will be provided for all subjects enrolled in Season 2. In addition, weight on Day 1, Season 2 will be summarized, and the corresponding weight on Day 1, Season 2 category will be: weight < 7 kg, weight ≥ 7 kg for safety subgroup analysis; weight < 10 kg, weight ≥ 10 kg for efficacy subgroup analysis. Demographic and baseline characteristics will also be summarized for CHD subjects and CLD subjects separately for each season. If a subject has both CHD and CLD, the subject will be included in both summary tables.

3.4.3 Study Drug Exposure

Summaries will be presented by treatment group for each season as well as for the two consecutive seasons using the respective as-treated population.

- Season 1: Summary of study drug exposure will include the number of doses received, number of active doses received, cumulative number of doses received (ie, at least 1, at least 2, etc.), cumulative number of active doses received, the number of subjects receiving planned volume of doses, the number of subjects receiving planned active doses, the number of subjects receiving at least 1 dose out of window (2-day and 7-day window will be considered), the number of subjects missing at least 1 dose. These summaries will be provided for each cohort (pre-term, CHD/CLD) and for all subjects combined.
- Season 2: Similar summary as described above for Season 1 will be provided for all subjects enrolled in Season 2 and the reporting period will be Day 1, Season 2 through Day 151, Season 2.
- Season 1 + Season 2: Similar summary as described above for Season 1 will be provided for all subjects enrolled in Season 2 and the reporting period will be Day 1, Season 1 through Day 151, Season 2.

In addition, subjects who have received mixed dose of investigational product will be listed.

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 sponsor, 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)-related deviations. This can be further categorized into IP administration-related deviations, IP assignment-related deviations, IP handling-related deviations, and IP compliance-related deviations.
  - IP administration-related deviations include but are not limited to:
    - Not getting subsequent IP doses after initial dose;

    - Failure to discontinue IP despite withdrawal of consent or not meeting eligibility prior to dosing;
  - IP assignment-related deviations include but are not limited to:
    - Inappropriate use of study IP (eg, giving IP to non-study subjects);
    - Incorrect IP dispensed to subject (eg, IP assigned via IWRS was different from IP dispensed to subject);
    - Kit dispensed without IWRS transaction
  - IP handling-related deviations include but are not limited to:
    - Dispensing of IP which had an unapproved temperature excursion or was not suitable for use upon inspection for whatever reason to a subject;
    - IP was administered to the subject after 4 hours post preparation
  - IP compliance-related deviations include but are not limited to:
    - Subject was administered IP but was not observed for at least 1 hour post dose;
    - Subject did not get replacement dose (at all or as soon as possible after cardiac bypass surgery)
    - Wrong dose of IP given
- Subjects who had no central RT-PCR RSV nasal sample collected for any of the LRTI visits
- 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).

3.4.5 Medical History

Medical history data will be summarized as number (%) of subjects by treatment, according to Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) categories. If a subject has more than 1 record in a specific category, the subject will be counted only once for the category. The denominators for calculating percentages will be based on the number of subjects in the AT population for each treatment group.

In addition, medical history findings which are ongoing at the time of signed informed consent will be also summarised by treatment.

The Season 1 medical history summaries will also be provided for each cohort (pre-term, CHD/CLD), CLD subjects, CHD subjects, subjects with GA < 29 weeks, subjects with GA < 29 weeks and without CLD or CHD, and CLD subjects with GA < 32 weeks. The Season 2 medical history summaries will also be provided for CLD subjects, CHD subjects, and CLD subjects with GA < 32 weeks.

3.5 Efficacy Analyses

The analyses of the efficacy endpoints, including the incidence of protocol-defined medically attended RSV LRTI (also described as the medically attended RSV LRTI) through 150 days post 1st dose, as well as the incidence of protocol-defined RSV hospitalization (also described as the RSV LRTI hospitalization) through 150 days post 1st dose, will be performed on the respective ITT population for Season 1 and 2. The incidence will be calculated as the proportion of subjects who meet the endpoint during the reporting period. Only summaries will be provided for the efficacy analyses unless specified otherwise. The summaries will be based on observed events.

3.5.1 Incidence of medically attended LRTI due to RT-PCR-confirmed RSV

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.

Based on a blinded review of data, it is determined that a medically attended LRTI will be counted as a medically attended RSV LRTI if there is a respiratory sample tested RSV positive and collected within [-7, 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). 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.

3.5.1.1 Analysis of incidence of medically attended LRTI due to RT-PCR-confirmed RSV in Season 1

The incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post 1st dose (ie, during a typical 5-month RSV season) in Season 1 is the primary efficacy endpoint and will be summarized by treatment group as well as for all subjects using ITT

population. The 95% Clopper-Pearson (exact) confidence interval of the incidence rate for each treatment group will be produced using the SAS Procedure PROC FREQ with the EXACT statement. For subjects with multiple medically attended RSV LRTI events, only the first occurrence will be used in the summary. Summary of the incidence of medically attended RSV LRTI will also be repeated for CHD subjects and CLD subjects separately.

In addition, the incidence of medically attended RSV LRTI will be further 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.

The incidence of medically attended RSV LRTI 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 (< 29 weeks, ≥ 29 weeks to <32 weeks, ≥ 32 weeks to < 35 weeks, ≥35 weeks)
- Sibling also participating in the study (yes/no)

In addition, the incidence of medically attended RSV LRTI that occurred through 360 days post 1st dose will be summarized by treatment group.

Age at onset of the first medically attended RSV LRTI through 150 days post 1st 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 1st dose, through 360 days post 1st dose will be summarized by treatment group.

To capture and summarize multiple medically attended RSV LRTIs through 150 days post 1st dose, the total number of new onset medically attended RSV LRTIs will be calculated for each subject. A new onset medically attended RSV LRTI is defined as an adverse event (AE) meeting the protocol specified criteria for a medically attended RSV LRTI and occurring at least 14 days after the resolution date of the previous AE for a medically attended RSV LRTI. A similar definition is applied with a 30-day interval between the resolution of the previous

event and onset of a new event (see Table 2 for details). A listing will be generated to provide the following information: age at randomization, hemisphere, total number of events (at least 14 days apart), total number of events (at least 30 days apart), days to event, adverse event (AE) verbatim term, date of AE onset/stop, days from previous event, visit setting, and RSV subtype.

AEs associated with medically attended RSV LRTI will be summarized overall, as well as categorized by MedDRA system organ class (SOC) and preferred term (PT). Summaries will be presented through 150 days post 1st dose, and through 360 days post 1st dose.

Above summaries will be repeated for each cohort (pre-term and CHD/CLD).

3.5.1.2 Analysis of incidence of medically attended LRTI due to RT-PCR-confirmed RSV in Season 2

The efficacy summary in Season 2 (ie, Day 1, Season 2 through Day 361, Season 2) will focus on the CHD/CLD subjects who have been randomized to palivizumab group in Season 1 and enrolled (re-randomized) in Season 2 to either palivizumab or MEDI8897 groups (ie, palivizumab/palivizumab and palivizumab/MEDI8897 groups), to facilitate understanding of the effects of MEDI8897 and palivizumab following an initial treatment by palivizumab in the 1st RSV season. Efficacy data of CHD/CLD subject who have been randomized to MEDI8897 group in both Season 1 and Season 2 (ie, MEDI8897/MEDI8897 group) will also be summarized.

There is no intention to directly compare efficacy of MEDI8897/MEDI8897 group with palivizumab/palivizumab or palivizumab/MEDI8897, since direct comparison between MEDI8897/MEDI8897 and the other 2 arms could potentially be biased if dropouts of Season 1 are associated with efficacy.

All the analyses described above in Section 3.5.1.1 for Season 1 will be repeated for Season 2, with the exception that the weight on Day 1 subgroup summary will be based on Season 2 and the corresponding categories will be: weight < 10 kg, weight ≥ 10 kg.

3.5.1.3 Sensitivity Analyses of incidence of medically attended LRTI due to RT-PCR-confirmed RSV

Sensitivity analyses will be carried out for incidence of medically attended RSV LRTI based on the following population for each season:

- ITT subjects excluding who received any dose of wrong treatment (ie, subjects who were randomized to palivizumab group but received MEDI8897 or placebo, and subjects who were randomized to MEDI8897 group but received palivizumab during the season), or missed any active dose, or had at least 1 active dose out of 7-day window.

3.5.2 Incidence of RSV hospitalization

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.

3.5.2.1 Analysis of Incidence of RSV hospitalization in Season 1

The incidence of RSV hospitalization through 150 days after dosing in Season 1 (ie, during the 5-month RSV season) will be summarized by treatment group for each cohort as well as for all subjects. 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 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 $\leq$ 3.0 months, age > 3.0 to $\leq$ 6.0 months, age > 6.0 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight $\leq$ 2.5 kg, weight > 2.5 kg)
- Weight on Day 1 (weight < 5 kg, weight $\geq$ 5 kg)
- GA (< 29 weeks, $\geq$ 29 weeks to < 32 weeks, $\geq$ 32 weeks to < 35 weeks, $\geq$ 35 weeks)
- Sibling also participating in the study (yes/no)

Above summaries will be repeated for each cohort (preterm and CHD/CLD).

3.5.2.2 Analysis of Incidence of RSV hospitalization in Season 2

The efficacy summary in Season 2 (ie, Day 1, Season 2 through Day 361, Season 2) will focus on the CHD/CLD subjects who have been randomized to palivizumab group in Season 1 and enrolled (re-randomized) in Season 2 in either palivizumab or MEDI8897 groups (ie, palivizumab/palivizumab and palivizumab/MEDI8897 groups), to facilitate understanding the effects of MEDI8897 and palivizumab following an initial treatment by palivizumab in the first RSV season. Efficacy data of CHD/CLD subjects who have been randomized to

MEDI8897 group in both Season 1 and Season 2 (ie, MEDI8897/MEDI8897 group) will also be summarized.

All the analyses described above in Section 3.5.2.1 for season 1 will be repeated for season 2, with the exception that the weight on Day 1 subgroup summary will be based on Season 2 and the corresponding categories will be: weight < 10 kg, weight ≥ 10 kg.

3.5.3 Other Efficacy Analyses

For each season, the following summaries will be provided using the respective ITT population. The Season 1 summaries will also be repeated for each cohort (preterm, CHD/CLD).

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 down 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, then further by 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.

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). The summaries for subjects with or without underlying lung disease will be provided separately. The elements include the following:

- For subjects without underlying lung disease: rhonchi, rales, crackles, wheeze, increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, retractions, grunting, dehydration due to respiratory distress requiring IV hydration
- For subjects with underlying lung disease: rhonchi, rales, crackles, wheeze, increased respiratory rate (from baseline), hypoxemia, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, retractions, grunting, dehydration due to respiratory distress,

prescription of new or increased (from baseline) dose of medications including bronchodilators, steroids, diuretics, cardiac medication

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 presented through 150 days post 1st dose (on ITT population), after 150 days post 1st dose (on the ITT population with Day 151 visit), and through 360 days post 1st dose (on ITT population).

For various LRTI events, including the primary endpoint, detailed definitions of new onset of events are defined in 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 three time-intervals: through 150 days post 1st dose (on the ITT population), after 150 days post 1st dose (on the ITT population with Day 151 visit), through 360 days post 1st dose (on ITT population). In addition, a listing that provides relevant information for subjects with more than one medically attended LRTI event throughout the study will be generated. The listing contains the following information: Age at randomization, Hemisphere, Total number of events, Days post 1st 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, and through 360 days post 1st dose on the following populations: ITT, ITT with Day 151 visit, ITT, respectively.

3.6 Exploratory Analyses

3.6.1 Healthcare Resource Utilization (HRU)

For each season, the following summaries will be provided using the respective ITT population. The Season 1 summaries will also be repeated for each cohort (pre-term, CHD/CLD).

The magnitude of healthcare resource utilization (HRU; as 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 and the duration of use; number requiring supplemental oxygen and the duration of use; number and type of visits to 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 1st dose (on ITT population), after 150 days post dose (on ITT population with Day 151 visit), and through 360 days post dose (on ITT population).

Specifically, 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 ITT population for time interval through 150 days post 1st dose, on ITT population with Day 151 visit for time interval after 150 days post 1st dose, and on ITT population for time interval through 360 days post 1st 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 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 the subject died in the hospital, the duration of that hospital stay will be calculated from admission to the minimum of {Death Date, End-of-Study Date, Data Cutoff Date at the time of Primary 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 1st dose, after 150 days post 1st dose, and through 360 days post 1st 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 will be summarized by treatment group and overall through one week after dosing. The number of pre-specified prescription medication (systemic antibacterial agents) use; the number of anti-wheezing medication use, and the number of antiviral therapy use will be summarized by treatment group and overall through 150 days post 1st dose. The Anatomical Therapeutic Chemical (ATC) codes for these medications will be provided in a separated file provided by medical monitor prior to DBL for 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-administerrated 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.

3.6.2 Caregiver Burden

For each season, the following summaries will be provided using the respective ITT population. The Season 1 summaries will also be repeated for each cohort (pre-term, CHD/CLD).

Caregiver burden (measured by days of work the caregiver missed, days of daycare/babysitting the subject missed) will be summarized for subjects with medically attended RSV LRTI (Protocol-defined) by treatment group for subjects who have had at least an event in the time-period of reporting. These summaries will be presented through 150 days post 1st dose, after 150 days post 1st dose, and through 360 days post 1st 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 have had at least one of the events divided by the total number of the events among these subjects in the time interval of interest. Similar summary will also be provided by the status of hospitalization (at least one or none) that is caused by a respective event mentioned above.

3.6.3 Anti-RSV neutralizing antibody

For each season as well as the two consecutive seasons (ie, Season 1, Season 2, Season 1 + Season 2) the following summaries will be provided using the respective as-treated population. The Season 1 summaries will also be repeated for each cohort (pre-term, CHD/CLD).

Individual MEDI8897 and palivizumab 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 and corresponding 95% CI for each treatment group at each visit. RSV neutralizing antibody level $t_{1/2}$ will be estimated using non-compartmental analysis, if data permit and may be reported outside the CSR.

Box plots of RSV neutralizing antibody levels in logarithm scale with base 10 will be provided by treatment group and by visit for each season.

3.6.4 RSV serology

For each season as well as the two consecutive seasons (ie, Season 1, Season 2, Season 1 + Season 2) the following summaries will be provided using the respective as-treated population. The Season 1 summaries will also be repeated for each cohort (pre-term, CHD/CLD).

RSV seroresponses will be evaluated as a measure of "RSV exposure" in the MEDI8897 and palivizumab groups. Analysis of serum antibody levels to RSV antigens in MEDI8897 and palivizumab recipients will be summarized by geometric mean concentration and geometric mean-fold rise from baseline and corresponding 95% CI for each treatment group at each visit. Seroresponses in MEDI8897 recipients will be determined by examining the fold-rise in antibodies to Post-F, Ga, Gb, and N antigens; seroresponses in palivizumab recipients will be determined by examining the fold-rise in antibodies to Ga, Gb, and N antigens. By measuring antibodies to Post-F, Ga, Gb, and N for MEDI8897 recipient, and measuring antibodies to Ga,

Gb and N for palivizumab recipient: 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 Abs for the infant's own immune system can be determined. In addition, number and percentage of subjects with RSV exposure (defined as ≥ 4-fold rise in serum antibody levels to any RSV antigen from the previous timepoint) will be summarized. A subject shows "evidence of exposure" if this criterion is met for any set of consecutive timepoints. The summary will be provided by treatment group 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.

Box plots of serum antibody levels to RSV antigens in logarithm scale with base 10 will be provided by treatment group and by visit for each season.

3.6.5 RSV resistance monitoring

Nasal samples collected from 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 to be 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 from Day 152 to Day 361 for Season 1 and Season 2

For each season, the summaries will be provided using subjects from the respective ITT population 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. More specifically:

- Season 1: The incidence of medically attended RSV LRTI that occurred > 150 days (from Day 152 to Day 361) post 1st 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. These summaries will also be provided for each cohort (pre-term, CHD/CLD).

- Season 2: Similar summaries described above for Season 1 will be provided for Season 2 and will focus on the CHD/CLD subjects in the following groups: palivizumab/palivizumab, palivizumab/MEDI8897, and MEDI8897/MEDI8897. who have been randomized to palivizumab group in Season 1 and enrolled (re-randomized) in Season 2 in either palivizumab or MEDI8897 groups. Summaries for CHD/CLD subjects who have been randomized to MEDI8897 group in both Season 1 and Season 2 will also be provided.

3.7 Safety Analyses

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

For each season as well as the two consecutive seasons combined (ie, Season 1, Season 2, Season 1 + Season 2) the summaries will be provided using the respective as-treated population. The Season 1 summaries will also be provided for each cohort (pre-term, CHD/CLD).

For each season, all safety analyses planned will be presented. For Season 1 + Season 2, number and percentage of subjects with treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), IP-related skin reactions, and new onset chronic diseases (NOCDs) will be summarized by MedDRA System Organ Class (SOC) and Preterm Term (PT) for palivizumab/palivizumab and MEDI88987/MEDI8897 groups. The Season 1 + Season 2 summaries will be presented for CLD/CHD cohort, for CLD subjects and CHD subjects, separately.

For Season 2 summaries and Season 1 + Season 2 summaries, direct comparison between MEDI8897/MEDI8897 with palivizumab/palivizumab groups are subject to potential bias if the dropouts of Season 1 are associated with safety.

Table 3 Reporting Period of Treatment-emergent Adverse Events

Reporting Period	Definition of Treatment-emergent AEs
Season 1	Any AEs that started on/after date of 1st dose of Season 1, and prior to the end of Season 1, Day 361 or the last day prior to 1st dose of Season 2, whichever comes earlier.
Season 2	Any AEs that started on/after date of 1st dose of Season 2 and prior to the end of Season 2, Day 361.
Season 1 + Season 2	Any AEs that started on/after date of 1st dose of Season 1 and prior to the end of Season 2, Day 361.

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, Season 1 for preterm cohort, or after Day 361, Season 1 and prior to Day 1, Season 2 for CHD/CLD cohort, or after Day 361, Season 2 for CHD/CLD cohort, or pre-planned surgeries that are coded with PT "Cardiac Operation" and occur during the study for CHD subjects 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 Query (SMQ) for hypersensitivity, the narrow and broad SMQ for anaphylactic reaction, and a study specific query based on compatible PTs for thrombocytopenia and immune complex disease occurring in the database. 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, NOCDs) and IP-related AEs (including TEAEs, TESAEs, AESIs, skin 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), weight on Day 1 (weight < 2.5 kg, weight ≥ 2.5 kg and < 5 kg, weight ≥ 5 kg on Day 1, Season 1 for Season 1 summary). Due to the small number of subjects with weight < 7 kg on Season 2 Day 1, Season 2 TEAEs will not be summarized by weight on Season 2 Day 1 (< 7 kg, ≥ 7 kg), and will only be listed for subjects with weight < 7 kg on Season 2 Day 1. The Season 1 AEs will also be summarized for CLD subjects, CHD subjects, subjects with GA < 29 weeks, subjects with GA < 29 weeks and without CLD or CHD, and CLD subjects with GA < 32 weeks. The Season 2 AEs will also be provided for CLD subjects, CHD subjects, and CLD subjects with GA < 32 weeks.

TEAEs, TESAEs, AESIs, IP-related skin reactions (including skin hypersensitivity reactions) will also be summarized by timing relative to dosing ('within 1 day', 'within 3 days', 'within 7 days', 'within 14 days'). As subjects in the MEDI8897 group will receive both MEDI8897 and placebo dosing, corresponding AEs for these subjects will be broken down further by the dosing category (MEDI8897 or placebo). For example, to summarize AEs within 7 days, if a subject receives the first dose which contains MEDI8897, and 4 subsequent doses which only contains placebo, then the AEs within 7 days of the first dose will be included in the MEDI8897 category, AEs within 7 days of any of the four doses will be included in the placebo category; if a subject receives 5 doses of palivizumab, then all the AEs within 7 days of any of the 5 doses will be included in the palivizumab category. If an AE occurred within 14 days relative to both the replacement dose and next dose, we will consider the AE associated with the replacement dose only and count it within the appropriate timing relative to the replacement dose.

TEAEs, TESAEs, AESIs, and IP-related skin reactions (including skin hypersensitivity reactions) will also be summarized by number of active doses received within each treatment group. The corresponding categories are: no more than planned active doses, more active doses than planned, further broken down by: 1 more active dose than planned, 2 more active doses than planned etc.

In addition, TEAEs occurring within 1 day, 3 days, 7 days, and 14 days post dose by age at randomization (≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months) will also be summarized,

respectively. Similar summaries will be provided by timing relating to the first dose for each season.

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. Data listings will be provided for these data. In addition, the vaccines given to the subjects throughout the study will be summarized by treatment group.

Upon review of the listings, additional summary tables may be generated as appropriate.

3.8 Anti-drug Antibodies

For each season as well as the two consecutive seasons (ie, Season 1, Season 2, Season 1 + Season 2) the summaries will be provided using the respective as-treated population. For Season 1, summaries of ADA to palivizumab and MEDI8897 will be provided for palivizumab and MEDI8897 group, respectively. The Season 1 summaries will also be provided for each cohort (pre-term, CHD/CLD). For Season 2, summaries of ADA to MEDI8897 will be provided for Palivizumab/MEDI8897 group only. For Season 1 + Season 2, summaries of ADA to palivizumab and MEDI8897 will be provided for

palivizumab/palivizumab and MEDI8897/MEDI8897 group, respectively. There is no intention to compare results of ADA to MEDI8897 and ADA to palivizumab.

The number and percentage of subjects who develop anti-MEDI8897 antibodies will be summarized at each visit by treatment group. For those with a positive assessment, the ADA titer results will also be summarized. The number and percentage of ADA positive samples with specificity to the YTE or 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 post-baseline assessment, and positive at ≥ 1 post-baseline assessment and not fulfilling the conditions for persistent positive.

To evaluate the impact of ADA on efficacy and safety, the efficacy endpoints (ie, incidence of medically attended RSV LRTI and RSV hospitalization), 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 1st dose). The efficacy endpoints will also be summarized by ADA post-baseline status through 150 days post 1st dose.

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

3.9 Pharmacokinetics

Individual MEDI8897 and palivizumab serum concentrations for each nominal sampling time will be listed and summary descriptive statistics presented by treatment group and cohort (pre-term, CHD/CLD) in Season 1, and by treatment group in Season 2, respectively. Geometric mean MEDI8897 serum concentrations will be plotted versus time. Individual MEDI8897 serum concentrations will be graphically illustrated, and summarized, by ADA status.

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

3.10 Impact on Analyses due to COVID-19 Pandemic

Scheduled visits, subject dosing, blood and nasal sample collection become difficult or impossible to perform according to protocol for subjects remaining in the study during COVID-19 pandemic.

Efforts are ongoing to collect outstanding data via alternative means where possible, when on-site visits cannot be performed. As a result, the following changes have been made to the planned analyses:

- Confirmed or suspected cases of COVID-19 will be listed as AEs and summarized as appropriate.
- An additional sensitivity analysis of medically attended RSV LRTI by Day 151 will be performed by excluding subjects who missed at least 1 active dose or had at least 1 active dose delayed for 7 or more days due to COVID-19 pandemic.
- COVID-19 related protocol deviations will be identifiable in the database with a 'COVID' prefix. COVID-19 related important protocol deviations will be summarized and described separately in the CSR.
- Subjects who miss a visit, miss blood or nasal sample collection, discontinue treatment or withdraw from study due to COVID-19 pandemic will be summarized.

4 REFERENCES

Carbonell-Estrany X, S. E. (2010). Motavizumab for prophylaxis of respiratory syncytial virus in high-rsk children: a noninferiority trial. *Pediatrics*, 125.

5 AMENDMENT HISTORY

Version	Date	Description of Change
1.0	26SEP2019	Initial version
2.0	05APR2021	• In section 1, replaced hypotheses testing by objectives to align with protocol v2.0. The study is descriptive by design and there is no formal hypothesis testing, therefore the hypotheses testing was removed to avoid potential confusion. • Updated sample size in section 2.2 to align with protocol v2.0. Given the challenge of study enrollment due to the COVID-19 pandemic, the sample size was reduced from originally planned in the protocol. • In section 3.1, added primary analysis and Season 2 analysis to allow earlier assessment of Season 1 and Season 2 data; added programming rule for multiple measurements within one scheduled visit to deal with multiple measurements within on scheduled visit for ADA, RSV neutralizing antibody, RSV serology and clinical laboratory data; elaborated the definition of baseline for each season and Season 1 + Season 2; added description about strategy to maintain the blind to ensure trial integrity and the blinding of the Season 2 treatment assignment for CLD/CHD subjects who were randomized to the palivizumab arm in Season 1 • In section 3.4.2, added GA groups and updated birth weight categories • Added section 3.4.4 Violations and Deviations • Added section 3.4.5 Medical History • In section 3.5 and 3.6, changed “post dose” to “post 1st dose” for report period of efficacy for clarity.

		• In section 3.5, removed side-by-side efficacy summaries for Season 1 + Season 2 to align with protocol v2.0. As the incidence of medically attended RSV LRTI and RSV hospitalization (and the relevant HRU) are expected to be lower in Season 2 (infant's second RSV season) than that in Season 1, combining the events from Season 1 and Season 2 may not confer value in addition to the individual summary for each season • In section 3.5.1, defined a RSV sample analysis window [-7, 14] days for medically attended RSV LRTI based on blinded data review • In sections 3.5 and section 3.7, clarified the potential bias of directly comparing MEDI8897/MEDI8897 with Palivizumab/Palivizumab: if dropouts in Season 1 are associated with efficacy or safety. If dropouts in Season 1 are associated with efficacy or safety, MEDI8897/MEDI8897 and Palivizumab/Palivizumab are not from the same population. • Demographics, baseline characteristics, selected efficacy and safety summaries will be provided for CHD subjects and CLD subjects separately. • Added section 3.5.1.3 Sensitivity Analyses of incidence of medically attended LRTI due to RT-PCR-confirmed RSV to evaluate the impact of wrong treatment, missing and out-of-window active doses on the primary efficacy endpoint analysis • In section 3.5.3, the summary of subjects with at least one medically attended LRTI will be broken down by RSV status only. Clarified rules to define severity among multiple medically attended LRTIs, and among multiple hospitalizations due to any respiratory illness, separately. • In section 3.6.1, removed HUR summaries for Season 1 + Season 2; removed HRU summaries for the following medically attended LRTI categories: non-RSV LRTI (protocol defined), RSV LRTI (non-protocol defined), non-RSV LRTI (non-protocol defined); added analyses on pre-specified OTC medications (analgesics/antipyretics), prescribed medications

		(systemic antibacterial agents), and anti-wheezing medications; removed original analyses on overall prescriptions or OTC medications • In section 3.6.2, removed caregiver burden summaries for Season 1 + Season 2; removed caregiver burden summaries for the following medically attended LRTI categories: non-RSV LRTI (protocol defined), RSV LRTI (non-protocol defined), non-RSV LRTI (non-protocol defined). • In section 3.6.3 and section 3.6.4, added box plot for serum antibody levels for all subjects by treatment group and by visit • In section 3.6.4, added summary of RSV exposure (≥ 4-fold rise in serum antibody levels to any RSV antigen from the previous timepoint); added Post-F antigen for seroresponses in MEDI8897 • In section 3.6.5, updated the scope of genotypic and phenotypic analyses, which will be detailed in a separate virology plan • In section 3.7, added definition of treatment-emergent AEs for each reporting periodIn section 3.7, clarified the scope of safety summaries for Season 1 + Season 2: Season 1 + Season 2 safety summary would provide 2-year incidence of AE. Considering the potential bias of directly comparing MEDI8897/MEDI8897 with Palivizumab/Palivizumab, only several key safety summaries will be repeated for Season 1 + Season 2. • In section 3.7.1, updated the definition for non-treatment emergent AE/SAE and clarified that pre-planned surgeries that occur during the study for CHD subjects are a part of non-treatment emergent AE/SAE • In section 3.7.2, added supplementary analysis of AESI based on SMQs/study-specific PTs, and updated the definition for AESI to align with the Safety Strategy and Management Plan • In section 3.7.3, changed “skin reactions” to “IP-related skin reactions” and clarified that skin hypersensitivity analyses are included in the IP-related skin reactions

		• In section 3.7.5, added "3 days" to time relative to dosing; removed TEAE summaries by vaccine status throughout the study; clarified that Season 1 AEs will also be summarized for CLD subjects, CHD subjects, subjects with GA < 29 weeks, subjects with GA < 29 weeks and without CLD or CHD, and CLD subjects with GA < 32 weeks. The Season 2 AEs will also be provided for CLD subjects, CHD subjects and CLD subjects with GA < 32 weeks. The purpose of adding the new sub-populations is to evaluate safety profile for the infants who are recommended to received palivizumab by American Academy of Pediatrics. • In section 3.7.6, removed toxicity grade of BUN, since toxicity grade of BUN in not defined in Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events • In section 3.8, clarified the treatment groups to be included in Season 2 ADA summaries and Season 1 + Season 2 ADA summaries: subjects in MEDI8897/MEDI8897 and Palivizumab/Palivizumab arms only have one baseline ADA measurement, which is the last non-missing measurement prior to 1st dose of Season 1, so corresponding reporting period should be Season 1 + Season 2, instead of Season 2 only. Subjects in Palivizumab/MEDI8897 arm receive MEDI8897 only in Season 2, so their reporting period for ADA to MEDI8897 should be Season 2. • In section 3.8, clarified that ADA influence of PK will be reported in the CSR (not in a separate PK report); clarified definitions for ADA persistent positive and transient positive. • In section 3.9, clarified that serum concentrations will be summarized by descriptive statistics within the CSR. Removed reference to non-compartmental method and PK parameters, as PK will be evaluated using a model-based approach only (described in a separate analysis plan and reported outside the CSR). This change has been made prior to DBL for Primary Analysis. Clarified how ADA influence on PK will be evaluated.

		• Added section 3.10 Impact on Analyses due to COVID-19 Pandemic • Editorial changes for clarity, including updating “3 months” and “6 months” to “3.0 months” and “6.0 months”. • Added Appendix 2 Analysis Window for ADA/RSV Neutralizing Antibody/RSV Serology • Added Appendix 3 Analysis Window for Clinical Lab Data • Added Appendix 4 Imputation Rule for Partial Adverse Event Start Date • Added Appendix 5 Imputation Rule for Other Partial Dates

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

Criteria for meeting the protocol-defined endpoint of Medically Attended RSV LRTI – for subjects without underlying lung disease

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive by central laboratory real-time RT-PCR assay	**Documented physical examination 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

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = real time reverse transcriptase-polymerase chain reaction; LRTI = lower respiratory tract infection;
Note: One item from each column is required to meet the case definition of RSV LRTI.

Criteria for meeting the protocol-defined endpoint of Medically Attended RSV LRTI – for subjects with underlying Lung Disease (CLD or CHD)

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive by central laboratory real-time RT-PCR assay	**Documented physical examination findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration • Prescription of new or increased (from baseline) dose of medications including bronchodilators, steroids, diuretics, cardiac medications

CHD = congenital heart disease; CLD = chronic lung disease; LRTI = lower respiratory tract infection; 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 Adverse Event Start Date

If date of last dosing prior to AE onset is known:

- Step 1:
  - Assume (date of last dosing prior to AE + 1 day) if AE started <= 7 days after dosing.
  - Assume (date of last dosing prior to AE + 7 days) if AE started 8 - 14 days after dosing.
  - Assume (date of last dosing prior to AE + 14 days) if AE started >14 days after dosing.
  - Assume (date of last dosing prior to AE + 1 day) if range of days started after dosing was not selected.
- Step 2: if only year of partial AE start date is known, check if year of partial AE start data is after the imputed AE start date; if year and month of partial AE start date is known, check if year and month of partial AE start data is after the imputed AE start date. If yes, then re-impute the AE start date
  - Assume January 1st if only year of the partial AE start date is known
  - Assume 1st day of the month if year and month of the partial AE start date is known

If date of last dosing prior to AE onset is unknown:

- Partial AE start dates where only the year is known:
  - If year is different from the year of any dose date, assume January 1st;
  - If year is same as the year of a dose 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. If the imputed date is after the known AE start year, assume (previous dose date + 13 days).
    - Assume (dose date + 14 days) if AE started >14 days after dosing. If the imputed date is after the known AE start year, assume (dose date -1) provided that it is not the first dose date.
    - Assume (dose date + 1 day) if range of days started after dosing was not selected.

- Partial AE start dates where only the month and year are known:
  - If year and month is different from the year and month of any dose date, assume 1st day of the month;
  - If year and month is same as the year and month of a dose 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. If the imputed date is after the known AE start month, assume (previous dose date + 13 days).

- Assume (dose date + 14 days) if AE started >14 days after dosing. If the imputed date is after the known AE start month, assume (dose date -1) provided that it is not the first dose date.
- Assume (dose date + 1 day) if range of days started after dosing was not selected.

Appendix 5 Imputation Rule for Other Partial Dates

- Partial dates where only the year is known: for start dates assume January 1st; for stop dates assume December 31st.
- Partial dates where only the month and year are known: for start dates assume the first of the month; for stop dates assume the end of the month.
- In addition, if a concomitant medication is associated with an AE and with partial dates, the concomitant medication start date will be imputed with the either observed or imputed AE start date. If there are multiple associated AEs, the earliest AE start date will be used for imputation. The concomitant medication end date will be imputed by the rules described above where applies.

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