Statistical Analysis Plan	
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A Phase III, Single-Arm, Open-Label Study to Evaluate the Safety, Pharmacokinetics, Anti-Drug Antibody, and Anti-RSV Neutralizing Antibody Following Administration of 2 Doses of Nirsevimab Given 5 to 6 Months Apart in Infants with Congenital Heart Disease, Chronic Lung Disease, Immunocompromise, Down Syndrome, or Born Pre-Term in Japan (JUBILUS)

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Vaccines and Immune Therapies

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Table of Contents

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ACQ	Asthma Control Questionnaire
ADA	Anti-Drug Antibody
AE	Adverse event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Class
ATP	According to Protocol
BLQ	Below the Limit of Quantification
BMI	Body mass index
CHD	Congenital Heart Defect
CI	Confidence Interval
CLD	Chronic Liver Disease
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
%CV	Coefficient of Variation
CV	Cardiovascular
DOB	Date of Birth
ECG	Electrocardiogram
GA	Gestational Age
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HADS	Hospital Anxiety and Depression Scale
Ig	Immunoglobulin
IM	Intramuscular
IMP	Investigative Medicinal Product
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intent-to-Treat
IV	intravenous
IXRS	Interactive voice/web response system
LLQQ	Lower Limit of Quantification

Abbreviation or Specialized Term	Definition
LRTI	Lower Respiratory Tract Infection
LSMD	Least Squares Mean Difference
MA	Medically Attended
nAb	Neutralizing Antibody
NOCD	New Onset Chronic Disease
PD	Pharmacodynamic
PK	Pharmacokinetics
PSSR	Product Specific Safety Requirements
PT	Preferred Term
RDMS	Regulatory Document Management System
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase–Polymerase Chain Reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SID	Subject ID
SMQ	Standard MedDRA Query
SOC	System Organ Class
TA	Therapeutic Area
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TFL	Tables, Figures, and Listings
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	7/10/2023 (Ed. 1.0)	Initial approved SAP	N/A	N/A
Data presentation	11/11/2024 (Ed. 2.0)	• 2: Considerations for participants receiving Palivizumab during the study added • 3.4.5: Handling of missing serum concentrations added per reporting standards • 4.1.3.1: Analysis sets for demographics and Family History summaries updated • 4.3.2: deleted text "PK parameters will also be examined for participants who undergo cardiac surgery with cardiopulmonary bypass." • Table 2: reporting periods updated to "X days after dose" style	Yes	Specified to support study objectives and align with study CSP and procedures
Statistical analysis method for secondary endpoint(s)	11/25/2024 (Ed. 3.0)	• 1.1: Handling of intercurrent events added for secondary endpoints • 4.3.2: PK data impacted by replacement dose will not be included in summary tables • Appendix 2 and appendix 3 analysis windows updated	Yes	Improved clarity and logic for handling out-of-window study procedures and administration of replacement doses or Palivizumab

1 INTRODUCTION

A single dose of nirsevimab is effective at preventing RSV LRTI for at least 5 months (MELODY) and has an acceptable safety profile (MELODY, MEDLEY, MUSIC). RSV seasons in temperate regions are typically less than 5 months duration but longer seasons predictably occur in certain regions in Japan. An additional dose of nirsevimab administered 5 to 6 months after the 1st dose may optimize protection for infants at higher risk living in certain regions with extended RSV seasons. There is no data on safety or PK of nirsevimab after 2 doses 5-6 months apart, although safety of nirsevimab at 1st and 2nd RSV season of life one year apart has been established.

This study will evaluate the safety, PK, occurrence of ADA, and anti-RSV neutralizing Ab after 2 doses of nirsevimab. The target population in this study is higher risk infants in Japan ≤12 months old with CLD, CHD, immunodeficiency, or Down syndrome, or born pre-term, according to Japanese palivizumab dosing guideline.

1.1 Study Objectives

Type	Objective	Endpoints/Estimands
Primary		
Safety	To evaluate the safety and tolerability of 2 doses of nirsevimab administered 5 to 6 months apart	**Treatment:** One dose of nirsevimab as a single, fixed intramuscular (IM) dose of 50 mg if body weight is <5 kg or 100 mg if body weight is ≥5 kg followed with a 2nd fixed IM dose of 50 mg if body weight is <5 kg or 100 mg if body weight is ≥5 kg administered 5 to 6 months following the 1st dose. **Population:** As-treated set 2, all participants who have received the 2 doses of IMP **Endpoint:** Incidence of all treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and new-onset chronic diseases (NOCDs) through 360 days post 2nd dose **Intercurrent Events:** Intercurrent events are defined as study discontinuations prior to Day 151 post 2nd dose. Intercurrent events will be handled using while on treatment strategy. That is, for participants with intercurrent events, treatment-emergent AEs, SAEs, AESIs, and NOCDs prior to the intercurrent events will be included in the analysis. **Population-level Summary:** The number and percentage of participants with TEAEs, TESAEs, AESIs, and NOCDs will be summarized by SOC and PT overall

Type	Objective	Endpoints/Estimands
Secondary		
Pharmacokinetics (PK)	To evaluate the PK of 2nd dose of nirsevimab administered 5 to 6 months after the first dose	**Treatment:** same as primary **Population:** PK Analysis Set **Endpoint:** Nirsevimab serum concentrations **Intercurrent Events:** Out-of-window PK assessments, out-of-window Nirsevimab dose, or receipt of replacement Nirsevimab dose(s) may result in exclusion of specific observations from PK summaries. **Population-level Summary**: Serum concentrations will be summarized by visit with descriptive statistics including number of observations, geometric mean, geometric standard deviation, %CV, arithmetic mean, arithmetic standard deviation, median, minimum, and maximum.
ADA	To evaluate ADA responses to 2 doses of nirsevimab administered 5 to 6 months apart	**Treatment:** same as primary **Population:** ADA Analysis Set **Endpoint:** Occurrence of ADA to nirsevimab in serum **Intercurrent Events**: Out-of-window ADA assessments or out-of-window Nirsevimab dose may result in exclusion of specific observations from ADA summaries. **Population-level Summary**: the incidence of ADA to nirsevimab will be summarized including the number and percentage of participants who are ADA positive by visit. Descriptive statistics will be presented by visit including median, minimum, and maximum ADA titre.
Anti-RSV neutralizing Ab	To determine anti-RSV neutralizing antibody (nAb) levels in serum to 2 doses of nirsevimab administered 5 to 6 months apart	**Treatment:** same as primary **Population:** Anti-RSV nAb Analysis Set **Endpoint:** Anti-RSV neutralizing Ab levels (IU/mL) in serum **Intercurrent Events**: Out-of-window nAb assessments, out-of-window Nirsevimab dose, receipt of Palivizumab, or replacement Nirsevimab dose(s) may result in exclusion of specific observations from anti-RSV nAb summaries. **Population-level Summary**: serum anti-RSV neutralizing antibody levels will be summarized by geometric mean titer (GMT), %CV, and geometric mean fold rise (GMFR) and corresponding 95% confidence interval (CI) by visit
Exploratory		
MA-RSV LRTI	To assess the occurrence of MA-RSV LRTI (inpatient and outpatient) and hospitalization due to RT-PCR-confirmed	• Occurrence of MA-LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150- and 360-days post 2nd dose

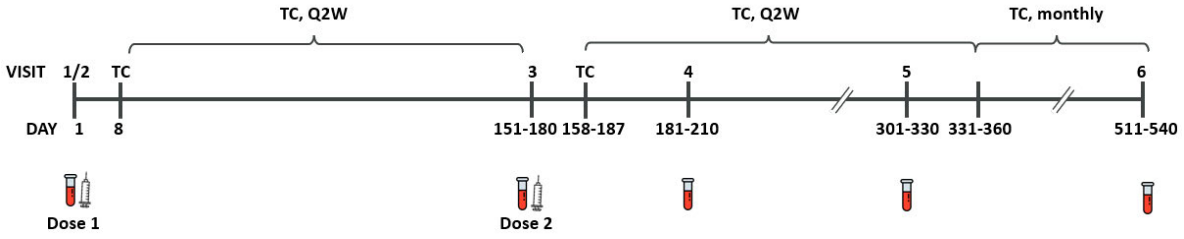
Type	Objective	Endpoints/Estimands
	RSV following administration of 2 doses of nirsevimab 5 to 6 months apart	• Occurrence of hospitalizations due to RT-PCR-confirmed RSV through 150- and 360-days post 2nd dose
RSV-resistance monitoring	To characterize resistance to nirsevimab through genotypic and phenotypic analysis	• Genotypic analysis and susceptibility of RSV variants to neutralization by nirsevimab

Ab = antibody; ADA = anti-drug antibody; IMP = investigational medical product; MA-LRTI = medically attended lower respiratory tract infection; PT = preferred term; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; SOC = system organ class

1.2 Study Design

This study is a phase III, open-label, uncontrolled, 2-dose (Day 1 & Day 150-180) study to assess the safety, PK, occurrence of ADA to nirsevimab, and anti-RSV neutralizing Ab in infants with CHD, CLD, immunocompromise, Down syndrome, or born pre-term ≤35 weeks GA. The study is planned to be conducted in Japan. Approximately 30 participants will be enrolled. Participants in the first year of life will receive the 1st dose of nirsevimab as a single, fixed IM dose of 50 mg if body weight is <5 kg or 100 mg if body weight is ≥5 kg. A 2nd fixed IM dose of 50 mg if body weight is <5 kg or 100 mg if body weight is ≥5 kg will be administered 5 to 6 months following the 1st dose. All participants will be followed until the end of study follow-up period (360 days after 2nd dose or last dose administered in the study).

Figure 1 Study Design



Q2W = Once 2 weeks; TC = telephone contact
First telephone contact post 2nd dose occurs 7 days post dose.
Visit 4: 30 days post 2nd dose
Visit 5: 150 days post 2nd dose
Visit 6: 360 days post 2nd dose

1.3 Sample Size and Number of Participants

Approximately 33 participants will be enrolled to receive 2 IM doses of nirsevimab to evaluate the safety, PK, and ADA to nirsevimab, and anti-RSV neutralizing Ab which will

be assessed descriptively. The proposed sample size of 33 participants in this study accounts for conservative estimate of 7% participant drop-out (based on 5% drop-out observed in Season 1 prior to Day 151 in MEDLEY study) between 1st and 2nd doses to get 30 participants exposed to 2 IM doses of nirsevimab in this study will provide about 79% probability of observing at least one AE if the true event rate is 5%. Thirty-three participants are considered to provide adequate sample size to evaluate the safety and to describe nirsevimab serum concentrations, and ADA to nirsevimab, and anti-RSV neutralizing Ab following 2nd dose.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

- Analysis of ADA and anti-RSV nAb objectives will be based on ADAS and NABS analysis populations, respectively.
- PK analysis set definition clarified by stating that protocol deviations may result in exclusion or data collected after the protocol deviation excluded

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

There are two planned analyses for this study: a primary analysis and a final analysis. The primary analysis will take place after all participants have been followed through visit 5 (approximately 150 days after the second dose). The final analysis will be conducted after all participants have completed the final visit (Visit 6) of the study (approximately 360 days after the second dose).

3.2 Analysis Populations

The study population of infants with CHD, CLD, immunocompromise, Down syndrome, or born pre-term ≤35 weeks GA in Japan will be described in five analysis populations as well as an "All Screened Participants" set. These analysis sets are presented in Table 1.

Table 1 Populations for Analysis

Population/analysis set	Description
All Screened Participants (SPS)	Includes all individuals screened for enrolment.
As-Treated Set 1 (ATS1)	The As-treated set 1 consists of all participants who receive at least 1 dose of IMP.

As-Treated Set 2 (ATS2)	The As-treated set 2 consists of all participants who receive the 2 doses of IMP.
PK Analysis Set (PKS)	Participants who receive at least 1 dose of IMP and who have at least 1 quantifiable serum PK observations. Protocol deviations that impact the PK results may result in exclusion of the participant or data. All PK summaries will be based on this analysis set.
ADA Analysis Set (ADAS)	Participants in ATS2 who have at least 1 quantifiable ADA observations after the second dose. Protocol deviations that impact the ADA results may result in exclusion of the participant or data.
Anti-RSV nAb Analysis Set (NABS)	Participants in ATS2 who have at least 1 quantifiable serum nAb observation(s) after the second dose. Protocol deviations that impact the nAb results may result in exclusion of the participant or data.

3.3 Statistical Hypothesis

There is no formal hypothesis testing for this study.

3.4 General Considerations

3.4.1 General Study Level Definitions

All safety data (scheduled and unscheduled) will be presented in the data listings.

Categorical data will be summarized by the number and percentage of participants in each category.

Continuous variables will be summarized by mean, median, standard deviation, minimum, and maximum. Some continuous variables will also be summarized by geometric mean, geometric SD, and % Coefficient of Variation (%CV). Descriptive statistics will only be presented if $n > 3$. If no participants have data at a given time point, $n = 0$ will be presented. If $n < 3$, only the n, minimum and maximum will be presented, and if $n = 3$, only the n, median, minimum and maximum will be presented; the other descriptive statistics will be left blank.

The CI to a geometric mean will be determined by log-transforming the observations, calculating the 95% confidence limits to the arithmetic mean of the transformed data and

back-transforming the confidence limits with the exponential function. Natural log will be used unless otherwise specified.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator. The denominator should be clearly presented in each table.

Rounding should be the last operation in the treatment of data. There should be no rounding of intermediate results during the calculation of any derived value. Zeros at the end of a number should be retained.

All statistical analyses and production of tables, figures, and listings will be performed using SAS® version 9.4 or higher. All other requirements and specifications for programming and presentation of TFLs will be specified in the TFL shells document.

3.4.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the dose of IMP. These can be assessments from screening, Visit 1 or unscheduled or repeated assessments prior to IMP administration.

3.4.3 Change from Baseline

Change from baseline will be defined as the value post-dosing minus the baseline defined, for each timepoint.

Percent change from baseline will be calculated as:

Percent change from baseline = ([visit value – baseline value]/baseline value) ×100

3.4.4 Study Day

Study Day 1 is defined as the date of first dose of IMP. Visit 1 (Screening) and Visit 2 (Day 1) may take place on the same day.

For visits (or events) that occur on or after first dose of study treatment, study day is defined as (date of visit [event] – date of first dose of study treatment + 1).

For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] – date of first dose of IMP). There is no study day 0 defined for this study.

3.4.5 Handling of Missing Data

Clinical Laboratory Parameters

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.

Adverse Events

Imputation rules for partial dates are described in Appendix 4. In general, there will be no other imputation of missing data unless explicitly stated.

Serum Concentrations

Individual concentrations below the LLOQ of the bioanalytical assay are reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant summaries. Individual plasma concentrations that are Not Reportable are reported as NR and those that are missing are reported as NS (No Sample) in the listings.

Any values reported as NR or NS are excluded from the summary tables and corresponding figures. At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly. At a time point where more than 50% (but not all) of the values are NQ, the mean, SD, gmean and gCV% are set to Not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set to NQ. If all concentrations are NQ at a time point, no descriptive statistics are calculated for that time point. The mean, SD, gmean, minimum, median and maximum are reported as NQ and the gCV% as NC.

The number of values below LLOQ (n < LLOQ) are reported for each time point together with the total number of collected values (n).

3.4.6 Visit Window

Scheduled visits will be analysed as captured in the electronic case report forms. Early discontinuation visits will be mapped to the chronologically closest not-performed visit.

For the visit-based summaries for PK, ADA, RSV neutralizing antibody, 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. 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 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 participant's visit, ADA positive will be reported.

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

The partial dates imputation rules are described in Appendix 4.

3.4.7 Handling of Unscheduled Visits

Unscheduled measurements will not be included in by-visit summaries; they may contribute to the baseline and post-baseline value, where applicable (including definition of baseline or identification of worst post-baseline evaluations). Visits for visit-based data will follow a windowing convention described in Section 3.4.6.

If there is an unscheduled and a scheduled assessment with the same date, the unscheduled assessment will be assumed to be a repetition and the scheduled results will be used for summaries.

Participant data listings will include data obtained from unscheduled visits chronologically. Across-visits summaries, e.g., summaries of occurrences will include unscheduled assessments.

3.4.8 Multiplicity/Multiple Comparisons

No hypotheses are planned to be formally tested using inferential statistics in this study, so multiplicity is not required.

3.4.9 Handling of Protocol Deviations in Study Analysis

Protocol deviations will be captured and presented as described in Section 4.1.4. The protocol deviations and their categorization as “important” or “non-important” are pre-defined as far as possible before inclusion of the first participant. Final categorization of protocol deviations and actions for analysis will be done continuously during the study but finalized prior to the final analysis and any interim analysis.

For details on definition of protocol deviations, please refer to the study-specific Protocol Deviation Specification.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivations and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication and study drug compliance.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Not applicable.

4.1.1.2 Presentation

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to study completion including potential re-screening. This will include summaries of participant eligibility as well as treatment received for all screened patients.

For each participant, the dates for each visit they participated in will be listed.

Participant disposition will be summarized and will include the following information: number of participants screened and dosed (See section 4.1.7), number and percentage of participants completing the study, and the number and percentage of participants who were withdrawn (including primary reason for withdrawal). The summary will be done for all screened participants.

Participant discontinuations will be listed including the date of study exit, duration of participation and primary reason for discontinuation.

Participants and/or data excluded from the PKS (see Section 4.1.2) will be listed including the reason for exclusion.

The analysis set to be used for these summaries and listings is the SPS (see Section 4.1.2).

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The analysis population definitions are presented in Table 1.

Before database lock for the planned analyses, protocol deviation categories and the analyses populations will be produced for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which participants and/or participant data will be excluded from certain analyses if required. Decisions made regarding the exclusion of participants and/or participant data from analyses will be documented and approved by the sponsor.

4.1.2.2 Presentation

The number of participants included in each analysis set will be reported. For each analysis set, the number of participants excluded and the number for each reason will be reported.

A listing will be provided presenting each participant's inclusion in each analysis set.

4.1.3 Demographics and Baseline Characteristics

4.1.3.1 Definitions and Derivations

Demographic information related to sex assigned at birth, age at baseline determined using the CRF age calculation, GA (weeks), ethnicity, race, weight (kg) on Day 1, birth weight (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 day-care (yes/no), Down syndrome (yes/no), and cystic fibrosis (yes/no) will be summarized for ATS1 and ATS2. Participants will be excluded from the summary (e.g., means and percentages) of an individual parameter if data are missing.

In addition, family history of atopy (including asthma, hay fever, eczema, wheezing) will be summarized for participants in ATS1 and ATS2.

Age

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

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

Once age at screening is converted to months,

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

Rounding will be the final step of any age calculations. Age calculations will always be rounded down.

4.1.3.2 Presentation

Demographics will be summarized for ATS1 and ATS2. The denominator for percentages will be the number of participants in the Analysis Set being summarized.

4.1.4 Protocol Deviations

4.1.4.1 Definitions and Derivations

Important deviations from the protocol (IPDs) may lead to the exclusion of participants or data from the PKS, ADAS, or NABS. Deviations will be assessed and classified during the study and finalized before database lock. IPDs include those deviations from the protocol that are likely to have an impact on the perceived safety of study treatments or outcome assessment.

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

- Inclusion criteria
- Exclusion criteria
- Study withdrawal
- Investigational product deviation
- Planned study procedures
- Possible impact on safety assessments

- Potential to interfere with serum concentrations of nirsevimab or interpretation of PK result
- Potential to interfere with the generation or interpretation of ADA result
- Potential to interfere with serum concentrations of anti-RSV nAb or interpretation of anti-RSV nAb result

All important protocol deviations will be listed. A qualitative summary table will be provided.

4.1.4.2 Presentation

IPDs will be listed including the deviation type. The number of participants with IPDs will be summarized qualitatively by deviation type. The denominator for percentages will be the number of participants in the ATS1.

4.1.5 Medical History and Concomitant Disease

4.1.5.1 Definitions and Derivations

Medical history will be coded using the medical dictionary for regulatory activities (MedDRA) dictionary.

Any medical history which is ongoing at time of informed consent will be considered an ongoing condition.

4.1.5.2 Presentation

Summary tables of medical history and ongoing conditions will be produced by system organ class (SOC) and preferred term (PT) for ATS1. Sorting is by internationally agreed order for SOC, and alphabetically for PT within SOC.

Number and proportion of patients with Immunodeficiency, CLD, CHD, Down-syndrome, and Pre-term birth (as described in CSP inclusion criteria 2) will be summarized overall.

4.1.6 Prior and Concomitant Medications

4.1.6.1 Definitions and Derivations

All medications will be coded using the World Health Organization (WHO) Drug Global dictionary.

Medication is regarded as prior if it is stopped before the 1st dose of study drug. A medication will be regarded as concomitant if the start date is on or after the date of the 1st dose of study drug or if it started on or before the 1st dose of study drug and ongoing after the 1st dose of study drug.

The handling of partial/missing dates is detailed in Appendix 4.

4.1.6.2 Presentation

Prior and concomitant medications will be listed based on the ATS1 population.

4.1.7 Study Drug Exposure

4.1.7.1 Definitions and Derivations

Not applicable.

4.1.7.2 Presentation

Exposure will be summarized in the Disposition table and listed for all participants.

4.2 Safety Analysis

Estimated incidence rates and 95% confidence intervals (Clopper-Pearson Exact) will be reported for all treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and new-onset chronic diseases (NOCDs) through 360 days post 2nd dose to evaluate the safety and tolerability of 2 doses of nirsevimab administered 5 to 6 months apart.

The primary analysis of the primary endpoint will be conducted using As-Treated Set 2 (ATS2) when all enrolled participants have been followed through Visit 5 (around 150 days post 2nd dose). Time to onset will be calculated from time of first and second dose where relevant.

No formal hypothesis testing will be done.

Summaries of safety data may be repeated at the final analysis, excluding the data of study participants who receive Palivizumab during the follow-up period. Only records from samples collected after administration of Palivizumab will be excluded.

4.2.1 Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be coded by MedDRA version 25.1 or higher and the type, incidence, severity and relationship to study investigational product will be summarized. Specific AEs will be counted once for each participant 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 participant, the highest severity and level of relationship observed will be reported. All treatment-emergent AEs (TEAEs) and treatment-emergent SAEs (TESAEs) occurring through the follow-up period (360 days after the 2nd or last dose administered in the study) will be summarized overall, as well as categorized by MedDRA SOC and PT. In addition, the TEAEs occurring at 1% or higher will be reported by PT.

Table 2 Reporting Period of Adverse Events

Reporting Period	Population	AEs
From 1st dose through 360 days after 2nd dose. (Primary Objective)	ATS2	Any AEs that started post 1st dose, and prior to the end of 360 days after the second dose.
From 1st dose through administration of second dose	ATS2	Any AEs that started post 1st dose, and prior to the administration of 2nd dose
From 1st dose through 360 days after the last dose	ATS1	Any AEs that started post 1st dose, and prior to the end of 360 days after the last dose

4.2.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will include immediate (type 1) hypersensitivity reactions including anaphylaxis, immune complex disease, and thrombocytopenia.

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 may be conducted which runs the narrow Standardised MedDRA Query (SMQ) for hypersensitivity, the broad SMQ for anaphylactic reaction, and a study specific query based on compatible PTs for thrombocytopenia and immune complex disease occurring in the database. SMQs and PTs for AESIs are defined in the PSSR. The PSSR will be provided by the Patient Safety Team before DBL for Primary Analysis.

4.2.3 Clinical Laboratory Parameters and Other Safety Evaluations

Individual hematology and serum chemistry samples as well as vital signs will be collected at baseline and at subsequent visits as specified in the schedule of activities. All clinical laboratory parameters and vital signs will be listed.

4.3 Pharmacokinetic Analyses

4.3.1 Definitions and Derivations

Not applicable

4.3.2 Presentations

Serum concentrations of nirsevimab at selected time points will be evaluated to characterize the PK of nirsevimab after the second IM dose. Serum concentrations will be summarized by time point with descriptive statistics including number of observations, geometric mean, geometric standard deviation, %CV, arithmetic mean, arithmetic standard deviation, median, minimum, and maximum. In addition, PK data pooled with data from other studies may be analysed using population PK methods and reported outside of the CSR.

PK data of participants after receiving a replacement dose will be included in the listing but excluded from summary tables.

4.4 Immunogenicity and Anti-RSV Neutralizing Antibody Assessments

4.4.1 Definitions and Derivations

Not applicable

4.4.2 Presentation

Serum anti-RSV nAb levels will be summarized by geometric mean titer (GMT), % CV, and geometric mean fold rise (GMFR) with corresponding 95% CI. Descriptive summaries of nAbs will be provided by time point for participants in the NABS. Summary, including n(%) and 95% CI, of GMFR Seroresponse (defined as a >=4-fold increase from baseline) will be described from baseline and from second dose.

Anti-RSV nAb data of participants after receiving a replacement dose will be included in the listing but excluded from summary tables.

Line plots with 95% confidence intervals of GMT and GMFR of serum anti-RSV neutralizing antibodies in logarithmic scale with base 10 will be provided.

Scatter plots of serum RSV neutralizing antibody levels versus serum nirsevimab concentration will be shown by post-baseline visit. Pearson correlation between log10-transformed serum RSV neutralizing antibody level and log10-transformed serum nirsevimab concentration will be provided. Summaries of RSV-nAb data may be repeated at the final analysis, excluding the data of study participants who receive Palivizumab during the follow-up period. Only records from samples collected after administration of Palivizumab will be excluded.

4.5 Anti-Drug Antibodies

4.5.1 Definitions and Derivations

1. Persistent positive is defined as positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment

2. Transient positive is defined as negative at 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.

3. ADA incidence is defined as the percentage of participants who are treatment-emergent ADA positive. Treatment-emergent ADA positive is defined as the sum of treatment-induced ADA positive (ADA negative at baseline and post-baseline ADA positive), and treatment boosted ADA positive (ADA positive at baseline and ≥ 4-fold increase in titre from baseline titre level at ≥1 post-baseline timepoint).

4. ADA prevalence is defined as the percentage of participants who are ADA positive at baseline and/or post-baseline.

5. nAb incidence is defined as the percentage of participants who are nAb negative at baseline (or ADA negative at baseline) and nAb positive at any post-baseline visit.

6. nAb prevalence is defined as the percentage of participants who are nAb positive at any time during the study, including baseline and/or post-baseline.

7. Anti-YTE incidence is defined as the percentage of participants who are anti-YTE negative at baseline (or ADA negative at baseline) and anti-YTE positive at any postbaseline visit.

8. Anti-YTE prevalence is defined as the percentage of participants who are anti-YTE positive at any time during the study, including baseline and/or post-baseline.

4.5.2 Presentation

The number and percentage of participants who develop anti-nirsevimab antibodies will be summarized at each visit. 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 nirsevimab will also be summarized. The ADA summaries will be based on the participants in the ADAS.

An additional table will summarize the number and percentage of participants positive for ADA at baseline and positive at any post-baseline time point. Anti-drug antibody prevalence, ADA incidence, treatment-boosted ADA positive, and treatment-induced ADA positive will also be summarized. Prevalence and incidence of ADA against nirsevimab

YTE domain, prevalence and incidence of neutralizing antibody of nirsevimab will be presented. The percentage of participants who were persistent positive and transient positive will also be presented.

To evaluate the impact of ADA on efficacy and safety, TEAE and SAE by SOC and PT based on MedDRA will be summarized by ADA post-baseline status (i.e., at least one post-baseline ADA positive or not through 360 days post dose). The safety summaries will be based on the ADAS.

4.6 Exploratory Analysis

4.6.1 MA-RSV LRTI

To assess the occurrence of MA-RSV LRTI (inpatient and outpatient) and hospitalization due to RT-PCR-confirmed RSV among the ATS2 population the following will be collected:

- Occurrence of MA LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150- and 360-days post 2nd dose

- Occurrence of hospitalizations due to RT-PCR-confirmed RSV through 150- and 360-days post 2nd dose

The 95% Clopper-Pearson (exact) confidence interval of the incidence rate will be calculated. For participants with at-least one MA-RSV LRTI event or hospitalization occurring between the administration of the first dose and the specified timepoint, the first occurrence will be included in the summary. All subsequent occurrences will be listed.

If there are a high number of participants lost to follow-up, a sensitivity analysis may be conducted in which only participants who complete follow-up are included.

4.6.2 RSV-resistance monitoring

Genotypic analysis of the full-length mature F protein will be conducted on all RSV-positive isolates confirmed centrally using the Lyra RSV + human metapneumovirus real-time RT-PCR assay manufactured by Quidel Corporation. RSV genotypic analysis will report the amino acid changes in the mature F protein sequence compared to contemporary RSV A and RSV B reference strains. Phenotypic analyses will report changes in susceptibility of engineered recombinant RSV variants to nirsevimab neutralization compared to laboratory-derived reference viruses.

A detailed description of participants/samples to be analysed, 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.

5 INTERIM ANALYSIS

There is no planned Interim Analysis for this study.

6 REFERENCES

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017].

7 APPENDICES

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/Laboratory data

Scheduled Study Day	Analysis Windows
Day 1	≤ 1
Day 151	2 – 180
Day 181	181-247[a]
Day 301	248-406
Day 511	≥ 407

[a] For participants who receive both scheduled doses of IP: Day 151 assessments that occur outside of window and within the Day 181 window instead will not be considered for by visit summaries

Appendix 3 Analysis Window for PK

Scheduled Study Day	Analysis Windows
Day 1	≤ 1
Day 151	151-180
Day 181	181-210[a]
Day 301	301-330
Day 511	511-540

[a] For participants who receive both scheduled doses of IP: Day 151 assessments that occur outside of window and within the Day 181 window instead will not be considered for by visit summaries

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 of 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.

In case of missing data in collection of AE start date or start time, which is not reported as unknown:

- AEs with completely unknown start dates will be imputed with the date and time of dosing, unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of Screening and a time of 00:00.

- AEs with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to the dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE, then the time will also be imputed with 00:00.

- Missing day: impute with the 1st of the month, unless the month and year in which the AE started is a month and year in which IMP was administered, then the day will be imputed with the first day on which IMP was administered in that month. If this results in a start date after the end date, then the day will be imputed with the first day of the month.

- Missing month: impute with the 1st month in which IMP was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which IMP was administered, then the month will also be imputed with JAN.

- Missing day and month: impute with the day and month of dosing. If this results in a start date after end date, then the day and month will be imputed with 01JAN. If the year is not a year in which IMP was administered, then the day and month will also be imputed with 01JAN.

- Missing year: impute with the year of dosing

- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

- When imputing a start date, care should be taken to ensure the start date is sensible, i.e., prior to the end date.

Imputation Rule for Partial Concomitant Medications Dates

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

- If a ConMed is co-reported with an AE:
  - The ConMed start date will be imputed with either observed or imputed AE start date. If there are multiple co-reported 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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