Clinical Study Protocol	
Study Intervention	Nirsevimab (MEDI8897)
Study Code	D5290C00009
Version	Version 2.0
Date	19 May 2023

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

Sponsor Name:

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This protocol has been subject to a peer review according to AstraZeneca Standard Procedures. The protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Version Scope: Version 2.0, Japan

Brief Title:

A study to investigate the safety, pharmacokinetics, occurrence of anti-drug antibody, and anti-RSV neutralizing antibody following 2 doses administration of nirsevimab (MEDI8897) in infants with certain health conditions or born pre-term in Japan

Study Phase: Phase III

Study Physician Name and Contact Information including administrative structure will be provided separately.

DOCUMENT HISTORY	
Document	**Date**
CSP Version 1.0	22- Mar -2023
CSP Version 2.0	19- May -2023

CSP Version 2.0 [19-May-2023]

Overall Rationale for the Modification:

CSP Version 2.0 (dated 19 May 2023)

The principal reason for this protocol amendment is to revise the period of once 2 weeks (Q2W) Telephone Contact after 2nd dose of MEDI8897, aligned to PMDA requirements.

Since this is the first study to evaluate the safety of administration of two doses of MEDI8897 in one RSV season, period of Q2W Telephone Contact is extended to180 days after 2nd Dose to ensure safety of study participants.

Section # and Name	Description of change	Brief Rationale	Substantial/ Non-substantial
1.2 Schema Figure 1 Study Design	Extended period of Telephone Contact for once 2 weeks (Q2W) to 180days after Dose 2.	To ensure the safety of subjects as this is the first study to evaluate the administration of 2 doses of MED18897 in a single RSV season.	Substantial
1.3 Schedule of Activities Table 2	Addition of procedures for Telephone Contact (Q2W) in period of Post-2nd Dose Follow-up.	To ensure the safety of subjects as this is the first study to evaluate the administration of 2 doses of MED18897 in a single RSV season.	Substantial
4.1.3 Subsequent Visit	Text added that Telephone contact for Q2W during 6 months after 2nd dose to be planned.	To ensure the safety of subjects as this is the first study to evaluate the administration of 2 doses of MED18897 in a single RSV season.	Substantial
6.6 Dose Modification/Replacement Dose	Text added that Telephone contact for Q2W during 6 months after replacement dose to be planned.	To ensure the safety of subjects as this is the first study to evaluate the administration of 2 doses of MED18897 in a single RSV season.	Substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
aa	Amino acid
Ab	Antibody
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CHD	Congenital Heart Disease
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLD	Chronic Lung Disease
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-Induced Liver Injury
DUS	Disease under Study
E/D	Early Study Intervention Discontinuation
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
ER	Emergency Room
FDA	(US) Food and Drug Administration
GA	Gestation age
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold-Rise

Abbreviation or special term	Explanation
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titer
HBS	Human Biological Sample(s)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
JMDC	Japan Medical Data Center
LRTI	Lower Respiratory Tract Infection
MA	Medically attended
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NIMP	Non-investigational Medicinal Product
NOCD	New-onset chronic disease
OTC	Over-the-Counter
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Preferred term
Q2W	Once every 2 weeks
RRR	Relative Risk Reduction
RSV	Respiratory Syncytial virus
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SoA	Schedule of Activities
SOC	System organ class
TBL	Total Bilirubin

Abbreviation or special term	Explanation
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper Limit of Normal

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Brief Title:

A study to investigate the safety, pharmacokinetics, occurrence of anti-drug antibody, and anti-RSV neutralizing antibody following 2 doses of administration of nirsevimab (MEDI8897) in infants with certain health conditions or born pre-term in Japan

Rationale: Nirsevimab has been established to provide 79.5% efficacy against medically attended (MA)-respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) over at least a 5-month RSV season. In Japan, the RSV season has shown variability with regard to onset and duration between different prefectures. In fact, it is reported that RSV circulation is prolonged in certain prefectures like Fukuoka and Hokkaido (IDWR Surveillance data, 2022). Prematurity, congenital heart disease (CHD), chronic lung disease (CLD), Down syndrome, and immunocompromise are important risk factors for RSV-related morbidity and mortality in infants and young children. The purpose of this phase III study is to assess the safety, pharmacokinetics (PK), anti-drug antibody (ADA) of nirsevimab, and anti-RSV neutralizing antibody (Ab) following administration of 2 doses of nirsevimab given 5 to 6 months apart to prevent RSV infection over possible prolonged RSV season in these higher risk infants.

Objectives and Endpoints:

Type	Objective	Hypothesis tested	Endpoints/Estimand
Primary			
Safety	To evaluate the safety and tolerability of 2 doses of nirsevimab administered 5 to 6 months apart	None	**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),

Type	Objective	Hypothesis tested	Endpoints/Estimand
			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
Secondary			
Pharmacokinetics (PK)	To evaluate the PK of 2nd dose of nirsevimab administered 5 to 6 months after the first dose	None	• Nirsevimab serum concentrations
ADA	To evaluate ADA responses to 2 doses of nirsevimab administered 5 to 6 months apart	None	• Occurrence of ADA to nirsevimab in serum
Anti-RSV neutralizing Ab	To determine anti-RSV neutralizing antibody (Ab) levels in serum to 2 doses of nirsevimab administered 5 to 6 months apart	None	• Anti-RSV neutralizing Ab levels (IU/mL) in serum
Exploratory			
MA-RSV LRTI	To assess the occurrence of MA-RSV LRTI (inpatient and outpatient) and hospitalization due to RT-PCR-confirmed RSV following administration of 2 doses of nirsevimab 5 to 6 months apart	None	• 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

Type	Objective	Hypothesis tested	Endpoints/Estimand
RSV-resistance monitoring	To characterize resistance to nirsevimab through genotypic and phenotypic analysis	None	• 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

Overall Design Synopsis:

This study is a phase III, single-arm, open-label, 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, Down syndrome, immunocompromise, or born premature (≤35 weeks gestation age: 35 wks GA) who are ≤12 months of age at enrollment. The study is planned to be conducted in Japan.

Brief Summary:

The purpose of this study is to measure the safety, PK, occurrence of ADA to nirsevimab, and anti-RSV neutralizing Ab in Japanese children with certain health conditions or pre-term infants aged ≤12 months.

Study details include:

- The study duration is approximately 21 months with a 2-month enrollment period.
- Study intervention is 2 doses administered 5- 6 months apart.
- The study has 5 or 6 site visits and several telephone contacts with a 2- or 4-week interval.

Disclosure Statement: This is an open-label study with a single arm.

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.

Note: 'enrolled' means participant's legally acceptable representative's agreement to participate in a clinical study following completion of the informed consent process, and participants have received the first dose of nirsevimab. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned in the study, are considered 'screen failures', unless otherwise specified by the protocol.

Study Arms and Duration:

Participants in the first year of life will receive the 1st 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.

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 the study follow-up period (360 days after the 2nd or last dose administered in the study).

Statistical Methods

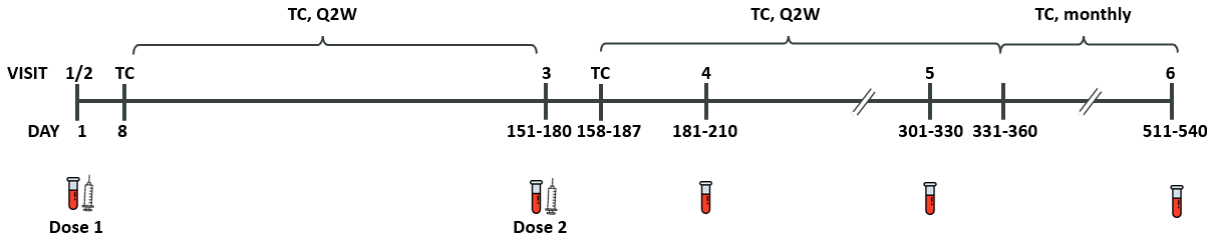
No statistical hypothesis analysis is planned.

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 from the previous 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.

There are 2 planned analyses for this study: a primary analysis and a final analysis. The primary analysis will be conducted when all enrolled participants have been followed through Visit 5 (ie, around 150 days post 2nd dose). The final analysis will be conducted after all participants have completed the last visit of the study (ie, around 360 days post 2nd or last dose). Descriptive statistics will be produced for all efficacy, safety, PK, ADA, and anti-RSV neutralizing Ab variables.

1.2 Schema

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 Schedule of Activities

Refer to Table 1 and Table 2.

Table 1 Study Plan Detailing the Procedures at Screening

Study Period	V1 (Screening)
Procedure/Study Day or Week	**Day -30 to Day 1**
Written informed consent/assignment of SID number	X
Medical history	X
Physical examination [a]	X
Weight	X
Vital signs [b]	X
Hematology [c, d]	X
Serum chemistry [c, d]	X
Blood sample for PK, ADA, anti-RSV neutralizing Ab [c]	X
Assessment of AEs/SAEs	X
Concomitant medications	X
To verify eligibility criteria	X
Other baseline information [e]	X

Ab = antibody, ADA = anti-drug antibody; AE = adverse event; LRI = lower respiratory infection;
PK = pharmacokinetics; RSV = respiratory syncytial virus; SAE = serious adverse event; SID = participant identification.

[a] A complete physical examination will be performed. It includes assessments of the following: height, weight, general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

[b] Vital signs include temperature, blood pressure, heart rate, and respiratory rate.

[c] If Visit 1/Screening and Visit 2/Day 1 do not occur on the same day, a blood sample for hematology/serum chemistry, and PK/ADA/anti-RSV neutralizing Ab can be collected at either Visit 1/Screening or Visit 2/Day 1 Predose.

[d] Hematology = RBC, WBC, Lymphocyte, Platelet count, and Hemoglobin; Serum chemistry = AST, ALT, Total bilirubin, BUN, and Creatinine

[e] Baseline information includes breastfeeding, smoking in the household, presence of sibling(s), and if the infant attends day care.

Table 2 Study Plan Detailing the Procedures during Treatment and Follow-up Period

Study Period	1st Dose	Post-1st Dose Follow-up		2nd Dose	Post-2nd Dose Follow-up					
Visit Number	V2 [a]	TC [h]		V3	TC [i]	V4 [j]	V5 [k]	V6 [l]	TC [h]	TC [h]
Procedure/Study Day	D1	D8 (±2 days)	Q2W D9-150 (±5 days)	D151-D180	D158-187 (±2 days)	D181-210 (±7 days)	D301-330 (±15 days)	D511-540 (±15 days)	Q2W From D159-188 Till D331-360 (±5 days)	Monthly From D332-361 Till D511-540 (±5 days)
Medical history update	X									
Physical examination [b]	X			X		X	X	X		
Weight [c]	X			X						
Vital signs [d]	X			X						
Hematology [e]	X [f]			X [m]		X	X	X		
Serum chemistry [e]	X [f]			X [m]		X	X	X		
Blood sample for PK, ADA, anti-RSV neutralizing Ab	X [f]			X [m]		X	X	X		
Assessment of AEs/SAEs	←							→	X	X
Assessment of AESIs and NOCDs	←							→	X	X
Concomitant medications/treatments	X	X	X	X	X	X	X	X	X	X
Verification of eligible criteria	X			X [n, o]						
Investigational product administration	X			X						
Assessment of LRTI or any respiratory infection that requires hospitalization, respiratory secretion sample collection, and blood sampling [g]	←							→		
Telephone contact [h]		X	X		X				X	X

Ab = antibody, ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; D = Day; LRTI = lower respiratory tract infection; NOCDs = new-onset chronic disease; PK = pharmacokinetic; Q2W = once every 2 weeks; RSV = respiratory syncytial virus; SAE = serious adverse event; TC = telephone contact; V = visit.

[a] V2/D1 and V1/Screening can occur on the same day. Blood sample to be drawn prior to the administration.

[b] A complete physical examination will be performed on the dosing day (prior to dosing at Visit 2 and 3). It includes assessments of the followings: height, weight, general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems. On other visits, symptom targeted physical examination will be performed.

[c] Body weight will be measured prior to dose on the dosing day.

[d] On the dosing day, vital signs (temperature, blood pressure, heart rate, and respiratory rate) should be obtained within 60 minutes before dose, and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-dose. In addition, participants will be carefully monitored for at least 60 minutes after each dose.

[e] Hematology = RBC, WBC, Lymphocyte, Platelet count, and Hemoglobin; Serum chemistry = AST, ALT, Total bilirubin, BUN, and Creatinine

[f] If V1/Screening and V2/D1 do not occur on the same day, blood sample for hematology/serum chemistry, and PK/ADA/anti-RSV neutralizing Ab can be collected at either V1/Screening or V2/D1.

[g] Respiratory secretion (nasal swab, or nasopharyngeal washes/tracheal aspirates are also acceptable if it has been collected) samples will be collected from all participants with LRTIs (inpatient or outpatient) and from all hospitalized participants with any new respiratory infection (upper or lower) within 2 days after the initial healthcare provider assessment and diagnosis. Blood samples will be collected from all participants hospitalized with LRTI or any respiratory infection within 2 days following hospital admission to measure PK/ADA/anti-RSV neutralizing Ab.

[h] Telephone contact must be verbal communication. Written communication via text, email, or other written forms is not acceptable.

[i] 7 ± 2 days post 2nd dose

[j] 30 ± 7 days post 2nd dose

[k] 150 ± 15 days post 2nd dose

[l] 360 ± 15 days post 2nd dose

[m] Blood sample to be drawn prior to the administration of 2nd dose

[n] If the replacement dose is administered, participants will receive the same procedures on replacement dose day as those listed for 2nd dose (V3/D151-180). In the case that participants receive replacement dose prior to administration of the 2nd dose, they will not receive further dose (See Section 6.1.3). All participants that receive a replacement dose will be followed through 360 days post replacement dose (the same follow-up/procedures that are outlined through 360 days post 2nd dose in the above table, See Section 6.6.

Refer to Section 6.1.3 on eligible criteria for 2nd dose.

2 INTRODUCTION

Nirsevimab is a recombinant human immunoglobulin G (IgG)1 kappa (IgG1κ) monoclonal antibody (mAb) directed against the prefusion conformation of F protein of the respiratory syncytial virus (RSV) and provides protection from serious RSV disease by binding with RSV.

2.1 Study Rationale

Pre-term birth (≤35 wks GA), congenital heart disease (CHD), chronic lung disease (CLD), Down syndrome, and compromised immune status are important risk factors for RSV-related morbidity and mortality in infants and young children.

Nirsevimab is a recombinant human IgG 1 kappa mAb with a longer efficacy than palivizumab, and safety and efficacy for at least 5 months after a single intramuscular (IM) dose has been already established together with pharmacokinetic (PK), and occurrence of anti-drug antibody (ADA) in previous pivotal phase III studies in pre-term infants and young children with CHD, CLD or Down syndrome (D5290C00003/MELODY and MEDLEY studies). In addition, no safety issues were reported after a single IM dose of nirsevimab in Japanese children with compromised immune system.

This study has been planned to assess safety, PK, ADA, and anti-RSV neutralizing Ab after 2nd dose of nirsevimab 5 to 6 months after the 1st dose in Japanese infants with certain health conditions or born pre-term.

2.2 Background

RSV is the most common cause of lower respiratory tract infection (LRTI) among infants and young children, resulting in annual epidemics worldwide (Hall et al, 2009; Shi et al, 2017). Almost all children are infected with RSV in the first 2 years of life. RSV-associated LRTI is characterized predominantly as bronchiolitis or pneumonia and represents a serious illness with acute and perhaps long-term consequences to the developing lungs in these young children. In 2015, an estimated 33.1 million (uncertainty range: 21.6 to 50.3 million) new episodes of RSV-associated LRTI occurred worldwide in children younger than 5 years (28% of LRTI episodes). Of those, a part of children with some underlying conditions, such as pre-term, CLD, CHD, or immunodeficiency, are at higher risk of progressing to severe RSV-associated LRTI leading to hospital admission, with 59600 hospital deaths globally (range: 48000 to 74500) (Shi et al, 2017).

The survey of the Japan Medical Data Center (JMDC) reported 9711 and 8509 children ≤2 years of age had RSV infection in 2017 and 2018, respectively. These numbers are estimated to correspond to 119000 and 138000 diagnoses each year in Japan, and it has been reported that 25% of participants, including those with high risk, required hospitalization (Kobayashi et al, 2022). In 2022 (as of 14 December), over 100000 RSV cases with at least approximately 300 cases per week has been reported, and this report suggested annual

circulation with variable epidemic peak and duration depend on prefectures (IDWR Surveillance data, 2022).

Variation and extended duration of RSV season has been reported globally (Bermudez Barrezueta et al, 2022), and necessity of a longer protection period from RSV is suggested in some children in certain regions (American Academy of Pediatrics, 2022; Bermudez Barrezueta et al, 2022). In Japan, the RSV epidemic period varies depending on the year and prefecture, and extended duration or change of onset epidemic season has been reported (Miyama et al, 2021; IDWR Surveillance data, 2022). For these reasons, sustained protection against the RSV infection for a longer time from early may be needed in some regions.

Nirsevimab is the mAb directed against the prefusion conformation of the RSV F protein and neutralizes RSV by binding the prefusion conformation of the RSV F protein. Nirsevimab has a longer half-life and is more potent than palivizumab, and only one administration can provide protection for at least 5 months. Given the need for optimal protection beyond a 5-month period in higher risk infants in some regions, this study evaluates the repeat dose at 5 to 6 months after the first dose.

In Oct 2022, nirsevimab was approved for the prevention of RSV lower respiratory tract disease in the European Economic Area (EEA), and it is under review by the US Food and Drug Administration (FDA).

2.3 Benefit/Risk Assessment

Nirsevimab is a recombinant human IgG1κ mAb directed against the prefusion conformation of the RSV F protein. Nirsevimab has a similar mechanism of action as the Sponsor-approved mAb for RSV prophylaxis, palivizumab (Synagis®).

More detailed information about the known and expected benefits and risks and reasonably predicted adverse events (AEs) of nirsevimab may be found in the Investigator's Brochure (IB).

2.3.1 Risk Assessment

Potential Risks

There are important potential risks associated with administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs. The important potential risks include, but are not limited to, immediate (type I) hypersensitivity reactions including anaphylaxis, immune complex disease, and thrombocytopenia.

Anaphylaxis is an acute onset and may cause a serious drop in blood pressure, difficulty in breathing, severe hives, and sometimes death. It is distinct from simple allergic reactions (eg,

rash, pruritus) because of the simultaneous involvement of several organ systems. A hypersensitivity reaction may be defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both, but it does not meet the definition of anaphylaxis. On guidance for anaphylaxis diagnosis, see Appendix B 4.

There were no events of serious hypersensitivity including anaphylaxis, immune complex disease or thrombocytopenia related to the investigational product reported during completed clinical studies.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, bruising, infection, or excessive bleeding at the site of injection.

Safety profile of nirsevimab has been demonstrated from a series of clinical studies in infants and young children.

1 Term and late pre-term infants

Safety profile of nirsevimab was based on 2 placebo-controlled clinical trials Study 3 (D5290C00003 – all participants) and MELODY (D5290C00004 – all participants) where 2966 infants received a single IM dose of nirsevimab in the broad population of healthy at term and pre-term infants born (≥29 wks GA). The types and frequencies of AEs were generally balanced between the nirsevimab and placebo groups within 1, 3, 7, 14, and 30 days post-dose timepoints and through 360 days post dose. Frequency of adverse drug reactions observed in these trials are rash including rash macular and rash maculopapular within 14 days (0.7% in nirsevimab arm as compared to 0.5% in placebo arm), injection site reactions within 7 days (0.3% in nirsevimab arm as compared to 0.0% in placebo arm) and pyrexia within 7 days (0.5% in nirsevimab arm as compared to 0.7% in placebo arm). The majority of events were non-serious with mild/moderate in severity.

2 For infants and children's vulnerable to severe RSV disease

Safety was evaluated in MEDLEY (D5290C00005) study in infants at higher risk for severe RSV disease, including extremely pre-term infants (≤28 wks GA) and infants with CLD, or CHD entering their first RSV season, who received nirsevimab or palivizumab. The safety profile of nirsevimab in infants who received nirsevimab in their first RSV season was comparable to the palivizumab and consistent with the safety profile of nirsevimab in term and pre-term infants ≥29 wks GA (D5290C00003 and MELODY). Safety was evaluated in MEDLEY in children with CLD or CHD who received nirsevimab or palivizumab in their first RSV season and went on to receive nirsevimab entering their second RSV season. The safety profile of nirsevimab in children who received nirsevimab in their first and second RSV season was comparable to that in children who received palivizumab in their first RSV season and then nirsevimab in their second RSV season. The safety profile of nirsevimab in these children from both arms was consistent with the safety profile of nirsevimab in term and pre-term infants ≥29 wks GA (D5290C00003 and MELODY) and comparable to children who

received palivizumab for both RSV seasons.

3 Immunocompromised population

Nirsevimab was also well tolerated in vulnerable, immunocompromised infants and children up to 24 months of age who received nirsevimab in RSV Season 1 or RSV Season 2 in MUSIC (D5290C00008). The safety profile of nirsevimab was consistent with that expected for a population of immunocompromised children and with the safety profile in infants of term and pre-term ≥29 wks GA (D5290C00003 and MELODY).

2.3.2 Benefit Assessment

The efficacy of nirsevimab was established in late pre-term and term infants. Efficacy findings were extrapolated based on PK data to infants and children ≤24 months of age at higher risk.

In Study D5290C00003 in pre-term infants, participants were followed-up through Day 361. A single dose of 50 mg IM nirsevimab resulted in a relative risk reduction (RRR) in the occurrence of medically attended (MA)-RSV LRTI through Day 151 of 70.1% (95% CI: 52.3%, 81.2%) when compared to placebo. The occurrence of MA-LRTI through Day 151 in participants who received the proposed dose was 17.4% in the nirsevimab group and 24.8% in the placebo group. In addition, a single dose of 50 mg IM nirsevimab resulted in an RRR in the occurrence of RSV LRTI hospitalization through Day 151 of 78.4% (95% CI: 51.9%, 90.3%) when compared to placebo.

In Study D5290C00004 (MELODY) in healthy late pre-term and term infants, all participants received a single IM dose of nirsevimab 50 mg or 100 mg depending on body weight (50 mg in infants with <5 kg body weight, or 100 mg with ≥5 kg body weight), and infants from the primary cohort were followed-up through Day 361. Primary analysis data showed that the occurrence of MA-RSV LRTI through Day 151 was 1.2% of participants in the nirsevimab group and 5.0% of participants in the placebo group, corresponding to efficacy of 74.5% (95% CI 49.6, 87.1; P< 0.0001), thus meeting the primary endpoint. The secondary endpoint of RSV LRTI hospitalization through Day 151 occurred in 0.6% of participants in the nirsevimab group and 1.6% of participants in the placebo group (efficacy 62.1% [95% CI -8.6, 86.8]; p = 0.0708). A pre-specified pooled analysis (data from participants weighing <5 kg in Study D5290C00003 with healthy late pre-term and term infants and all primary cohort participants from Study D5290C00004) demonstrated efficacy of 77.3% (95% CI 50.3, 89.7; p = 0.0002) in reducing hospitalization due to RSV in the target population (pre-term and normal term infants) on commercial dose. Post-baseline ADAs were detected in only 6.1% of participants in the nirsevimab group. ADAs were also detected in the placebo group.

In Study D5290C00005 (MEDLEY) in infants with CHD/CLD and pre-term infants who received the same single IM dose as that in MELODY study, the data-lock point of the primary analysis corresponded to all participants having been followed through their first RSV

season (Day 151). Seven presentations of respiratory illness met the per-protocol definition of MA-RSV LRTI. These were balanced by treatment group (nirsevimab 0.6%, palivizumab 1.0%) and 2 in each arm required hospitalization. The proportion of ADA-positive participants at Season 1 Day 151 was low for both treatment arms (nirsevimab 0.4%, palivizumab 3.7%).

2.3.3 Overall Benefit/Risk Conclusion

Based on the favorable efficacy and safety profile across the broad population of infants entering their first RSV season, and for children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season, combined with the advantage of a single dose, nirsevimab offers the ability to provide protection against RSV lower respiratory tract disease and significantly reduce the disease burden for all infants.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Refer to Table 3 for objectives and associated endpoints of the study. No formal hypothesis testing for this study is planned.

Table 3 Objectives and Endpoints/Estimand

Type	Objective	Hypothesis tested	Endpoints/Estimand
Primary			
Safety	To evaluate the safety and tolerability of 2 doses of nirsevimab administered 5 to 6 months apart	None	**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
Secondary			
Pharmacokinetics (PK)	To evaluate the PK of 2nd dose of nirsevimab administered 5 to 6 months after the first dose	None	• Nirsevimab serum concentrations

Table 3 Objectives and Endpoints/Estimand

Type	Objective	Hypothesis tested	Endpoints/Estimand
ADA	To evaluate ADA responses to 2 doses of nirsevimab administered 5 to 6 months apart	None	• Occurrence of ADA to nirsevimab in serum
Anti-RSV neutralizing Ab	To determine anti-RSV neutralizing antibody (Ab) levels in serum to 2 doses of nirsevimab administered 5 to 6 months apart	None	• Anti-RSV neutralizing Ab levels (IU/mL) in serum
Exploratory			
MA-RSV LRTI	To assess the occurrence of MA-RSV LRTI (inpatient and outpatient) and hospitalization due to RT-PCR-confirmed RSV following administration of 2 doses of nirsevimab 5 to 6 months apart	None	• 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
RSV-resistance monitoring	To characterize resistance to nirsevimab through genotypic and phenotypic analysis	None	• Genotypic analysis and susceptibility of RSV variants to neutralization by nirsevimab

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

4 STUDY DESIGN

4.1 Overall 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 wks GA. The study is planned to be conducted in Japan. Approximately 30participants 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). Refer to Figure 1 for an outline of the study plan. If a participant requires cardiac surgery with cardiopulmonary bypass during the study, replacement dose may be administered after bypass surgery (see Section 6.6 in detail).

Participants will be monitored for treatment-emergent adverse events (TEAEs), treatment-emergent serious AEs (TESAEs), adverse event of special interests (AESIs), new-onset chronic diseases (NOCDs), PK, ADA, anti-RSV neutralizing Ab, and MA-RSV LRTI throughout the study.

All participants seeking medical attention for a respiratory illness (inpatient or outpatient setting) will be evaluated for the occurrence of LRTI.

All participants found to have a LRTI and all participants who require hospitalization for a respiratory infection, even if there is not a diagnosis of LRTI, should have respiratory secretion samples (nasal swab, or nasopharyngeal washes/tracheal aspirates is also acceptable if it can be collected) obtained and respiratory assessment completed. Samples should be collected for all participants with these respiratory events even those not meeting the protocol-defined endpoint of LRTI. Participants who have a primary hospitalization for a respiratory infection (ie, upper or lower respiratory tract), a respiratory deterioration during a hospitalization, or who seek outpatient medical attention (including emergency room [ER] visits) for a lower respiratory illness, will be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory secretions. For participants with hospitalization (upper or lower respiratory tract illness), additional blood samples will be collected to measure PK, ADA, and anti-RSV neutralizing Ab.

In addition to the clinical assessment of LRTI, there is a protocol definition using objective criteria for the determination of a protocol-defined MA-LRTI. To meet the protocol-defined endpoint of MA-LRTI, participants should have sign of lower respiratory tract involvement with an indicator of disease severity present. Refer to Section 8.2.1, Table 6.

Testing for RSV will be performed centrally using the US FDA-cleared and Conformité

Européenne or European Conformity-marked in vitro diagnostic real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay (Lyra RSV + hMPV Assay, Quidel, San Diego, CA; www.quidel.com). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by the central laboratory RT-PCR.

4.1.1 Screening Visit

All potential participants will have a screening visit, which may take place up to 30 days prior to Day 1. Informed consent will be obtained from participant's parent(s)/legally authorized representative(s) prior to performing any protocol-related procedures, including screening evaluations.

A complete medical history and other baseline information will be obtained at screening. Assessment will include history and current medical conditions, past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, developmental, and genitourinary disorders, drug and surgical history, and any other diseases or disorders.

Screening visit can occur on the same day as the 1st dose visit (Visit 2).

On screening visit, see Section 1.3 Schedule of Activities (SoA), Table 1 in detail.

4.1.2 Visit for Dose

Participants will be considered enrolled into the trial at the point of nirsevimab dose. Before 1st dose, a medical history update will be obtained, and the eligibility of participants will be reviewed. The eligibility of criteria will be also reviewed prior to 2nd dose (refer to Section 6.1.3).

Body weight, a complete physical examination, and vital signs will be evaluated before dosing. Vital signs will be measured pre- and post- dose. And participants will be carefully monitored for at least 60 minutes after each dose. Vital signs (temperature, blood pressure, heart rate, and respiratory rate) should be obtained within 60 minutes before dose, and at 30 minutes (± 5 minutes), and 60 minutes (± 5 minutes) post-dose.

4.1.3 Subsequent Visit

Follow-up visits will take place as per the schedule of assessment described in Table 2. All participants will be assessed for local and systemic AE, and symptom target physical examination at pre-specified time points as detailed in the schedule of assessment (Section 1.3 SoA, Table 2). At specified visits, blood will be taken for assessment of hematology and chemistry, PK, ADA, and anti-RSV neutralizing Ab.

Telephone contact will be conducted once 2 weeks (Q2W) after 1st dose and during 6 months after 2nd dose, and monthly thereafter.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Population

A single dose of nirsevimab is effective at preventing RSV LRTI for at least 5 months and has an acceptable safety profile. 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. Therefore, it is necessary to give participants 2nd dose of nirsevimab would prevent RSV infection for whole RSV season in such regions. 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 with CLD, CHD, immunodeficiency, or Down syndrome, or born pre-term, according to Japanese palivizumab dosing guideline.

4.2.2 Rationale for Study Endpoints

The primary objectives for this study are safety and tolerability. The standard measures of TEAEs, TESAEs, AESIs, and NOCDs will be used as endpoints. All participants will be followed up for approximately one year after a 2nd dose or last dose.

Serum concentrations of nirsevimab at selected time points will be measured as a secondary endpoint to evaluate the PK of a 2nd dose of nirsevimab administered 5 to 6 months after the first dose. In addition, ADA and anti-RSV neutralizing Ab levels will be also measured at the same time points as serum concentrations of nirsevimab. For infants and children who require hospitalization for LRTI or any respiratory infection, an additional serum sample will be obtained contemporaneous with time of hospitalization for measurement of serum nirsevimab concentration, ADA, and anti-RSV neutralizing Ab.

Exploratory endpoints include occurrence of MA-LRTI and hospitalization due to RT-PCR confirmed RSV infection. In addition, to monitor for RSV resistance, the F protein from collected RSV isolates will be genetically characterized and novel variants will be phenotypically characterized for nirsevimab susceptibility.

4.3 Justification for Dose

Dose level is dependent on body weight. Participants 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. These participants will receive a 2nd fixed IM dose of 50 mg if body weight is <5 kg or 100 mg if body weight is ≥5 kg 5 to 6 months following 1st dose. Dose based on body weight was

adopted in previous studies, and the efficacy and safety of nirsevimab after a single IM dose at the regimen based on body weight were demonstrated.

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).

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including their last scheduled procedure.

The end of the study is defined as the date of the last scheduled procedure for the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Written informed consent and any locally required authorization obtained from the participant's parent(s)/legally authorized representative(s) before performing any protocol-related procedures, including screening evaluations
2. Japanese infants of ≤12 months of age eligible to receive palivizumab in accordance with national or local guidelines and those who must meet at least one of the following conditions at the time of informed consent.
   (a) Immunodeficiency
      i) Diagnosed with combined immunodeficiency (severe combined immunodeficiency, X-linked hyper-immunoglobulin M [IgM] syndrome, etc.); Ab deficiency (X-linked agammaglobulinemia, common variable immunodeficiency, non-X-linked hyper-IgM syndromes, etc.); or other immunodeficiencies (Wiskott-Aldrich syndrome, DiGeorge syndrome, etc.), or
      ii) Diagnosed with human immunodeficiency virus infection, or
      iii) History of organ or bone marrow transplantation, or
      iv) Participant is receiving immunosuppressive chemotherapy, or
      v) Participant is receiving systemic high-dose corticosteroid therapy (prednisolone equivalents ≥0.5 mg/kg every other day, other than inhaler or topical use), or
      vi) Participant is receiving other immunosuppressive therapy (eg, azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, cytokine inhibitors, etc.)

(b) CLD

i) Diagnosed with CLD of prematurity requiring medical intervention/management (ie, supplemental oxygen, bronchodilators, or diuretics) within 6 months prior to screening

(c) CHD

i) Diagnosed with hemodynamically significant CHD (must be unoperated or partially corrected CHD)

Note: Children with hemodynamically significant acyanotic cardiac lesions must have pulmonary hypertension (≥40 mmHg measured pressure in the pulmonary artery) or the need for daily medication to manage CHD

(d) Down syndrome

(e) Born pre-term ≤28 wks GA and aged ≤12 months, or born pre-term >28 wks and ≤35 wks GA and aged ≤6 months

3. The participant's parent(s)/legally authorized representative(s) can understand and comply with the requirements of the protocol including follow-up visits as judged by the investigator.
4. The participant is available to complete the follow-up period for approximately 19 months, which will be approximately 1 year after receipt of 2nd dose of nirsevimab.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1 Requirement for mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure (CPAP), or other mechanical respiratory or cardiac support at the time of enrollment

2 A current, active RSV infection at the time of screening and investigational product administration

3 Any fever (≥100.4°F [≥38.0°C], regardless of route) or acute illness at the time of prior to investigational product administration

4 Any serious concurrent medical condition (except those resulting in an immune deficiency condition), including:

(a) Known renal impairment

(b) Known hepatic dysfunction including known or suspected active or chronic hepatitis infection

(c) Any seizure disorder or evolving or unstable neurological condition

5 Anticipated cardiac surgery within 5-6 months after enrollment

6 Prior history of a suspected or actual acute life-threatening event

7 Receipt or intended use of palivizumab in the current enrollment season

8 Any known allergy or history of allergic reaction to any component of nirsevimab

9 Any known allergy or history of allergic reaction to immunoglobulin products, blood products, or other foreign proteins

10 Concurrent enrollment in another interventional study, or prior receipt of any investigational agent

11 Anticipated survival of less than 1 year at the time of informed consent

12 Any condition that, in the opinion of the investigator, would interfere with the evaluation of the investigational product or interpretation of study results

13 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

5.3 Lifestyle Considerations

There are no specific lifestyle restrictions identified for this study. Restrictions related to concomitant medications can be found in Section 6.9.2. However, it is desirable for children to avoid situations susceptible to infectious diseases as much as possible.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 Criteria for Temporarily Delaying

Not applicable

5.6 Study Suspension or Termination

The study may be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis because of any reason, eg, but not limited to;

- Death of any participant in which the cause of death is assessed as related to study intervention.
- Any event that, in the judgment of the sponsor or the investigator, are deemed serious enough to warrant immediate review.
- Sponsor decides to suspend/terminate the study.

6 STUDY INTERVENTION(S) AND CONCOMINANT THERAPY

6.1 Study Intervention(s) Administered

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol. For this study, only nirsevimab is defined as study intervention.

6.1.1 Study Intervention Administered

Refer to Table 4.

Table 4 Investigational Intervention

Intervention Name	Nirsevimab (MEDI8897)
Type	Monoclonal antibody.
Dose Formulation	The solution contains 100 mg/mL nirsevimab, 30 mM histidine/histidine-HCl, 80 mM arginine-HCl, 120 mM sucrose, 0.02% (w/v) polysorbate 80, pH 6.0. The nominal fill volume is 0.5 mL.
Unit Dose Strength(s)	Supplied as 50 mg (nominal) per vial solution.
Dosage Level(s)	See Section 6.1.2.
Route of Administration	Intramuscular
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the Sponsor.
Packaging and Labelling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement.

IMP = investigational medicinal product; NIPM = non-investigational medicinal product.

The investigational medicinal product (IMP) should be stored at 2°C to 8°C.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

The IMP will be supplied to the site in open-labelled kits. Each kit has a unique number printed on all labels within the kit (ie, the outer carton label and the label of each vial).

6.1.2 Dose Preparation Steps and Treatment Administration

The dose administration steps are as follows:

1. Dose level

(a) Infants <5 kg body weight at time of dosing:
- A dose of 50 mg (ie, 0.5 mL) nirsevimab will be obtained by withdrawing the entire contents of 1 investigational product vial with an appropriately sized syringe, and administered as 1 single (ie, 0.5 mL) injection, regardless of 1st and 2nd dose.

(b) Infants ≥5 kg body weight at time of dosing:
- A dose of 100 mg (ie, 1.0 mL) nirsevimab will be obtained by withdrawing the entire contents of 2 investigational product vials with an appropriately sized syringe and administered as 1 single (ie, 1.0 mL) injection, regardless of 1st and 2nd dose.

2. Switch the needle to a higher gauge prior to administration. Nirsevimab should be administered using the appropriate size needle ranging from 22 to 25 gauge and 5/8 to 1.0 inches based on muscle size and weight of the participant.
3. Nirsevimab should be administered in the anterolateral aspect of the thigh according to standard practice procedures for IM injections. The injection should be given using standard aseptic technique.
4. Nirsevimab should be administered within 4 hours at room temperature from needle puncture of the investigational product vial to administration. If the time exceeds these limits, a new vial should be used (refer to Section 6.2). If there is a delay in the administration of nirsevimab such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

6.1.3 Eligibility for 2nd Dose

Participants who received 1st dose and do not meet any of the below exclusion criteria's:

1. Participants who undergo cardiac surgery with cardiopulmonary bypass after receipt of 1st dose but prior to receipt of 2nd dose (see Section 6.6)
2. Any allergic reaction to 1st dose of nirsevimab
3. A current, active infection, including RSV infection, or any ongoing AE at the time of investigational product administration
4. Any fever (≥100.4°F [≥38.0°C], regardless of route) or acute illness within 7 days prior to investigational product administration.
5. Any condition, that in the opinion of investigator, would interfere with the evaluation of the investigational product or interpretation of study results

If participants cannot be dosed because they meet criteria 3 and/or 4 above, they may still be eligible to receive a 2nd dose. Participants may be reassessed for 2nd dose eligibility, and assuming none of the above criteria are met upon reassessment, they may receive the 2nd dose as long as more than one week have been passed after the recovery and the 2nd dose is administered within 6 months (+14 days) after the 1st dose.

6.2 Preparation, Handling, Storage, and Accountability

- IMP (nirsevimab) will not be delivered to the study site until the contract is completed between the study site and AstraZeneca (and/or designee).
- The investigator or designee (eg, pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorization is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. Study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to authorized site staff.
- The head of the study site is responsible for ensuring the control of accountability, reconciliation, and return for IMP received at the site. The head of the study site will designate designee (eg, pharmacist) to delegate all responsibility, ie, receipt, reconciliation, and final disposition records.
- Nirsevimab does not contain preservatives and any unused portion must be discarded. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used.

6.3 Assignment to Study Intervention

Not applicable

6.4 Blinding

Not applicable

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention(s) directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Dose Modification/Replacement Dose

If dose modification/replacement dose is necessary, the study intervention will be administered as follows:

Replacement dose in participants who undergo cardiac surgery with cardiopulmonary bypass:

(a) If surgery is done after receipt of 1st dose but prior to 2nd dose, participants will receive a replacement dose immediately following the surgery when they are determined by the physician to be medically stable for an IM injection. Participants who have received a replacement dose do not receive regular 2nd dose.
   i) If surgery is done within 90 days after 1st dose, participants will receive a single dose of 50 mg (current body weight <5 kg) or 100 mg (current body weight ≥5 kg).
   ii) If surgery is done after 90 days of 1st dose, participants will receive a single 50 mg replacement dose, regardless of body weight, to cover the remainder of the RSV season.

(b) If surgery is done after receipt of 2nd dose but prior to end of study follow-up (until Day 511-Day 540, ie, 360 days after 2nd dose), the replacement dose for protection in the current/ongoing season will be determined by clinical judgment of the investigator. When replacement dose is needed at the discretion of the investigator, participant will receive 50 mg of nirsevimab IM dose regardless of body weight.

(c) Participants that receive a replacement dose will be followed for 360 days after dosing. Follow-up after a replacement dose will be the same as follow-up after 2nd dose, as shown below;
   i) Visit: Day 30, Day 150, and Day 360 after a replacement dose
   ii) Telephone contact: Day 7, Q2W during 6 months after replacement dose and monthly thereafter.
   iii) Blood sample will be collected to measure PK, ADA, and anti-RSV neutralizing Ab pre-surgery, post surgery (before replacement dose), and Day 30, Day 150, and Day 360 after a replacement dose.

(d) During the follow-up period after replacement dose, surveillance for MA-RSV LRTI will be maintained until the study end.

Refer to Section 1.3 SoA, Table 2.

6.7 Continued Access to Study Intervention After the End of the Study

Study intervention after the end of the study is not planned.

6.8 Treatment of Overdose

For this study, any dose of nirsevimab greater than pre-decided dose in this protocol will be considered an overdose, ie, in the case that dose level in each dosing is exceeds 50 mg if body

weight is <5 kg or 100 mg if body weight is ≥5 kg.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator and/or participant's parent(s) should:

- Closely monitor the participant for any AE/SAE for at least hour after administration. Refer to Section 8.4.12 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose.

6.9 Concomitant Therapies

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Permitted Concomitant Medications or Treatments

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care, including routine vitamins and iron. Specifically, participants should receive full supportive care during the study, including transfusions of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care, if considered appropriate.

6.9.2 Prohibited Concomitant Medication

Use of any new medications from Day 1 through Day 15 post dose is to be avoided, if possible. This includes OTC medications (except for routine vitamins and iron) and herbal supplements. Participants' parent(s)/legal representatives should be instructed not to administer any new medications, including OTC products, without first consulting with the investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANTS DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study are handled as part of Appendix A.

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is not the same thing as a discontinuation or

withdrawal from the study (see Section 7.2). If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study.

Each participant will receive 2 doses of study intervention. An individual participant will not receive 2nd study intervention if any of the following occur in the participant in question:

1. Withdrawal of consent
2. Hypersensitivity reaction or SAE assessed as related to study drug or in the judgment of the site investigator, is related to study intervention and may jeopardize the safety of the study participant
3. Participants who apply to exclusion criteria (refer to the Section 5.2)
4. Participants who receive a replacement dose associated with cardiac surgery

Participants who have received any study drug will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn specifically from further study participation (Section 7.2) or the participant is lost to follow-up. Participants who have not received study drug, regardless of reason, will not be followed.

7.2 Participants Discontinuation/Withdrawal from the Study

Discontinuation of the participant from the study by the investigator:

- A participant may be discontinued from the study at any time at the discretion of the investigator for medical reasons.

Voluntary withdrawal from the study by the participant (his/her parent[s])/legal representative[s]):

- A participant may withdraw from the study at any time at his/her parent(s)/legal representative(s)'s discretion for any reason (or without providing any reason).
- A participant (his/her parent[s]/legal representative[s]) who wishes to withdraw from the study must be informed by the investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant (his/her parent[s]/legal representative[s]) withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator and the investigator must inform the Local and Global Study Team. Destruction of any samples

taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counseled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant should or wishes to continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant' parent(s)/legal representative(s) (where possible, telephone calls, texts, emails, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study/being lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Section 1.3 SoA. Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).Instructions for the collection and handling of human biological sample (HBS) will

be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of HBS, see Appendix C.In the event of a significant study-continuity issue (eg, caused by pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the investigator, as per local health authority/ethics requirements.

The amount of blood collected from each participant will be as follows (Table 5):

Table 5 Estimated Volume of Blood to be Collected

Visit/Study Day	Estimated Blood Volume
Visit 1/Screening or Visit 2/Day 1 prior to 1st dose	Target collection depending on body weight; <3kg – 1.5 mL 3 to <5 kg – 2.5 mL ≥5 kg – 4 mL
Visit 3/Day 151 - 180 prior to 2nd dose	4 mL
Visit 4/Day 181 - 210	4 mL
Visit 5/Day 301 - 330	4 mL
Visit 6/Day 511 - 540	4 mL
Total	Max. 20 mL

Additional blood samples will be collected, eg, at the time of hospitalization due to any respiratory infection, at the time of surgery, or when considered to be needed due to participant's safety issues at the discretion of the investigator.

8.1 Administrative Procedures

A complete medical history will be obtained at screening and a medical history update will be obtained before 1st dose as defined in Section 1.3 SoA. Assessments will include history and current medical conditions, past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, developmental, genitourinary, drug and surgical history, or any other diseases or disorders. In addition, a physical examination and vital sign assessment will be performed (refer to Section 8.3).

Body weight, a complete physical examination, and baseline information on breastfeeding, presence of siblings, smoking in the household, and if the infant attends day care, will be collected.

8.2 Surveillance for MA-RSV LRTI

8.2.1 Lower Respiratory Tract Infection

Participants will be monitored for LRTI throughout the study (refer to Section 1.3 SoA, Table 2).

All participants seeking medical attention for a respiratory illness (in either the inpatient or outpatient setting) will be evaluated for LRTI. Participants who have a primary hospitalization for a respiratory infection (ie, upper or lower tract), a respiratory deterioration during a hospitalization, or who seek outpatient medical attention (including ER visits) for a lower respiratory illness will be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory sample. Criteria for meeting the protocol-defined endpoint of MA-RSV LRTI is shown in Table 6. They include signs of lower respiratory tract involvement, a clinical indicator of disease severity and a respiratory sample positive for RSV by the central laboratory RT-PCR assay. Respiratory secretion samples that test positive for RSV by the central lab will be sequenced to assess RSV subtype and for RSV F polymorphisms.

In infantas without underlying lung disease, to meet the protocol-defined endpoint of MA-RSV LRTI, participants with signs of LRTI must have documented at least one physical examination finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs:

- Increased respiratory rate at rest (age: <2 months, ≥60 breaths/min; 2 to 6 months, ≥50 breaths/min; >6 months, ≥40 breaths/min), OR
- Hypoxemia (in room air: oxygen saturation <95% at altitudes ≤1800 meters or <92% at altitudes >1800 meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal, or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

In infants with underlying lung disease, to meet the protocol-defined endpoint of MA-RSV LRTI, participants with signs of LRTI must have documented at least one new or worsened physical examination finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs:

- Increase in baseline respiratory rate by ≥20% at rest and that rate is greater than the age-based criteria established for children with no underlying lung disease (age: < 2 months, ≥60 breaths/min; 2 to 6 months, ≥50 breaths/min; >6 months, ≥40 breaths/min), OR
- Hypoxemia (oxygen saturation <95% in room air or oxygen saturation drop of 5 percentage points from baseline in children with baseline oxygen saturation <95% in

room air, or acute documented need for supplemental oxygen or increased oxygen requirement compared with baseline), OR

- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal, or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid), OR
- Prescription of new or increased (from baseline) dose of medications including bronchodilators, steroids, diuretics, cardiac medications.

Table 6 Criteria for Meeting the Protocol-defined Endpoint of Medically Attended RSV LRTI

RSV	Lower Respiratory Tract	Medical Significance
RSV Confirmed: • Positive by central laboratory RT-PCR assay of respiratory secretion sample	**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 • For infants with underlying lung disease: Prescription of new or increased (from baseline) dose of medications including bronchodilators, steroids, diuretics, cardiac medication

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

8.2.2 RSV Hospitalization

An RSV hospitalization is defined as either (1) a respiratory hospitalization with a positive RSV test within approximately 2 days of hospital admission (primary) or (2) a new onset of respiratory symptoms in an already hospitalized participant, with an objective measure of worsening respiratory status and positive RSV test (nosocomial). Primary and nosocomial RSV hospitalization are further defined below.

Primary RSV Hospitalization

RSV diagnostic testing will be performed on respiratory secretion samples (nasal swab, or other respiratory aspirates) obtained within 2 days before or after admission for participants hospitalized for any respiratory infection (upper or lower respiratory tract infection). If the RSV diagnostic test (performed centrally via RT-PCR) is positive, the hospitalization will be classified as a primary RSV hospitalization. Deaths that can be attributed to RSV (by autopsy or clinical history and virologic evidence) will also be considered primary RSV hospitalization endpoints. Whilst a 2-day window for sampling is strongly preferable, a sample taken up to 14 days after the event remains useful and should be taken.

Nosocomial RSV Hospitalization

Participants hospitalized for a respiratory illness or non-respiratory illness whose RSV diagnostic test is negative may develop nosocomial RSV illness during the hospitalization.

If signs (such as retractions, rhonchi, wheezing, crackles, or rales) of a new lower respiratory illness occur during a hospitalization, whatever the reason for hospitalization, and there is an objective measure of worsening respiratory status (that is, new requirement for supplemental oxygen, increase in supplemental oxygen requirement from prior to the onset of symptoms, or need for new or additional mechanical ventilation), any respiratory secretion (nasal swab, or other respiratory aspirates) will be collected within 2 days from worsening of respiratory status for RSV diagnostic testing by the central laboratory. For any participant who is hospitalized for a respiratory infection (upper or lower respiratory tract), the participant must return to his/her baseline respiratory status or be clearly resolving from the preceding respiratory illness before a subsequent respiratory deterioration for a nosocomial RSV hospitalization event can be determined.

If the RSV diagnostic test (performed centrally via RT-PCR) is positive, the subsequent hospital days will count as a nosocomial RSV hospitalization. The days of RSV hospitalization will be counted beginning with the start of the respiratory deterioration that resulted in the RSV diagnostic test.

RSV LRTI Outpatient Events

Participants who seek outpatient medical attention, including ER and urgent care visits, for an LRTI, should have respiratory secretions obtained within 2 days after the initial healthcare provider assessment. Whilst a 2-day window for sampling is strongly preferable, a sample taken up to 14 days after the event remains useful and should be taken.

8.2.3 Respiratory Secretions for RSV Detection

Respiratory secretions for RSV testing will be collected from all participants with LRTIs (inpatient or outpatient) and from all hospitalized participants with any new respiratory

infection (upper or lower) within 2 days after the initial healthcare provider assessment and diagnosis. Whilst a 2-day window for sampling is strongly preferable, a sample taken up to 14 days after the event remains useful and should be taken. Nasal swab or other tracheal aspirates will be obtained.

Respiratory secretions will be tested in a central laboratory for RSV using the US FDA-cleared and CE-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + hMPV assay; Quidel Corporation, San Diego, CA, www.quidel.com). Testing may include other respiratory pathogens.

8.2.4 Monitoring for RSV Resistance

As an exploratory endpoint, RSV-positive respiratory secretion specimens from all participants will be evaluated by genotypic and phenotypic methods to monitor potential susceptibility changes to nirsevimab neutralization. The subtype and genotypic determination of RSV will be performed directly on the nasal specimens that are collected from all participants who are confirmed RSV-positive using the Lyra RSV + hMPV real-time RT-PCR assay manufactured by Quidel Corporation (Lyra RSV + hMPV assay; Quidel Corporation, San Diego CA, www.quidel.com). The full-length F gene will be sequenced by a Sanger and/or next generation sequencing methodology. Amino acid (aa) substitution(s) within the nirsevimab binding site (aa 62-69 and aa 196-212) and outside the binding site in the extracellular regions of mature F protein (aa 24-109 and aa 137-524) will be reported and compared to F protein sequences of contemporary reference RSV strains. In vitro phenotypic analysis (susceptibility to nirsevimab neutralization) will be attempted using an RSV neutralization assay with either RSV viruses constructed through site-directed mutagenesis of the F gene and reverse genetics or by cloning the F gene from the isolate into a laboratory-adapted RSV strain such as A2 or B9320.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in Section 1.3 SoA.

8.3.1 Physical Examinations

A complete physical examination will be performed on the dosing days (prior to doing at Visit 1/Visit 2, and Visit 3) and include assessments of the following: height, weight, general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems. On other visits, symptom targeted physical examination will be performed. All physical examinations will be performed by a licensed healthcare provider (eg, physician).

Physical examination will be performed at timepoints as specified in Section 1.3 SoA.

8.3.2 Vital Signs

Vital signs will be performed at timelines as specified in Section 1.3 SoA.

Vital signs (temperature, blood pressure, heart rate, and respiratory rate) will be collected at screening and the day of administration. On days when study intervention is administered, vital signs will be obtained within 60 minutes prior to dose, and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post dose.

8.3.3 Electrocardiograms

No regular ECG assessments are planned during the study.

8.3.4 Clinical Safety Laboratory Tests

Blood samples will be collected for centrally measuring hematology and clinical chemistry parameters. Additional samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The following clinical laboratory variables will be measured at screening and during the study period as pre-specified in Section 1.3 SoA.

Serum Chemistry

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Total bilirubin (TBL)
- Creatinine
- Blood urea nitrogen (BUN)

Hematology

- White blood cell count
- Lymphocyte count
- Red blood cell
- Hemoglobin
- Platelet count

8.4 AEs, SAEs, and Other Safety Reporting

The Principal Investigator (PI) is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator, and if considered an AE, it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity or changes in intensity (on intensity, refer to Appendix B 2)
- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken regarding IMP(s)
- AE caused participant's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from time of signature of the ICF throughout the follow-up period.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP during the study in a participant, the investigator shall, without undue delay, report the SAE to AstraZeneca.

8.4.2 Follow-up of AEs and SAEs

Any AE that is unresolved at the participant's last AE assessment in the study is followed up

by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 Causality Collection

The investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B

8.4.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated assessments, such as vital sign, should only be reported as AEs if they meet any of the following:

- fulfill any of the SAE criteria
- are the reason for discontinuation of the IMP
- are clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP, eg, dose adjustment or drug interruption).

If deterioration is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE, and the unscheduled test results associated with AEs, if any, or vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical term (eg, anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study (DUS).

The results from the tests specified in the study protocol and vital signs will be summarized in the clinical study report (CSR).

8.4.5 AEs Based on Signs and Symptoms

All signs or symptoms spontaneously reported by legal representative(s)/parent(s)/care provider or reported in response to the open question from the study site staff: 'Has the child had any health problems since the previous visit/you were last asked?' or revealed by

observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.4.7 Disease Under Study

DUS are those which might be expected to occur as a direct result of procedures to diagnose or treat the condition under study. Events which are unequivocally due to DUS should not be reported as AEs during the study unless they meet SAE criteria or lead to discontinuation of the IMP.

8.4.8 Definition of Adverse Events of Special Interest

AESIs will be collected during the study.

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events to characterize and understand them in association with the use of this IMP. It should be informed to appropriate sponsor study representatives **immediately**, or **no later than 24 hours** of when the investigator becomes aware of the event.

8.4.8.1 Hypersensitivity, Including Anaphylaxis

Administration of polyclonal immunoglobulin preparations and mAbs has been associated with immediate (type I) hypersensitivity (including anaphylaxis) that occurs during or after dosing. Type I hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during administration of investigational product (but does not meet the definition of anaphylaxis). Anaphylaxis is a rare event, usually occurring after subsequent exposure to antigen, and it is most accompanied by severe systemic skin and or mucosal reactions. It is potentially a fatal, systemic allergic reaction that is distinct from simple allergic reactions (eg, skin or skin-related reactions, such as rash, pruritus) because of the simultaneous involvement of several organ systems (Sampson et al, 2006). A full definition of anaphylaxis is provided in Appendix B 4.

8.4.8.2 Immune Complex Disease

Immune complex disease can manifest in the form of several conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. Drug-induced immune complex (type III) hypersensitivity reactions can occur when host immune system generates ADA resulting in soluble circulating antigen-antibody complexes formation and their deposition in blood vessels. Subsequently this induces tissue damaging inflammatory reactions mediated by complement and/or leukocytes and mast cells. The pathology and clinical manifestations are dependent on the tissues/organs involved, with vascular, skin, and renal tissues being common sites of injury. Common examples of immune complex hypersensitivity reactions are serum sickness (systemic) and Arthus reactions (local). The clinical manifestations of serum sickness include skin rash, fever, malaise, and polyarthralgias or polyarthritis. Symptoms typically develop 1 to 2 weeks after first exposure to an antigen and usually resolve in several weeks after withdrawal of the causative agent. Serum sickness needs to be differentiated from other 'serum-sickness-like' reactions that have a similar clinical presentation (eg, viral infections, anti-seizure drugs), but are believed to have different pathogenic mechanisms. Both serum sickness and serum sickness-like reactions have been reported with mAbs (eg, rituximab, infliximab). Clinical presentation and time to onset should be considered for the diagnosis and differentiation of these reactions. Diagnosis of these suspected reactions is best confirmed via biopsy of the affected tissues.

8.4.8.3 Thrombocytopenia

Thrombocytopenia is a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150,000 to 450,000 platelets per µL. The 3 major causes of low platelet counts include: 1) insufficient platelet synthesis in the bone marrow; 2) increased breakdown of platelets in the bloodstream; and 3) increased breakdown of platelets in the spleen or liver. General symptoms of thrombocytopenia include bleeding in the mouth and gums, bruising, nosebleeds, and petechiae (pinpoint red spots/rash). Severe bleeding is the major complication, which may occur in the brain or gastrointestinal tract. Drug-induced thrombocytopenia is a reversible form of thrombocytopenia that should be suspected in a participant who presents with new onset thrombocytopenia or recurrent episodes of acute thrombocytopenia, without an obvious alternative etiology. It is commonly induced by drug-dependent antibodies that cause platelet destruction or clearance by the reticuloendothelial system (drug-induced immune thrombocytopenia), and less commonly by drug-induced bone marrow suppression or autoimmune thrombocytopenia that is initiated by exposure to the offending drug but persists in its absence. The initial approach to the participant with suspected drug-induced thrombocytopenia involves confirming thrombocytopenia, establishing a temporal relationship to a drug, and eliminating other causes of thrombocytopenia. The diagnosis is made clinically by documenting prompt resolution of thrombocytopenia after discontinuation of the suspected drug (typically within 1 week). Most participants with drug-induced thrombocytopenia require no specific treatment, as their

platelet counts will recover promptly following withdrawal of the causative agent.

8.4.9 Definition of New-Onset Chronic Diseases

A NOCD is a newly diagnosed medical condition that is of a chronic, ongoing nature. It is observed after receiving the investigational product and is assessed by the investigator as medically significant. Examples of NOCDs include, but are not limited to diabetes, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy). Events that would not be considered as NOCDs are mild eczema, diagnosis of a congenital anomaly present at study entry, or acute illness (eg, upper respiratory infection, otitis media, bronchitis).

8.4.10 Reporting of SAEs

All SAEs must be reported whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate sponsor representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform the designated sponsor representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the Electronic Data Capture (EDC) system, an automated email alert is sent to the designated sponsor representative.

When the EDC is temporarily not accessible or the EDC system is not available, the investigator or other study site staff reports to IQVIA Safety Operations by the contact information below. The sponsor study representative will advise the investigator/study site personnel how to proceed.

IQVIA Safety Operations
Fax: PPD
Email: PPD

For further guidance on the definition of an SAE, refer to Appendix B.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca IMP.

8.4.11 Medication Error

8.4.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca (or designee) representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.10) and **within 30 days** for all other events.

8.4.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 5.

8.4.12 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca (or designee) representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (refer to Section 8.4.10) and **within 30 days** for all other overdoses.

8.5 Pharmacokinetics

- Serum samples will be collected for measurement of concentrations of nirsevimab as specified in Section 1.3 SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for urgent safety reasons, and this may be reflected as a protocol deviation.
- The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Samples collected for analyses of serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.
- For storage, re-use, and destruction of samples for PK, see Appendix C.
- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future use analysis.
- Additional analyses may be conducted on the anonymized, pooled, or individual PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Collection of Samples for Pharmacokinetics

Blood samples will be collected for measurement of nirsevimab in serum at specified time points in Section 1.3 SoA. In addition, unscheduled blood samples will be collected for measuring nirsevimab serum levels from participants hospitalized with LRTI or any respiratory infection (regardless of upper or lower infection) within approximately 2 days following hospitalization.

8.5.2 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of the sponsor, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.6 Immunogenicity and Anti-RSV Neutralizing Antibody Assessments

- Blood samples for determination of ADA and anti-RSV neutralizing Ab in serum will be assayed by bioanalytical test sites operated by or on behalf of the sponsor, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.
- Samples will be collected to evaluate ADA responses to nirsevimab in serum. Evaluation will be performed using validated immunoassays. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, using the previously described positive-negative cut points.
- Samples for pharmacodynamic (anti-RSV neutralizing Ab) assessments will be collected according to the SoA (see Section 1.3 SoA).
- Samples collected will be labelled, stored, and shipped as detailed in the Laboratory Manual.
- For storage, re-use, and destruction of samples, see Appendix C.

Extra blood samples will be collected for measurement of ADA and anti-RSV neutralizing Ab will be collected from participants hospitalized with LRTI or any respiratory infection within 2 days following hospitalization.

9 STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalized prior to clinical data lock, and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

No statistical hypothesis analysis is planned.

9.2 Sample Size Determination

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.

9.3 Populations for Analyses

The following populations are defined in Table 7:

Table 7 Populations for Analysis

Population/analysis set	Description
As-treated set 1	The As-treated set 1 consists of all participants who have received at least 1 dose of IMP.
As-treated set 2	The As-treated set 2 consists of all participants who have received the 2 doses of IMP.
PK Analysis Set	Participants who receive at least 1 dose of IMP and who had at least 1 quantifiable serum PK observations. Data issues that impact the PK results may result in exclusion from the PK summaries. All PK summaries will be based on this analysis set. PK in participants with replacement dose is separately summarized.

ICF = informed consent form; IMP = investigational medicinal product; PK = pharmacokinetics

9.4 Statistical Analyses

9.4.1 General Considerations

There are 2 planned analyses for this study: a primary analysis and a final analysis. The primary analysis will be conducted when all enrolled participants have been followed through Visit 5 (ie, around 150 days post 2nd dose). The final analysis will be conducted after all participants have completed the last visit (Visit 6) of the study (ie, Day 360 post the 2nd dose or last dose).

All data, including baseline characteristics, safety, and efficacy, will be summarized as below:

- Categorical data will be summarized by the number and percentage of participants in each category.
- Continuous variables will be summarized by mean, SD, median, Q1, Q3, minimum, and maximum. In general, unless stated otherwise, baseline characteristics will be defined as the last non-missing value prior to dosing.
- In general, unless stated otherwise, baseline will be defined as the last non-missing value prior to dosing.

More details on statistical analyses will be provided in the SAP.

Data analyses will be conducted using SAS® System Version 9.4 or higher.

9.4.2 Safety

Adverse events (AEs) will be graded based on of the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) where applicable

for pediatric assessments. It is shown in Appendix B 2 'Intensity Rating Grade'. AEs will be coded according to the current version of Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity, and relationship to the study intervention will be summarized. Other safety assessments will include the occurrence of AESIs of immediate hypersensitivity reactions (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis) following investigational product administration, and the occurrence of NOCDs following investigational product administration.

The primary estimand is presented below:

- Treatment: One 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 followed with a 2nd fixed IM dose of 50 mg if current weight is <5 kg or 100 mg if current weight is ≥5 kg administered 5 to 6 months following the 1st dose.
- Population: As-treated set 2, all participants who have received 2 doses of IMP.
- Endpoint: Incidence of TEAEs, TESAEs, AESIs, and NOCDs through 360 days post 2nd dose.
- Intercurrent Events: Intercurrent events are defined as study discontinuations prior to Day 151 after 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.

Safety analyses may also be repeated in As-treated set 1 population.

9.4.3 Secondary Endpoints

9.4.3.1 Pharmacokinetics

In PK analysis set, serum concentrations of nirsevimab at the specific timepoints will be evaluated following 2 doses of nirsevimab given 5 to 6 months apart. Nirsevimab serum concentration data will be presented in descriptive statistics.

9.4.3.2 Anti-Drug Antibody

Based on the As-treated set 2 population, the occurrence of ADA to nirsevimab will be assessed and summarized by number and percentage of participants who are ADA-positive. The impact of ADA on PK, and association with TEAEs and TESAEs, will be assessed, if data permitted.

9.4.3.3 Anti-RSV Neutralizing Antibody Evaluation

Based on the As-treated set 2 population, analysis of serum anti-RSV neutralizing Ab in nirsevimab recipients will be summarized by geometric mean titer (GMT) and geometric mean fold-rise (GMFR) with corresponding 95% CI.

9.4.4 Exploratory Endpoint(s)

9.4.4.1 Occurrence of MA-RSV LRTI

Based on the As-treated set 2 population, the number and percentage of participants with MA-RSV LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days (primary timepoint analysis) and 360 days (final timepoint analysis) post 2nd dose will be summarized. For participants with multiple MA-RSV LRTI events, only the first occurrence will be used in the analysis.

The analysis will be repeated for occurrence of hospitalizations due to RT-PCR-confirmed RSV through 150 and 360 days post 2nd dose.

9.4.4.2 Monitoring RSV Resistance to Nirsevimab

Genotypic analysis of the full-length mature F protein will be conducted on all RSV-positive isolates confirmed centrally using the Lyra RSV + hMPV real-time RT-PCR assay manufactured by Quidel Corporation. RSV genotypic analysis will report the sequence changes in the mature F protein from all RSV-positive isolates compared to contemporary RSV A and RSV B reference strains. Susceptibility of novel RSV variants to nirsevimab will be tested and compared to control viruses.

Results on RSV resistance analyses will be reported separately from CSR.

9.5 Deviations from Clinical Study Protocol

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between PI and the sponsor or the institutional review board (IRB) approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the participants or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (eg, changes to the name/department name of the study site, the address or phone number of the study site or the sponsor/designee, and monitors).

The investigator(s) should document any deviation from the protocol regardless of reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the participants or for other medically compelling reason, the PI must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to the sponsor (or designee), the head of the study site, and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as the sponsor should be obtained via the head of the study site.

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