Title Page

Protocol Title:

A Phase IIIb randomized open-label study of nirsevimab (versus no intervention) in preventing hospitalizations due to respiratory syncytial virus in infants (HARMONIE)

Study Code: VAS00006 (HARMONIE)

Amendment Number: 3

Compound: 526 – human Monoclonal Antibody Respiratory Syncytial Virus (RSV)

Brief Title:

Study of a single intramuscular dose of nirsevimab in the prevention of hospitalizations due to respiratory syncytial virus (RSV) infection in healthy term and preterm infants during the first year of life

Study Phase: IIIb

Sponsor Name and Legal Registered Address:

Sanofi Pasteur
14 Espace Henry Vallée, 69007 Lyon, France

Manufacturer:

MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC
One MedImmune Way, Gaithersburg, Maryland, 20878, USA

Regulatory Agency Identifier Numbers:

EudraCT: 2022-000099-20

WHO UTN: U1111-1272-2514

Protocol Version Number: 5.0

Approval Date: 05 FEB 2024

Responsible medical officer (RMO), and designee(s), and pharmacovigilance (PV) representative names and contact information are provided in the investigator site file.

The study centers, the Investigators at each center, and the Coordinating Investigators are listed in a separate document.

Document History

Previous Version	Date	Comments
1.0	01 March 2022	Version not approved by all IECs/IRBs
2.0	17 June 2022	First version used in the study
3.0	19 July 2023	Second version used in the study
4.0	01 February 2024	Version not used in the study

IEC: Independent Ethics Committee; IRB: Institutional Review Board

Version in bold font has been approved by the IECs/IRBs and used in the study

Amendment 2 – Version 4.0 (01-February-2024)

The objectives of this amendment are:

- To extend the time window for signing the Addendum to the Inform Consent Form (ICF) for UK's participants.
- To add routine immunization with Beyfortus® as reportable concomitant medications. For countries where Beyfortus has been made commercially available during the study conduct, the sites will be asked to report any routine immunization with Beyfortus.
- To clarify the data collection during the 12-month extension period in case of wheeze (including any concomitant medications during wheezing episodes) for UK reconsented participants.

Amendment 3 – Version 5.0 (05-February-2024)

The objective of this amendment is to clarify the definition of a wheezing episode (see Section 8.1.2.4).

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase IIIb randomized open-label study of nirsevimab (versus no intervention) in preventing hospitalizations due to respiratory syncytial virus in infants (HARMONIE)

Brief Title:

Study of a single intramuscular dose of nirsevimab in the prevention of hospitalizations due to respiratory syncytial virus (RSV) infection in healthy term and preterm infants during the first year of life

Rationale:

This study is being proposed to collect and analyze data on the safety of the monoclonal antibody (nirsevimab) and its efficacy compared to that of no intervention in preventing hospitalizations[a] for lower respiratory tract infection (LRTI) due to RSV as confirmed by test (henceforth referred to as RSV LRTI hospitalization). Data will be collected from infants born during the RSV season as well as from infants born out of RSV season. The typical RSV season in the Northern Hemisphere spans approximately 5 months and usually starts in October or November. As the start and end dates of the RSV season may change in response to the actual circulation of RSV, in this study, the RSV season will be defined on country-by-country basis and will be based on country-specific epidemiological surveillance.

The study will also assess health care utilization parameters associated with hospitalization for LRTI due to RSV as confirmed by test. This could provide some insights into the potential benefits of an all-infant nirsevimab implementation strategy.

[a] "Hospitalization" is defined as the decision to admit to in-patient care by the treating physician.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization compared to no intervention	• Overall incidence of RSV LRTI hospitalization through the RSV season
Key Secondary	
• To assess the efficacy of nirsevimab in preventing very severe RSV LRTI compared to no intervention	• Incidence of very severe RSV LRTI defined as RSV LRTI hospitalization with oxygen saturation < 90% (at any time during hospitalization) and oxygen supplementation, through the RSV season
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization compared to no intervention in each country	• Incidence of RSV LRTI hospitalization through the RSV season in each country
• To describe in each study group the incidence of RSV LRTI hospitalization and all-cause LRTI hospitalization in UK reconsented participants from D366 to D731	• Incidence of RSV LRTI hospitalization • Incidence of hospitalization for all-cause LRTI

Overall Design

Type of design	Open-label, multi-center, parallel 2-arm study: nirsevimab compared to no preventive RSV intervention
Phase	IIIb
Control method	Comparison to no preventive intervention
Study population	Healthy infants born ≥ 29 weeks gestational age (WGA) entering their first RSV season and not eligible for palivizumab (born either in-season or out-of-season)
Countries	France, Germany, and the United Kingdom
Level and method of blinding	Open-label
Study intervention assignment method	Randomization will be stratified by the following: • Country • Age group at time of randomization (ie, age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months)

Brief Summary

The purpose of this study is to determine the efficacy and safety of a single intramuscular (IM) dose of nirsevimab, compared to no intervention, for the prevention of hospitalizations due to

LRTI caused by confirmed RSV infection (henceforth referred to as RSV LRTI hospitalizations) in all infants under 12 months of age who are not eligible to receive palivizumab.

Study Duration: 12 months post-dosing/randomization for France, Germany, and UK non-reconsented participants, 24 months post-dosing/randomization for UK reconsented participants. D01 will be the day of randomization (both study groups) and immunization (nirsevimab group).

Treatment Duration: 1 IM injection

Study Calendar:

- Planned date of first participant in: 01 September 2022
- Planned date of last participant in: 28 February 2023
- Planned date of last visit last participant: 28 February 2025

Note: As much as operationally feasible, the date of inclusion of the first participant will be aligned with the beginning of the RSV season. It is thus possible that the first participants are enrolled earlier than 01 September 2022.

Visit Frequency: 1 in-person dosing/randomization visit, with monthly safety follow-up electronic contacts through the first 6 months post-dosing/randomization for all participants. The study will also include a 12-month (D366) follow-up telephone call. The D366 follow-up telephone call will be the final follow-up telephone call for France, Germany, and UK non-reconsented participants. The study will include a 18-month (D546) and a 24-month (D731, final telephone call) follow-up telephone calls for UK reconsented participants.

Condition/Disease: RSV LRTI hospitalization.

Study Hypotheses: Compared with no preventive intervention, a single IM nirsevimab dose (50 mg if weight < 5 kg or 100 mg if weight ≥ 5 kg) will prevent RSV LRTI hospitalizations in healthy infants born ≥ 29 WGA and entering their first RSV season in all 3 countries combined.

Health Measurement/Observation:

Participants will be followed for safety for up to 12 months (for France, Germany, and UK non-reconsented participants) or for up to 24 months (for UK reconsented participants) after the dosing/randomization visit (Visit 01) to collect information on the following:

- Any immediate adverse events (AEs) reported in the 30 minutes after immunization
- Presence of non-serious AEs until 30 days after Visit 01
- Presence of serious adverse events (SAEs), adverse events of special interest (AESIs), and medically attended adverse events (MAAEs) up to D366 phone-call for all participants
- Presence of SAEs (considered as related to the administration of the IMP by the Investigator) from D366 to D731 phone-call for UK reconsented participants

Participants will be able to connect to the electronic diary (eDiary) at any time during the first year of the study. By answering to the eDiary's Yes/No questions, they will be able to report any safety events that may occur in their infant, including hospitalizations, throughout the first year of

the study. An automatic monthly electronic message through the first 6 months post-dosing/randomization will remind parents or legally acceptable representatives (LARs) of participants to report any safety events that occurred. Efficacy data (ie, RSV LRTI hospitalization and very severe RSV LRTI) will be collected through the participants' medical records and reported in the eCRF by the site personnel or designee.

A follow-up phone call will be made to the parents or LARs of the participant by the site personnel or designee at D366 (end of the study for France, Germany, and non-reconsented UK participants) to collect any safety event that may have occurred in the 6-month period since the last electronic contact.

Two additional follow-up phone calls – at D546 and D731 post-dosing/randomization (end of the study) – will be made to the parents or LARs of the UK reconsented participants by the site personnel to collect any LRTI hospitalizations or related SAEs that might have occurred from D366 to D731 post-dosing/randomization. A memory aid will be provided to the parents or LARs of the UK reconsented participants to record any of these events that may occur during the second year of the study.
During the 12- and 24-month follow-up calls, the site investigator or staff designee will ask to parents/LARs of UK reconsented participants if the participants had experienced any medically attended cough, chest or breathing problems throughout the study period. After the 12-month follow-up phone call (when possible) and the 24-month follow-up phone call, the site investigator or staff designee (including third parties authorized by the site investigators) will access the UK reconsented participants' medical record (general practitioner's or hospital's record) to determine if the medical event meets with the definition of wheeze provided by the Sponsor (see Section 8.1.2.4). If so, the event and related complementary information (including any medications prescribed during wheeze) will be retrospectively collected.

Number of Participants:

A total of 28 860 participants is expected to be randomized. This study is event driven.

For each country, at least 74 events of RSV LRTI hospitalization through the RSV season are needed to ensure the 90% power to conclude the efficacy of nirsevimab in preventing RSV LRTI hospitalization in that country, compared to no intervention, taking the multiplicity adjustment into consideration.

Intervention Groups and Duration:

Eligible participants will be randomized in a 1:1 ratio to receive a single IM injection of 50 mg (if weight < 5 kg) or 100 mg (if weight ≥ 5 kg) of nirsevimab or no RSV preventive intervention on D01. Randomization will be stratified by country and by age group at the time of randomization (ie, age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, and age > 6.0 months).

Participants will be followed for approximately 12 months after dosing/randomization for France, Germany, and UK non-reconsented participants and approximately 24 months after dosing/randomization for UK reconsented participants.

Study intervention

The study intervention is described in Table 1.1.

Table 1.1: Identity of study intervention

Intervention Name	Nirsevimab
Use	Experimental
IMP and NIMP	IMP
Type	Extended half-life monoclonal antibody
Dose Form	Sterile solution for injection
Unit Dose Strength	100 mg/mL
Excipients/Diluent	• 30 mM histidine/histidine-HCl • 80 mM arginine-HCl • 120 mM sucrose • 0.02% (w/v) polysorbate 80 • pH 6.0 water for injection
Dosage Levels	0.5 mL presentation corresponding to 50 mg (if weight < 5 kg) or 1.0 mL presentation corresponding to 100 mg (if weight ≥ 5 kg) at D01
Number of Doses / Dosing Interval	1 dose
Route of Administration	IM
Site of Administration	Anterolateral aspect of the thigh according to standard practice procedures for IM injections in infants
Injection Site Side	Either
Sourcing	Provided by AstraZeneca
Packaging and Labeling	AstraZeneca
Current/Former Name or Alias	n/a
Batch Number	TBD
Storage Conditions	The IMP will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The IMP must not be frozen, shaken, or exposed to light. Keep the prefilled syringe in the outer carton in order to protect from light.

Abbreviations: IM, intramuscular; IMP, Investigational Medicinal Product; n/a, not applicable; NIMP, Non-Investigational Medicinal Product; TBD, to be determined

Statistical considerations:

Primary endpoint

The primary endpoint is the overall incidence of RSV LRTI hospitalization through the RSV season in healthy term and preterm infants in all 3 countries combined.

The efficacy of nirsevimab in preventing RSV LRTI hospitalization compared to no RSV intervention will be estimated accounting for the follow-up time post-dosing/randomization up to the data cut-off date for the Primary Analysis as follows:

(1- (CN / NN) / (CC / NC)) × 100%

where:

- CN and CC are the numbers of all RSV LRTI hospitalization through the RSV season in the nirsevimab and the no intervention groups, respectively.
- NN and NC are the total person-time contributed by participants randomized in the nirsevimab and the no intervention groups, respectively.

The 95% CI for the efficacy will be calculated by an exact method assuming a binomial distribution of the number of RSV LRTI hospitalization in the nirsevimab group conditional on the total number in both groups accounting for the follow-up time post-dosing/randomization.

The superior efficacy of nirsevimab in preventing RSV LRTI hospitalization will be concluded if the lower bound of the efficacy is > 0%. The primary efficacy analysis of the primary endpoint will be performed on all randomized participants.

Main secondary endpoints

Very severe RSV LRTI

A very severe RSV LRTI is defined as confirmed RSV LRTI hospitalization with oxygen saturation < 90% (at any time during hospitalization) and oxygen supplementation.

If the efficacy of nirsevimab in preventing RSV LRTI hospitalization in all 3 countries combined is demonstrated in the primary efficacy analysis, the very severe RSV LRTI through the RSV season will be compared between the nirsevimab and no intervention groups on all randomized participants using the same method for the primary efficacy analysis of the primary endpoint. If the lower bound of the 95% CI for the efficacy is > 0%, the superior efficacy of nirsevimab in preventing very severe RSV LRTI compared to no intervention will be demonstrated.

RSV LRTI Hospitalization in each country

If the efficacy of nirsevimab in preventing very severe RSV LRTI compared to no intervention is concluded, the prevention of any RSV LRTI hospitalization by nirsevimab will be evaluated in each of the 3 countries. The same analysis as described for the primary efficacy analysis for the primary endpoint with Bonferroni-Holm procedure based on the adjusted CIs for the multiplicity adjustment will be used to calculate the efficacy on all randomized participants in each country. The superior efficacy of nirsevimab in preventing RSV LRTI hospitalization will be concluded for the country if the lower bound of the efficacy is > 0%.

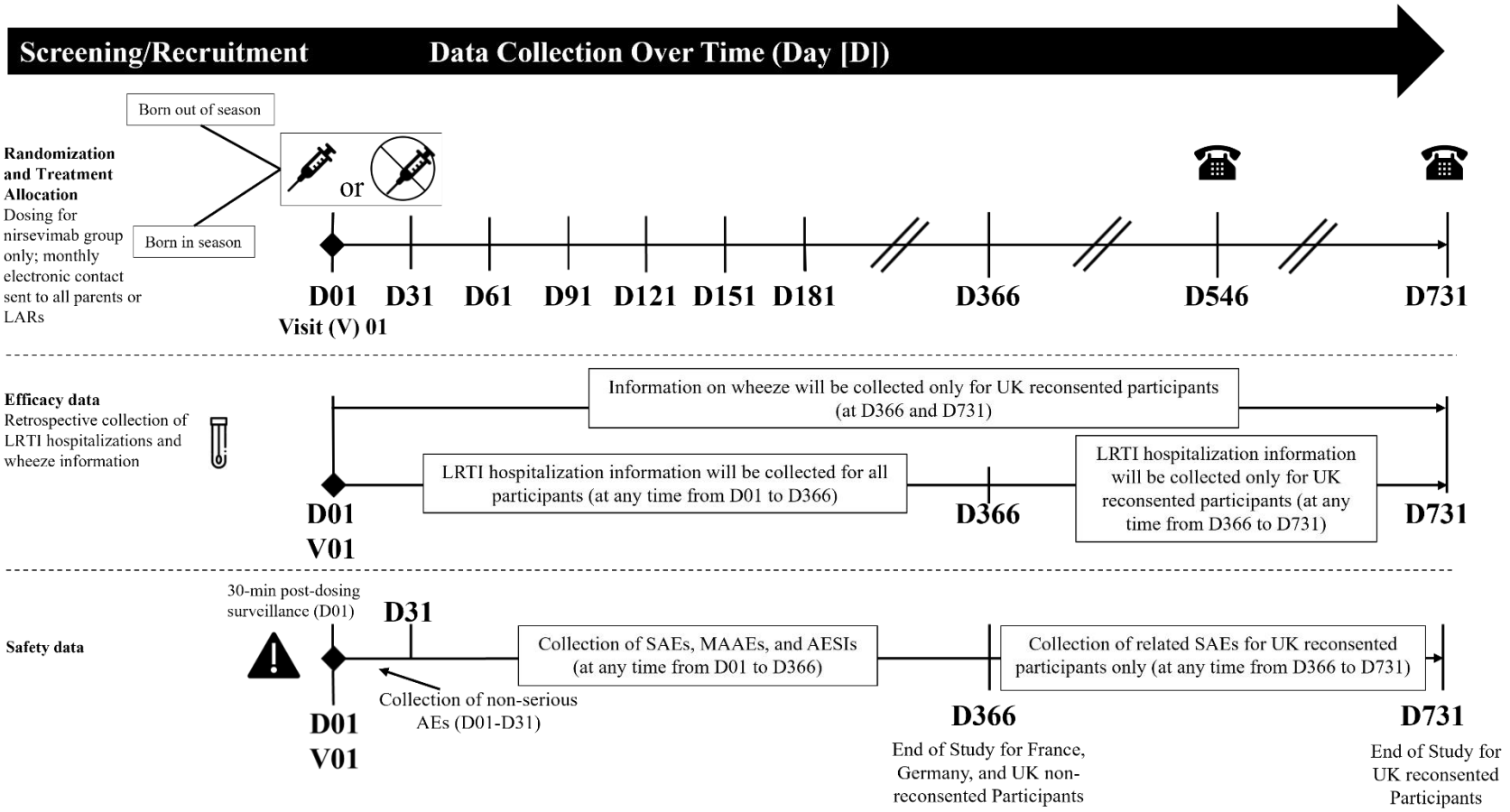
Data Monitoring/Other Committee:

No

1.2 Schema

The graphical design of the VAS00006 (HARMONIE) study is presented in Figure 1.1.

Figure 1.1 – Graphical study design



Abbreviations: AESI, adverse event of special interest; D, day; LAR, legally acceptable representative; LRTI, lower respiratory tract infection; MAAE, medically attended adverse event; SAE, serious adverse event; UK, United Kingdom; V, visit

1.3 Schedule of Activities (SoA)

Table 1.2: Schedule of activities

Phase IIIb Study, 1 Visit, 1 Immunization (if randomly assigned to the nirsevimab group), 6 monthly follow-up contacts, 1 phone call at Day 366 for all participants, 2 phone calls at Day 546 and Day 731 for UK reconsented participants, 12 months' Duration Per Participant (France, Germany, and UK non-reconsented participants) or 24 months' Duration Per Participant (UK reconsented participants)

Visit (V)/Contact	***Collection of information in the eCRF***	**V01**	**6-month efficacy and safety follow-up, monthly through the first 6 months post-dosing/randomization**						**12-month safety follow-up**	**18-month safety follow-up §§§**	**24-month safety follow-up §§§**
Study timelines (days [D])		D01 *	D01-D181						D366	D546	D731
			D31	D61	D91	D121	D151	D181			
Time interval		NA	V01 + 180 days						V01 + 365 days	V01 + 545 days	V01 + 730 days
Time windows		NA	[+14 days]						[+14 days]	[+14 days]	[+14 days]
Visit procedures:											
In-person visit		X									
Electronic reminders			X†	X†	X†	X†	X†	X†	X†		
Phone Contact	X								X ‡‡	X ****	X ****
Informed consent	X	X #									

Visit (V)/Contact	***Collection of information in the eCRF***	**V01**	**6-month efficacy and safety follow-up, monthly through the first 6 months post-dosing/randomization**						**12-month safety follow-up**	**18-month safety follow-up §§§**	**24-month safety follow-up §§§**
Study timelines (days [D])		D01 *	D01-D181						D366	D546	D731
			D31	D61	D91	D121	D151	D181			
Time interval		NA	V01 + 180 days						V01 + 365 days	V01 + 545 days	V01 + 730 days
Time windows		NA	[+14 days]						[+14 days]	[+14 days]	[+14 days]
Addendum to Informed consent (for parents/LARs of UK participants only) ††††	X								X		
Inclusion/exclusion criteria	X	X									
Collection of demographic data	X	X									
Collection of medical history	X Significant Medical History	X									
Collection of concomitant medications***	X Reportable concomitant medications	X	X	X	X	X	X	X	X	X‡‡‡‡	X‡‡‡‡
Collection of concomitant vaccines	X	X †††									
Measurement of participant's weight	X	X									

Visit (V)/Contact	***Collection of information in the eCRF***	**V01**	**6-month efficacy and safety follow-up, monthly through the first 6 months post-dosing/randomization**						**12-month safety follow-up**	**18-month safety follow-up §§§**	**24-month safety follow-up §§§**
Study timelines (days [D])		D01 *	D01-D181						D366	D546	D731
			D31	D61	D91	D121	D151	D181			
Time interval		NA	V01 + 180 days						V01 + 365 days	V01 + 545 days	V01 + 730 days
Time windows		NA	[+14 days]						[+14 days]	[+14 days]	[+14 days]
Contact IRT system for participant randomization number allocation	X	X									
Contact IRT system for randomization and treatment allocation	X	X									
Pre-immunization temperature (only for the nirsevimab group)		X									
Immunization (only for the nirsevimab group)	X	X‡‡‡									
Immediate surveillance (30 min; only for the nirsevimab group)	X	X									
eDiary access provided ‡		X									
Study card provided		X §§§									

Visit (V)/Contact	***Collection of information in the eCRF***	**V01**	**6-month efficacy and safety follow-up, monthly through the first 6 months post-dosing/randomization**						**12-month safety follow-up**	**18-month safety follow-up §§§**	**24-month safety follow-up §§§**
Study timelines (days [D])		D01 *	D01-D181						D366	D546	D731
			D31	D61	D91	D121	D151	D181			
Time interval		NA	V01 + 180 days						V01 + 365 days	V01 + 545 days	V01 + 730 days
Time windows		NA	[+14 days]						[+14 days]	[+14 days]	[+14 days]
Instruct participant's parents/LARs on the reporting of follow-up information (ie, SAEs, MAAEs, AESIs, concomitant medications, and concomitant vaccines)		X									
eDiary data reviewed §			X	X	X	X	X	X	X		
Memory Aid provided**									X		
Memory Aid reviewed**										X	X
Collection of non-serious adverse events ††	X	X††	X								
Collection of SAEs, AESIs, and MAAEs	X	To be reported at any time up to D366								Related SAEs to be reported from D366 to D731 for UK reconsented participants only	
Diagnosis of LRTI ‡‡	X	To be reported at any time up to D366								To be reported from D366 to D731 for UK reconsented participants only	

Visit (V)/Contact	***Collection of information in the eCRF***	**V01**	**6-month efficacy and safety follow-up, monthly through the first 6 months post-dosing/randomization**						**12-month safety follow-up**	**18-month safety follow-up §§§**	**24-month safety follow-up §§§**
Study timelines (days [D])		D01 *	D01-D181						D366	D546	D731
			D31	D61	D91	D121	D151	D181			
Time interval		NA	V01 + 180 days						V01 + 365 days	V01 + 545 days	V01 + 730 days
Time windows		NA	[+14 days]						[+14 days]	[+14 days]	[+14 days]
Collection of wheeze information §§§§	X								X		X
12-month follow-up; End of participation record (for France, Germany, and non-reconsented UK participants only) §§	X								X		
24-months follow-up, End of participation record (for UK reconsented participants only)	X										X

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CRF, case report form; D, Day; eCRF, electronic case report form; eDiary, electronic diary; IRT, interactive response technology; LAR, legally acceptable representative; LRTI, lower respiratory tract infection; MAAE, medically attended adverse event; min, minutes; RSV, respiratory syncytial virus; SAE, serious adverse event; V, Visit

* D01 is the day of inclusion in the study (ie, verification of inclusion/exclusion criteria, dosing/randomization, access to eDiary, etc.)

† Electronic reminders to participants' parents or LARs to complete the eDiary in case of an AE or hospitalization. These reminders will be made through the eDiary on a monthly basis until 6 months post-dosing/randomization and at 12 months post-dosing/randomization. It is to be noted that parents or LARs will be able to connect to the eDiary at any time during the first year of the study to report any health events that may occur.

\# Signature of the ICF by parents or LARs can be undertaken before V01. In countries where both parents or LARs are required to provide consent for their infant's participation, signature of the ICF needs to be completed before dosing/randomization and any assessments done at V01. An electronic ICF process can be implemented if applicable as per country regulations. Other procedures/assessments such as checking inclusion/exclusion criteria must be performed on D01.

‡ The Investigator or an authorized designee will provide parents or LARs instructions on how to use the eDiary to report AEs, hospitalizations or any health-related events in their infant, and on how to answer the monthly reminder. The Investigator or an authorized designee will also describe the process through which information on AEs and hospitalization will be collected by the call center.

§ From D01 to D366, each time a health event is captured in the eDiary, a medical call center will contact parents or LARs to collect and report the health event's information in the eCRF. The Investigator or an authorized designee will review information reported in the eCRF and interview the participants' parents or LARs if any additional information needs to be collected.

** From D366 to D731, UK reconsented participants' parents/LARs are requested to capture in a memory aid any hospitalizations and emergency-room visits experienced by the participants. The memory aid will be reviewed by the investigator or site staff during the 18-month and 24 month follow-up calls to collect any information on SAE or LRTI hospitalizations that may have occurred since the previous contact. If an SAE is reported, the investigator or site staff will assess the relationship and only related SAE will be reported in the eCRF.

†† Immediate AE occurring within 30 minutes after immunization will be collected on V01.

‡‡ Assessment of LRTI (inpatient) requiring hospitalization. In case of hospitalization due to LRTI symptoms at any time during the study after randomization, an RSV test is to be performed as per the hospital routine practice. Test results and information about the LRTI hospitalization such as O2 saturation, respiratory rate, oxygen supplementation, intravenous fluid administration, admission to intensive care unit, date of admission and of discharge are to be collected retrospectively.

It is to be noted that, for participants hospitalized due to LRTI symptoms whose participation in the study is prematurely terminated, the Investigator or designee may seek information on the LRTI hospitalization for the assessment of efficacy endpoints. This retrospective collection of information on LRTI hospitalization for participants withdrawn from the study will be possible only if the parents or LARs provided consent by ticking the corresponding box in the informed consent form.

§§ A safety follow-up phone contact is to be made at 12 months post-dosing/randomization. For participants who have prematurely terminated the study (eg, no answer to monthly electronic contact within the first 6 months post-dosing/randomization), the site or authorized designee should attempt to contact them and complete this 12-month safety follow-up to identify the occurrence of any SAEs, MAAEs, and AESIs that had not yet been reported, except if they specified that they do not want to be contacted again and it is documented in the source document.

*** Be certain to record concomitant medications at the time of dosing/randomization, including vaccine administered in the 14 days prior to Visit 01, during Visit 01, and up to 14 days after Visit 01. Concomitant reportable medications will be collected in the event of an AE (including an LRTI hospitalization) through a phone contact by the medical call center or through the participant's medical records, as applicable. Sites will also be asked to report any routine immunization with nirsevimab (Beyfortus®). See Section 6.8 for details on concomitant reportable medications.

††† Vaccine history is to be recorded in the eCRF. This includes vaccines co-administered during Visit 01, as well as vaccines administered up to 14 days before and up to 14 days after dosing/randomization.

‡‡‡ Immunization is only for Group 1, the nirsevimab arm. Participants randomly assigned to Group 2 will receive no RSV preventive intervention.

§§§ Parents or LARs of the participant will be instructed to keep a study card that indicates study participation. The study card is to be presented to the hospital in the event of hospitalization due to any cause. The site or the Investigator's contact details should be reported on it.

**** A safety follow-up phone contact is to be made at 18 months and at 24 months post-dosing/randomization for UK reconsented participants only. During these calls, the investigator or site staff will interview the participant's parents/LARs to review the memory aid and collect any information on SAE or LRTI hospitalizations that may have occurred since the previous contact. If an SAE is reported, the investigator or site staff will assess the relationship and only related SAE will be reported in the eCRF.

†††† Consent of the Addendum to Informed Consent Form can be obtained from parents/LARS at any time prior or after the D366 phone call (up to D731). An electronic ICF process or consent by email can be implemented if applicable as per country regulations. Following the D366 phone call, an on-site visit can be organized for participants' parents/LARs unable to realize the e-consent or email consent in order to collect the paper consent.

‡‡‡‡ Only concomitant medication related to related SAE and/or LRTI hospitalization will be collected. Sites will also be asked to report any routine immunization with nirsevimab (Beyfortus).

§§§§ During the 12- and 24-month follow-up call, the site investigator or staff designee will ask to parents/LARs of UK reconsented participants if the participants had experienced any medically attended cough, chest or breathing problems throughout the study period. After the 12-month follow-up phone call (when possible) and the 24-month follow-up phone call, the site investigator or staff designee (including third parties authorized by the site investigators) will access the UK reconsented participants' medical record (general practitioner's or hospital's record) to determine if the medical event meets with the definition of wheeze provided by the Sponsor (see Section 8.1.2.4). If so, the event and related complementary information (including any medications prescribed during wheeze) will be retrospectively collected.

2 Introduction

Nirsevimab is being developed for the prevention of LRTI caused by RSV in all infants (healthy term or preterm infants, and infants with underlying conditions) entering their first RSV season. It is being developed under a commercial agreement between Sanofi and AstraZeneca.

2.1 Study Rationale

Respiratory syncytial virus (RSV) is a common respiratory pathogen that causes disease throughout life but particularly in the early years. It is the most common cause of acute respiratory illness in infants and is associated with significant morbidity and mortality.

Currently, the only licensed preventive measure against RSV is palivizumab, a monoclonal antibody licensed for use in a small subset of the pediatric population. Although it depends on guidelines from recommending bodies in individual countries, the eligible pediatric population usually includes infants born at ≤ 35 weeks gestational age and up to 6 months of age at the start of the RSV season, and those with chronic lung disease and congenital heart disease up to 24 months of age[a]. Overall, the group of eligible infants represents 2-6% of the birth cohort annually depending on each country's guidelines (1) (2) (3). In the population of infants who do not qualify for palivizumab administration, the standard of care does not include any preventive measure and is limited to supportive care in the event of RSV infection.

Nirsevimab is a recombinant human immunoglobulin G1 kappa monoclonal antibody that neutralizes RSV by binding to a highly conserved, neutralizing epitope on the prefusion conformation of the RSV F protein. This binding prevents the RSV F protein from mediating fusion between the viral and cellular membranes, which is an essential step for viral entry.

The primary objective of the clinical development program for licensure was to demonstrate that nirsevimab will protect preterm and term infants from medically-attended lower respiratory tract infection (LRTI) caused by RT-PCR confirmed RSV during their first RSV season as measured by a significant reduction in disease incidence.

The Phase IIb pivotal study conducted in healthy preterm infants born at ≥ 29 to < 35 weeks gestational age included a secondary endpoint specifying RSV-confirmed hospitalizations (4). Based on a similar study design, a Phase III study (MELODY) was conducted in healthy late preterm and term infants ≥ 35 weeks gestational age. It also included RSV hospitalizations as a secondary endpoint. In both studies, RSV hospitalizations was defined as the subset of cases

[a] Recommendations from the French Haute Autorité de Santé: https://www.has-sante.fr/jcms/c_2756580/fr/synagis-palivizumab;
Recommendations from the British Joint Committee on Vaccination and Immunisation: https://www.nitag-resource.org/sites/default/files/ddf283f66b77b34a6821e8d6f000947b74f6b68b_1.pdf;
Recommendations from the German Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften: https://www.awmf.org/uploads/tx_szleitlinien/048-012l_S2k_Prophylaxe-von-schweren_RSV-Erkrankungen-Risikokindern-Palivizumab_2018-11.pdf

meeting the criteria for the primary endpoint (ie, medically-attended RSV LRTI) that were also hospitalized.

During the planning of the MELODY study, it was recognized that the management of more serious RSV disease had been shifting to the outpatient setting (see Section 7b of FDA 2017) and that the incidence of RSV hospitalization in late preterm and term infants may be too low for the secondary endpoint to reach statistical significance within MELODY alone. This effect was compounded by the reduction in virus circulation and healthcare attendance as a result of public health measures taken during the COVID-19 pandemic, resulting in a much smaller number of hospitalizations.

The decision to hospitalize an infant with respiratory illness is made upon the judgment of the attending physician, but these decisions are underpinned by national guidelines that determine sets of criteria that, when met, indicate illness requiring secondary care input. These guidelines are broadly similar internationally and include signs of increased respiratory effort (tachypnea > 50 breaths/minute, moderate or severe retractions), compromised oral intake or hypoxia, all of which are associated with very severe illness. Many guidelines set the threshold for hypoxia at 90-92% oxygen saturation and this is widely accepted as an indicator of severe enough disease to require hospitalization. However, the decision to hospitalize is not contingent only on evident hypoxia as the presence of above-mentioned signs are also accepted as indicators of very severe disease (5).

The hospitalization of an infant with RSV constitutes a significant individual, family, and healthcare burden (6). Preventing serious deterioration in clinical condition due to RSV infection to the point of requiring hospitalization –a widely accepted indicator of disease severity– is one of the primary aims of the management and prevention of RSV in infants. The impact of nirsevimab on hospitalization of infants with RSV and its inclusion in the approval process is of key importance to physicians, for use in their clinical decision making, and parents/LARs alike. Hospitalization of infant due to RSV LRTI does have some far-reaching consequences as as many as one-third of all children who are hospitalized due to RSV are unnecessarily treated with antibiotics (7), even though routine antibiotic therapy for bronchiolitis is discouraged (8) (9). The unnecessary use of antibiotics is associated with short term adverse events (gastrointestinal complaints, diarrhea, exanthema), increased selective pressure on resistant bacteria, and it displays an adverse impact on the composition of the infant's microbiome (10).

The nirsevimab clinical development program has demonstrated the safety profile of the product, supporting investigation in a larger population, and delivered convincing efficacy results in both preterm and term infant populations, supporting its use in all infants.

In this context, an investigation of the prevention of hospitalization[a] and of very severe disease due to RSV is planned for healthy late preterm and term infants, under conditions as similar as possible to the real world.

[a] "Hospitalization" is defined as the decision to admit to in-patient care by the treating physician.

2.2 Background

RSV Seasonality

In much of the Northern Hemisphere, including the UK, France, and Germany, RSV infection is a clearly identified winter illness with most cases observed over a period of approximately 5 months that usually starts in October or November. Whilst the timeframe can vary slightly from year to year, this period of approximately 5 months is commonly referred to as the "RSV season" in this region. In this study, "RSV season" will be used to refer to this period of increased RSV infection. For the purpose of efficacy analyses, the start and end dates of the RSV season will be defined on a country-by-country basis and will be based on country-specific epidemiological surveillance. As a result of the COVID-19 pandemic, the seasonality of RSV has been modified (11). During 2020, the circulation of RSV was substantially reduced, presumably due to the widespread implementation of non-pharmacological interventions such as face mask use, increased handwashing practices, social distancing, and travel restrictions. This reduced circulation of RSV produced a larger-than-usual RSV-susceptible population.

RSV Infections Prevalence and Epidemiology

Lower respiratory tract infection due to RSV, characterized predominantly as bronchiolitis or pneumonia, can manifest with acute and sometimes long-term consequences for the developing lungs of young infants and children (12). It is estimated that RSV infections account for around 60% to 80% of infant bronchiolitis. In addition, RSV is one of the leading causes of pediatric pneumonia (up to 40% of pneumonias all causes in particular in infants and toddlers) (13).

Children who have experienced severe RSV bronchiolitis in early life subsequently show an increased risk of recurrent wheeze (triggered by other respiratory viral infections), asthma, and possibly allergic sensitization later in life (14) (15) (16) (17) (18) (19) (20). Early childhood wheeze after RSV infection has a high prevalence. It has an impact on quality of life and is responsible for substantial health care costs (21) (22) (23) (24). Although the evidence establishing a causal association between RSV LRTI in early childhood and the development of recurrent wheeze or asthma in later childhood is still inconclusive, children with severe RSV infection in infancy have been observed to be prone to recurrent wheeze triggered by viral respiratory infections up to the age of 12 years (25) (26) (27) (28) (29). RSV infection pathogenesis is not well understood (12). However, it has been suggested that RSV bronchiolitis may interfere with normal lung development, immune maturation, or that it may be an early stimulus for those children already predisposed to wheeze by genetic susceptibility.

Overall, about 90% of children will be infected with RSV in their first 2 years of life and up to 40% of these will develop a LRTI with the initial episode (30) (31) (32) (33). RSV is a leading cause of hospitalization in infants globally, and the majority of hospitalized infants were born at term and did not have comorbidities (13) (34) (35). RSV infection is also one of the leading causes of acute respiratory distress syndrome in infants and a significant proportion of those children do not have predefined risk factors for a complicated RSV disease (36). Infants are at the highest risk for very severe RSV disease at the time they are entering their first RSV season (37) (38). They represent up to 75% of the hospitalizations due to RSV infections in children < 5 years of age (34) (35) (39) (40).

Severe RSV bronchiolitis requires treatment in the intensive care unit more often than bronchiolitis caused by other pathogens in particular due to necessity to utilize high flow nasal cannula respiratory support (41) (42) (43). Severe RSV acute respiratory infections are also a significant contributor to pediatric mortality (37) (44) (45), especially in infants younger than 3 months of age (46). Infants with clinically significant preexisting neuromuscular impairment are at an increased risk for a complicated course of RSV infection and an increased RSV-related mortality which underscores the indication for passive immunization in these vulnerable patients (47) (48). In a comparative study, RSV infection in early infancy showed a more severe clinical course than COVID-19 (49).

France

Data on RSV-associated hospital admissions in children < 5 years of age during the 2010-2018 period were extracted from the French national hospital discharge database (Programme de Médicalisation des Systèmes d'Information – PMSI). On average, 45 225 RSV-associated hospitalizations per RSV season were reported in France, with 69% of hospitalizations among children < 1 year of age. This amounts to approximately 28% of hospitalizations occurring among children < 1 year of age during an RSV season (35).

Germany

Interpretation of secondary data and modelling results are supported by results from active surveillance and testing of LRTI in prospective hospital studies in Germany. The PRI.DE study, a population-based study of viral LRTI in children < 3 years of age, calculated incidence rates of 11 RSV hospitalizations per 1000 children (50). Similarly, a study of RSV-positive hospitalizations in children < 1 year of age in Kiel over a 7-year period described an incidence rate of 16 per 1000 in children (51).

UK

In the UK, the burden of RSV infections in children < 5 years of age was estimated and RSV was found to be responsible for 12 primary care consultations (95% confidence interval [CI]: 11.9; 12.1) and 0.9 admissions to the hospital (95% CI: 0.89; 0.90) annually per 100 children annually (52). The same study outlined that general practice (GP) consultations for RSV infections during the first year of life fluctuated between 13.9 per 100 children to up to 27.4 per 100 children for children born in March and November, respectively (52).

***

This study will be conducted in the population of infants born ≥ 29 WGA for which the current standard of care involves no preventive option. Those infants who qualify for a palivizumab prescription based on routine practices will not be included.

This study seeks to demonstrate the efficacy of nirsevimab in preventing RSV LRTI hospitalizations (a crucial determinant for recommending bodies) on a large scale while emulating real-world conditions, owing to the proposed use of nirsevimab in a vaccine-like program.

2.3 Benefit/Risk Assessment

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

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.1.

Table 2.1: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Monoclonal Antibody: Nirsevimab		
Hypersensitivity, including anaphylaxis Refer to the IB Section 5.5 (Summary of Risks) for more information regarding potential risks.	All monoclonal antibodies have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the monoclonal antibody. There have been no cases of hypersensitivity, including anaphylaxis, attributed to nirsevimab up to the cut-off for the IB (ie, 09 April 2022).	Exclusion criterion E04 for those at increased risk. Observation period after immunization for early detection and treatment. Addressed in IB (administration precautions, potential adverse events), defined AESI in the trial.
Thrombocytopenia Refer to the IB Section 5.5 for more information regarding potential risks	Risk reported post approval for palivizumab There have been no cases of thrombocytopenia attributed to nirsevimab up to the cut-off for the IB (ie, 09 April 2022).	Exclusion criterion E05 and E06 for those at increased risk. Addressed in IB (administration precautions, potential adverse events), defined AESI in the trial.
Immune complex disease Refer to the IB Section 5.5 for more information regarding potential risks	As a monoclonal antibody, nirsevimab can induce the development of ADAs and the occurrence of such ADAs could result in immune complex disease or altered nirsevimab levels or activity. There have been no cases of immune complex disease attributed to nirsevimab up to the cut-off for the IB (ie, 09 April 2022).	No risk mitigation actions. Addressed in IB (potential adverse events), defined AESI in the trial.

2.3.2 Benefits from Study Participation

In a Phase IIb study, the incidence of RSV LRTI hospitalization was 78.4% lower (95% CI: 51.9; 90.3) in the group of healthy preterm infants who were administered nirsevimab compared to the group administered a placebo (4).

Also, since nirsevimab is an anti-viral monoclonal antibody that is highly specific to RSV, it is unlikely that it could interfere with the immune response to other vaccines. It is thus anticipated that nirsevimab could be concomitantly administered to infants with routine pediatric vaccines during the same clinic visit (53).

Overall, and regardless of participants group allocation (ie, nirsevimab or no study intervention), study participation and study conduct are considered fundamental from the societal perspective towards the goal of finding a prophylaxis helping dampen both the individual and public health impact of RSV infections during the seasonal epidemic.

2.3.3 COVID-19 Risk Assessment

COVID-19 Risk Assessment

- Nirsevimab is a monoclonal antibody being developed for the prevention of RSV in all infants. Nirsevimab would not cause immune suppression. Therefore, the risk that a participant in this trial will contract COVID solely due to the administration of the study intervention will be similar to the risk that a person not participating in this trial will contract COVID.
- Risk mitigation:
    - Delay the start of the study on a site-by-site basis, depending on each individual site safety restriction measures.
    - Continued risk assessment by the Investigator and Sponsor before deciding to start the trial.

2.3.4 Overall Benefit-Risk Conclusion

Based on the favorable efficacy and safety profiles from the previous studies of nirsevimab in infants entering their first RSV season, nirsevimab offers the ability to provide protection against RSV lower respiratory tract disease.

For participants randomly assigned to receive nirsevimab, considering the measures taken to minimize risk to enrolled participants, the potential risks that may result from study participation are balanced by the anticipated benefits that may be afforded to participants.

For participants randomly assigned to the no intervention group, there are no unreasonable and significant risks of illness or injury foreseen.

All participants will receive the standard of care and routine health care. This includes being informed on current recommendations on RSV prevention through hygiene measures.

3 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 3.1.

Table 3.1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization compared to no intervention	• Overall incidence of RSV LRTI hospitalization through the RSV season
Secondary	
• To assess the efficacy of nirsevimab in preventing very severe RSV LRTI compared to no intervention	• Incidence of very severe RSV LRTI defined as RSV LRTI hospitalization with oxygen saturation < 90% (at any time during hospitalization) and oxygen supplementation, through the RSV season
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization compared to no intervention in each country	• Incidence of RSV LRTI hospitalization through the RSV season in each country
• To assess the efficacy of nirsevimab in preventing hospitalizations for all-cause LRTI compared to no intervention	• Incidence of hospitalizations for all-cause LRTI through the RSV season
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization through 150 days post-dosing/randomization (overall and in each country)	• Incidence of RSV LRTI hospitalization through 150 days post-dosing/randomization (overall and in each country)
• To assess the efficacy of nirsevimab in preventing very severe RSV LRTI through 150 days post-dosing/randomization	• Incidence of very severe RSV LRTI defined as RSV LRTI hospitalization with oxygen saturation < 90% (at any time during hospitalization) and oxygen supplementation, through 150 days post-dosing/randomization
• To assess the efficacy of nirsevimab in preventing hospitalizations for all-cause LRTI through 150 days post-dosing/randomization	• Incidence of hospitalizations for all-cause LRTI through 150 days post-dosing/randomization

Objectives	Endpoints
• To further characterize the safety profile of nirsevimab	• Any immediate adverse events (AEs) reported in the 30 minutes after immunization • Non-serious AEs from D01 (post-dosing/randomization) to D31 • Adverse events of special interest (AESIs) from D01 visit through 1-year post-dosing/randomization or D366 • Medically attended adverse events (MAAEs) from D01 visit through 1-year post-dosing/randomization or D366 • Serious adverse events (SAEs) from D01 visit through 1-year post-dosing/randomization or D366 • Related SAEs from D366 to D731 for UK reconsented participants
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization through 180 days post-dosing/randomization (overall and in each country)	• Incidence of RSV LRTI hospitalization through 180 days post-dosing/randomization (overall and in each country)
• To assess the efficacy of nirsevimab in preventing hospitalizations for all-cause LRTI through 180 days post-dosing/randomization	• Incidence of hospitalizations for all-cause LRTI through 180 days post-dosing/randomization
• To assess the incidence of RSV LRTI hospitalization from 181 days post-dosing/randomization until D366 (overall and in each country)	• Incidence of RSV LRTI hospitalization from 181 days post-dosing/randomization until D366 (overall and in each country)
• To assess the incidence of hospitalizations for all-cause LRTI from 181 days post-dosing/randomization until D366	• Incidence of hospitalizations for all-cause LRTI from 181 days post-dosing/randomization until D366
• To describe in each study group the incidence of RSV LRTI hospitalization and all-cause LRTI hospitalization in UK reconsented participants from D366 to D731	• Incidence of RSV LRTI hospitalization • Incidence of hospitalizations for all-cause LRTI
• To assess the incidence of recurrent wheeze in UK reconsented participants from D01 to D731	• Incidence of recurrent wheeze
Exploratory	
• To assess the efficacy of nirsevimab in preventing of very severe RSV LRTI through 180 days post-dosing/randomization	• Incidence of very severe RSV LRTI defined as RSV LRTI hospitalization with oxygen saturation < 90% (at any time during hospitalization) and oxygen supplementation, through 180 days post-dosing/randomization

Objectives	Endpoints
• To assess health care utilization	• Duration of hospitalization • Admission to the intensive care unit and duration of stay • Number of participants who require oxygen supplementation • Number of participants who require intravenous fluid administration

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Open-label, multi-center, parallel 2-arm study: nirsevimab compared to no preventive intervention for RSV
Phase	IIIb
Control method	Comparison to no preventive intervention
Study population	Healthy infants born ≥ 29 weeks gestational age (WGA) entering their first RSV season and not eligible for palivizumab (born either in-season or out-of-season)
Level and method of blinding	Open-label
Study intervention assignment method	Randomization will be stratified by the following: • Country • Age group at time of randomization (ie, age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months)
Number of participants	28 860 participants
Intervention groups	Eligible participants will be randomized in a 1:1 ratio to receive a single IM injection of 50 mg (if weight < 5 kg) or 100 mg (if weight ≥ 5 kg) of nirsevimab or no RSV preventive intervention on D01
Total duration of study participation	12 months post-dosing/randomization for France, Germany, and UK non-reconsented participants and 24 months post-dosing/randomization for UK reconsented participants
Countries	France, Germany, and the United Kingdom

Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

Study Calendar

- Planned date of first participant in: 01 September 2022
- Planned date of last participant in: 28 February 2023
- Planned date of last visit last participant: 28 February 2025

Note: As much as operationally feasible, the date of inclusion of the first participant will be aligned with the beginning of the RSV season. It is thus possible that the first participants are enrolled earlier than 01 September 2022.

4.2 Scientific Rationale for Study Design

Rationale for the Study Design

Nirsevimab has the potential to address a serious unmet medical need by protecting all infants from severe RSV disease and hospitalization with once per season dosing. A dose of 50 mg nirsevimab was first evaluated in healthy preterm infants born between ≥ 29 to < 35 WGA in a Phase IIb study with a favorable benefit-risk ratio. The evaluation of nirsevimab was then extended to a population of healthy term/late preterm infants born ≥ 35 WGA in a Phase III study (MELODY) with a dose of either 50 mg or 100 mg.

This Phase IIIb study will further extend the evaluation of nirsevimab to infants without underlying medical conditions and assess its efficacy in preventing hospitalization due to RSV disease (henceforth referred to as RSV LRTI hospitalizations) in infants entering their first RSV season.

In the available data from the completed pivotal nirsevimab studies, no increase in incidence or severity of disease in nirsevimab recipients as compared to placebo recipients was observed in the second RSV season. To reinforce these data, a follow-up extension of the HARMONIE study is intended to further address the evaluation of second season antibody-dependent enhancement of RSV disease in children who received nirsevimab prior to, or during their first RSV season.

As of today, there is no approved RSV prophylaxis in the general infant population, thus precluding the set-up of a clinical study involving an active comparator arm. However, this situation offers the possibility to collect real-world data by adopting a mostly pragmatic study design (54). Indeed, and although the study participants will be randomized to receive either the investigational intervention (nirsevimab) or no intervention (standard of care), study procedures will be limited in scope and data collection will be done in such a way as to minimize the study imprint on participants and their parents/LARs. This study should also circumvent one of the known shortcomings of pragmatic studies –that is, the variability of the data collected– as efficacy objectives will all be assessed through a common very narrowly-defined endpoint kernel, namely infant RSV LRTI hospitalization.

Infant RSV LRTI hospitalization has been selected as the primary endpoint since hospitalization for LRTI due to RSV is a significant part of RSV burden of disease and the assessment of cases does not impose additional clinical procedures on participants or parents/LARs. The assessment of very severe RSV LRTI cases will be used as one of the main secondary endpoints as it will allow evaluating the impact of nirsevimab on the incidence of RSV infection in its rarer but direst manifestations.

This study's design does not permit blinding. Parents/LARs will know whether their infant received the study intervention or not and, depending on the enrollment setting (eg, hospital or medical office), the child's pediatrician or the family doctor may be the person performing inclusion in the study, administering or not administering the study intervention, and later advising parents/LARs on the course of action in case of respiratory infection. These "real-world" conditions are bound to introduce some bias that the use of a blind assessor or of an adjudicating committee would not entirely alleviate (55). However, and although this study is open-labelled, the selection of a very robust and patient-oriented endpoint kernel (ie, RSV LRTI hospitalization) will allow for a scientifically sound and clinically relevant assessment of nirsevimab efficacy.

Despite being a monoclonal antibody, nirsevimab will be administered by intramuscular injection like routine pediatric vaccinations. Furthermore, nirsevimab can be co-administered along with routine pediatric vaccines planned in the vaccination schedule of each country (53). This will facilitate its administration during routine appointments, making it possible to immunize the entire intervention cohort at the start of the season using existing healthcare appointments when possible. This, in line with the mostly pragmatic study design, will further help minimize the burden on parents/LARs of participants and on the healthcare system of each country.

Rationale for the Study Population

The participants to be enrolled are all infants from France, Germany, and UK, under the age of 12 months entering their first RSV season that are not eligible to receive RSV prophylaxis with palivizumab, which indication is limited to infants with certain underlying conditions such as chronic lung disease, congenital heart disease, or very premature.

In order to minimize the burden on sites, families and participants, while still answering the objective of this protocol amendment, it was decided to invite in the study extension only the UK participants, who represent 50% of the study population.

Enrollment of Study Participants

A total of 28 860 participants will be enrolled from sites in France, Germany, and the United Kingdom. The study will enroll infants born either out of the RSV season or in the RSV season.

Definition of the RSV season

There is an important variability of RSV seasonality from year to year in each country. The typical RSV season in the Northern Hemisphere (NH) last approximately 5 months and usually starts in October or November. Therefore, the "Out-of-Season" period refers to the approximately 7 months period from March or April to September or October. The actual start date and length of the RSV season will depend on the actual circulation of RSV in the NH in 2022.

Cases of LRTI hospitalization will be collected throughout the study to ensure that all cases occurring during the next RSV season are captured. For the need of this study, the start and end dates of the RSV season will be defined on a country-by-country basis and will be based on country-specific epidemiological surveillance. For the mothers of infants to be born in-season, recruitment will start at 30 weeks gestation in women with an estimated delivery date during the RSV season.

Rationale for the Collection of Safety Data

Immediate AEs

As nirsevimab is not a marketed product, a 30 minutes immediate surveillance period of infants enrolled in the nirsevimab group will be done on the site where immunization was performed.

Non-serious AEs

For a period of 30 days post-dosing/randomization, non-serious AEs will be captured in the eCRF for all study participants. The relation of AEs to interventional product will be determined by the Investigator.

The use of the eDiary by parents and the process for reporting AEs in the eCRF is outlined in Section 8.2.3.

Hospitalizations

In this study, "LRTI hospitalizations" occurring up to 12 months post-dosing/randomization for all participants are considered as part of the efficacy assessments and "LRTI hospitalizations" occurring up to 24 months post-dosing/randomization for UK reconsented participants are considered as part of the descriptive analyses. Consequently, these LRTI hospitalizations will not be reported as SAEs. Definition of hospitalization, RSV LRTI hospitalization, and very severe RSV LRTI are provided in Section 8.1.2.

It is to be noted that testing for RSV is expected to be performed by the hospital as part of routine practice.

SAEs, AESIs, and MAAEs

After dosing/randomization, all participants will be followed-up for SAEs, AESIs, and MAAEs up until the 12 months follow-up phone contact.

Additionally, UK reconsented participants will be followed-up for SAEs until the 24-month follow-up phone contact. Only SAE considered as related by the investigator or site staff will be collected in the CRF.

Rationale for Dose of Investigational Products

In nonclinical cotton rat (*Sigmodon* genus) efficacy studies, MEDI8897 (ie, nirsevimab internal identifier) serum concentrations of 6.8 µg/mL were shown to result in a 3-log decrease in RSV titers in cotton rat lungs. A population PK model, developed using PK data from both a Phase Ia study in healthy adults and Phase Ib/IIa study in healthy preterm infants, was used to simulate PK profiles in the Phase IIb population. PK profiles were simulated in 1000 infants for each of the

following populations: preterm infants (29 to 35 WGA) at birth, full-term infants at birth, and full-term infants at 12 months of age. A single 50 mg fixed IM dose of MEDI8897 was predicted to be the likely efficacious dose that would sustain serum concentrations above the target level of 6.8 μg/mL in the majority of infants over the entire RSV season and provided complete protection for infants entering their first RSV season.

In the Phase IIb study D5290C00003, a single fixed 50 mg IM dose was shown to be efficacious in preterm infants (29 to < 35 WGA) in their first RSV season. Model-based analyses of the Phase IIb clinical PK and efficacy data identified a projected serum AUC0-∞ of 13.4 day.mg/mL as the protective exposure threshold. The risk of medically attended RSV-confirmed LRTI over the course of the RSV season was significantly lower in infants with higher projected AUC0-∞. Infants with AUC0-∞ above 13.4 day.mg/mL had a statistically significantly higher probability of protection based on exposure-response analysis using Cox proportional hazard regression. Although, the fixed 50-mg dose resulted in clinically efficacious exposures for 97% of infants weighing < 5 kg in the Phase IIb study, this dose resulted in suboptimal exposures for infants weighing ≥ 5 kg. Overall, 3% and 59% of the infants in groups weighing < 5 kg and ≥ 5 kg, respectively, were in the lowest AUC0-∞ quartile (4.5 to 13.4 day.mg/mL) that was determined to be suboptimal. Additionally, a cut-point analysis of the weight-normalized doses of all treated infants revealed that a 10 mg/kg dose was the corresponding clinically efficacious and protective threshold dose. Henceforth, based on these analyses, a stratified fixed dosing strategy by weight bands is proposed to ensure maintenance of MEDI8897 serum concentrations above the target AUC throughout the RSV season. Based on dose optimization analysis designed to maximize the proportion of infants with clinically efficacious MEDI8897 serum exposure, a single fixed 50 mg IM dose is proposed for infants < 5 kg in their first RSV season while a single fixed 100 mg dose is proposed for infants weighing ≥ 5 kg entering their first RSV season.

This dosing regime is used in two ongoing pivotal studies for registration, the Phase III study D5290C00004 (MELODY) and the Phase II/III study D5290C00005 (MEDLEY).

4.3 End of Study Definition

A participant is considered to have completed the study if the parents or LARs have completed the last contact planned in the SoA (telephone contact at D366 for France, Germany, and UK non-reconsented participants and telephone contact at D731 for UK reconsented participants).

The end of the study is defined as the date of the last contact of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the clinical study report is finalized.

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 for the study only if all of the following criteria are met:

Age

I01: Born at ≥ 29 weeks gestational age and aged 0 to 12 months (calendar age), who are entering their first RSV season on the day of randomization in the study (D01)[a]

Informed Consent

I02: Informed consent form has been signed and dated by the parent(s) or other LAR(s) (and by an independent witness if required by local regulations)

Other

I03: Participant and parent/LAR are able to attend the scheduled visit and to comply with all study procedures[b].

5.2 Exclusion Criteria

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Active confirmed RSV infection at the time of dosing/randomization

E03: Active LRTI at the time of dosing/randomization

E04: Known systemic hypersensitivity to any of the study intervention components, or history of a life-threatening reaction to the study intervention used in the study or to a product containing any of the same substances[c]

E05: Laboratory-confirmed thrombocytopenia, or known thrombocytopenia, as reported by the parent/LAR, contraindicating intramuscular injection

E06: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular injection

E07: Any condition that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion

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[a] "0 to 12 months" means from the day of birth to the day before the 13th month after birth.

[b] It is to be noted that "complying with all study procedures" includes the parents or LARs willingness to install the study's dedicated application on their smartphone.

[c] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure (IB).

E08: Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

Prior/concomitant therapy

E09: Mother of the infant participant was administered an RSV vaccine during her pregnancy with the infant participant

E10: Receipt of any monoclonal antibody by the infant participant

E11: Receipt of immune globulins, blood or blood-derived products in the past 3 months by the infant participant

Prior/concurrent clinical study experience

E12: Participation at the time of study enrollment or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure[a]

Other exclusions

E13: Eligible to receive palivizumab at time of inclusion (as per local guidelines)

E14: In an emergency setting or hospitalized involuntarily[b]

E15: Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

5.3 Lifestyle Considerations

No restrictions other than the ones listed in the exclusion criteria are required.

5.4 Screen Failures

Screen failures are defined as participants whose parents or LARs consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/no intervention. Screening information is recorded in the source documents.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened.

[a] It is to be noted that strictly observational studies do not fall under this exclusion criterion.

[b] An infant in an emergency setting could include one who may be with next of kin or emergency services in case the parents are hospitalized, in jail, or dead. Involuntary hospitalization of an infant could be due to a court order or mediated by social services, without the consent of the parents.

6 Study Intervention and Concomitant Therapy

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

Note: Concomitant therapies such as vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the eCRF as reportable medications (see Section 6.8).

6.1 Study Intervention Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study intervention

Intervention Name	Nirsevimab
Use	Experimental
IMP and NIMP	IMP
Type	Extended half-life monoclonal antibody
Dose Form	Sterile solution for injection
Unit Dose Strength(s)	100 mg/mL
Excipients/Diluent	• 30 mM histidine/histidine-HCl • 80 mM arginine-HCl • 120 mM sucrose • 0.02% (w/v) polysorbate 80 • pH 6.0 water for injection
Dosage Levels	0.5 mL presentation corresponding to 50 mg (if weight < 5 kg) or 1.0 mL presentation corresponding to 100 mg (if weight ≥ 5 kg) at D01
Number of Doses / Dosing Interval	1 dose
Route of Administration	IM
Site of Administration	Anterolateral aspect of the thigh according to standard practice procedures for IM injections in infants
Injection Site Side	Either
Sourcing	Provided by AstraZeneca
Packaging and Labeling	AstraZeneca
Current/Former Name or Alias	n/a

Batch Number	TBD
Storage Conditions	The IMP will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The IMP must not be frozen, shaken, or exposed to light. Keep the prefilled syringe in the outer carton in order to protect from light.

Abbreviations: IM, intramuscular; IMP, Investigational Medicinal Product; n/a, not applicable; NIMP, Non-Investigational Medicinal Product; TBD, to be determined

The participant's weight at enrollment will determine the dose of nirsevimab to be administered. The dose of nirsevimab will be 50 mg for participants weighting < 5 kg and 100 mg for participants ≥ 5 kg at D01.

Study arms and associated study intervention are summarized in Table 6.2.

Table 6.2: Arms and Associated Study Interventions

Arm name	Group 1	Group 2
Associated study interventions	Nirsevimab	No intervention

6.2 Preparation/Handling/Storage/Accountability

Detailed guidance and information are provided in the investigator site file/regulatory binder.

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the IMP operating manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

On the day of randomization, participants who meet all the inclusion criteria but none of the exclusion criteria with a signed informed consent from the parent(s) or other LAR will be

randomly assigned to Group 1 (nirsevimab) or Group 2 (no intervention) in a 1:1 ratio, stratified according to country and age at the time of randomization (ie, age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, and age > 6.0 months).

Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the subject randomization number and the group assignment and have the site staff confirm it. The full detailed procedures for group allocation are described in the IRT user guidelines. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log. If the parents or LARs of a participant have signed the consent but the participant is not randomized, the participant number and the reason of the screening failure will be recorded in the IRT database and then transferred in the clinical database.

Participant randomization numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). For example, Participant 250000100005 is the fifth participant enrolled in Center Number 1 in France (250 being the France country code). Participant numbers should not be reassigned for any reason.

The randomization codes will be kept securely in the IRT.

6.3.2 Blinding and Code-breaking Procedures

Code-breaking procedures are not applicable as this is an open-label study.

Blinding remains a methodological safeguard in clinical trials and is important for limiting bias, such as selection bias, detection bias, and performance bias. In this open-label pragmatic study, nirsevimab immunization will be compared to standard-of-care, ie, no intervention, and having a blinded third party or clinician assessing the patient outcomes is not feasible. Whether the compared groups will receive similar amount of attention cannot be ensured and this, in turn, can result in biased treatment effect estimates with uncertainties on the direction of the bias (under-ascertainment/over-ascertainment). Methods that decrease risk of bias will be used, such as standardization of questionnaires, a narrowly-defined and objective primary outcome, and when possible electronic health records to retrieve the primary clinical endpoints. Response rates to the questionnaires between the 2 groups will inform about the risk of bias.

6.4 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 6.1), and that any non-compliance is documented so that it can be accounted for in the data analyses:

- Nirsevimab immunization will be performed by qualified and trained study personnel
- The person in charge of study intervention management at the site will maintain accountability records of study intervention delivery to the study site, study intervention inventory at the site, dose given to each participant, and unused or wasted doses

6.5 Dose Modification

Not applicable.

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

Not applicable.

6.7 Treatment of Overdose

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the investigator or other site personnel should:

1) Contact the RMO immediately.
2) Closely monitor the participant for any AE/SAE.
3) Document the quantity of the excess of the overdose in the source documents.

6.8 Concomitant Therapy

The following concomitant reportable medications will be collected:

- Medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an AE)
- All vaccines administered within 14 days before and after dosing/randomization. It is to be noted that routine childhood vaccines scheduled at the time of the enrollment visit should be administered as planned
- All medications administered within 14 days before and after admission for LRTI hospitalization
- Routine immunization with nirsevimab (Beyfortus). For countries where Beyfortus has been made commercially available during the study conduct, the sites will be asked to report any routine immunization with Beyfortus.

Reportable medications will be collected in the eCRF. Dosage, homeopathic medication, topical steroids, as well as topical, ophthalmic, and ear treatments will not be recorded (except topical analgesics applied at the injection site of study intervention). Inhaled steroids will be recorded only when prescribed during a wheezing episode (see below).

Medications given in response to an AE will be captured in the “Action Taken” section of the AE eCRF.

For UK reconsented participants, the following concomitant medications will be collected:

- Medications related to related SAE and/or LRTI hospitalization
- Any medications prescribed during a wheezing episode.

Medications will be coded using the WHODrug dictionary.

6.8.1 Rescue Medicine

Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available at the study site in the event of an anaphylactic or other immediate allergic reaction.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Not applicable as there is only one immunization visit.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may be withdrawn from the study at any time at her/his parents or LARs request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the eCRF: Adverse Event, Lost to Follow-up, Protocol Deviation, or Withdrawal by Parents or LARs.
- For participants hospitalized due to a LRTI symptoms who are withdrawn from the study, the Investigator or designee may seek information from the facility where medical attention was sought to complete the participant's eCRF and assess the case. This retrospective collection of information on LRTI hospitalization for participants withdrawn from the study will be possible only if the parents or LARs provided consent by ticking the corresponding box in the informed consent form.
- The participant will be permanently discontinued from the study at that time.
- If the parents or LARs of the participant withdraw consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Withdrawn participants will not be replaced.

Follow-up of Discontinuations

For participants who have prematurely terminated the study, the site should attempt to contact their parents or LARs and complete all scheduled safety follow-ups, except if they specified that they do not want to be contacted again and it is documented in the source document.

For participants where the reason for early termination is lost to follow-up, the site will not attempt to obtain further safety information after last contact attempt on the 12-month follow-up for France, Germany, and UK non-reconsented participants and on the 24-month follow-up for UK reconsented participants. See Section 7.3 for definition of "lost to follow-up".

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if her or his parents or LARs cannot be contacted by the site or designee.

The following actions must be taken if the parents or LARs of the participants do not follow-up on the monthly electronic contact (until 6 months after dosing/randomization) or cannot be contacted by phone at the end of the study as planned in the SoA:

- For the monthly electronic contact: the electronic platform will send one reminder for 3 consecutive days. If there is no answer after the e-reminders, the site and/or designee will call the parents or LARs of the participant as soon as possible, discuss the importance of answering the follow-up questions with them, and ascertain whether or not they wish their infant to continue participating in the study.

  It is to be noted that if both the electronic and phone reminders fail, the next monthly electronic contact (up until 6 months post-dosing/randomization) will take place. The participant will not be deemed lost to follow-up before the 12-months follow-up phone contact for France, Germany, and UK non-reconsented participants or the 24-months follow-up phone contact for UK reconsented participants takes place.

- For the 12 months follow-up phone contact for France, Germany, and UK non-reconsented participants or the 24 months follow-up phone contact for UK reconsented participants, and before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the parents or LARs of the participants (where possible, 3 telephone calls 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 parents or LARs continue to be unreachable, the participant will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- 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.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA.

Efficacy data for the first year of study and descriptive data for the second year of the study are collected through the participant's medical records and reported in the eCRF. Hospitalizations will be reported by parents/LARs of participants through an eDiary for the first year of the study. From D01 to D366, each time a health event will be captured on the eDiary, a medical call center will contact parents/LARs to collect and report the health event's information in the eCRF. The Investigator or delegated site staff will review information reported in the eCRF and interview the participants' parents/LARs if any additional information needs to be collected. Parents/LARs who don't have access to the eDiary will be requested to contact directly the investigation site to report any health event.

From D366 to D731, UK reconsented participants' parents/LARs will record in the memory aid any hospitalization that occurred. During the 18-month and 24 month phone calls, the Investigator or delegated site staff will interview parents/LARs to collect information reported in the memory aid and report only LRTI hospitalization's information in the eCRF.
During the 12- and 24-month follow-up calls, the site investigator or staff designee will ask to parents/LARs of UK reconsented participants if the participants had experienced any medically attended cough, chest or breathing problems throughout the study period. After the 12-month follow-up phone call (when possible) and the 24-month follow-up phone call, the site investigator or staff designee (including third parties authorized by the site investigators) will access the UK reconsented participants' medical record (general practitioner's or hospital's record) to determine if the medical event meets with the definition of wheeze provided by the Sponsor (see Section 8.1.2.4). If so, the event and related complementary information (including any medications prescribed during wheeze) will be retrospectively collected.

8.1.1 Baseline Assessments at the Time of Immunization

All parents or LARs will be asked to provide demographic information on the participant such as gestational age, date of birth (or month of birth, depending on local regulations), weight, gender, medical history, vaccine history, and postal code at the time of enrollment. The type of demographic information collected is determined by laws in each country.

8.1.2 Efficacy Assessments

Efficacy assessments will be based on RSV LRTI hospitalization throughout the study period (Section 8.1.2.2), and very severe RSV LRTI (Section 8.1.2.3) throughout the first year of the study (see Section 8.1.2.1), through 150 days post-dosing/randomization, and through 180 days post-dosing/randomization as described in Section 3.

8.1.2.1 Definitions

"Hospitalization" is defined as the decision to admit to in-patient care by the treating physician.

"RSV season" is the period of increased RSV infection. For the purpose of efficacy analyses, the start and end dates of the RSV season will be defined on a country-by-country basis and will be based on country-specific epidemiological surveillance.

8.1.2.2 RSV LRTI Hospitalization

Participants will be monitored for RSV LRTI hospitalization.

Parents or LARs can report the hospitalization through the eDiary (for the first year of the study for all the participants) which will trigger a contact by the site and/or designee. Site staff and/or designee will inquire about the hospitalization and report it in the eCRF. For the second year of the study, parents or LARs of UK reconsented participants will report hospitalizations in a memory aid. Information reported in the memory aid will be collected by sites during the 18-month and 24-month phone calls.

Whether a hospitalization is effectively due to an RSV LRTI or not will be assessed by the Investigator:

- If the attending physician is the Investigator, the assessment of the case will be done directly as the participant information (eg, RSV test result and medical interventions) will be readily available.
- If the attending physician is not the Investigator, the collection of participant information will be done retrospectively. In this situation, the Investigator or designee will seek the required information from the facility where medical attention was sought to complete the participant's electronic case report form (eCRF).

Based on the information captured, the Investigator will assess whether hospitalization was due to RSV LRTI and categorize the case accordingly. It is to be noted that testing for RSV is expected to be performed by the hospital as part of routine practice.

Symptoms commonly associated with LRTI include (but are not limited to):

- Clinical finding of rhonchi, rales, crackles, or wheeze,
- Increased respiratory rate at rest (age: < 2 months, ≥ 60 breaths/min; 2 to 6 months, ≥ 50 breaths/min; > 6 months, ≥ 40 breaths/min),
- Hypoxemia (in room air: oxygen saturation $< 95\%$)

Each potential case of RSV LRTI hospitalization should be documented with the RSV test result, the lowest rate of oxygen saturation recorded, duration of hospital stay, and the list of medical interventions leading to end of the hospitalization (eg, oxygen supplementation, intravenous fluid administration, admission to intensive care unit).

It is to be noted that, for hospitalization due to respiratory infection, parents or LAR of the participant will be instructed to present the participant card (paper version or digital version through the eDiary) to the hospital. RSV test will be performed at the hospital as part of routine practice. The participant card will contain a reminder for RSV testing.

8.1.2.3 Very severe RSV LRTI

A very severe RSV LRTI case is defined as:

- RSV LRTI hospitalization
- oxygen saturation < 90% (at any time during hospitalization)
- oxygen supplementation

With the addition of oxygen saturation < 90% and oxygen supplementation, very severe RSV LRTI cases are to be identified, described, and documented in the same way as RSV LRTI hospitalization (Section 8.1.2.2).

8.1.2.4 Wheeze

During the 12- and 24-month follow-up call, the site investigator or staff designee will ask to parents/LARs of UK reconsented participants if the participants had experienced any medically attended cough, chest or breathing problems throughout the study period.

After the 12-month follow-up phone call (when possible) and the 24-month follow-up phone call, the site investigator or staff designee (including third parties authorized by the site investigators) will access the UK reconsented participants' medical record (general practitioner's or hospital's record) to determine if the medical event meets with the definition of wheeze provided by the Sponsor (see below). If so, the event and related complementary information (including any medications prescribed during wheeze) will be retrospectively collected.

For this study, wheeze will be defined as a physician-diagnosed wheeze or asthma or related ear, nose and throat (ENT)/respiratory symptoms at an office visit or an illness for which the child was prescribed medication to treat an ENT/respiratory condition.

8.1.3 Immunogenicity Assessments

No immunogenicity data will be obtained in the study.

8.2 Safety Assessments

This section presents safety assessments other than adverse events which are presented in Section 8.3.

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

Safety data are reported by parents/LARs of participants through an eDiary. From D01 to D366, each time a health event will be captured on the eDiary, a medical call center will contact parents/LARs to collect and report the health event's information in the eCRF. The Investigator or delegate site staff will review information reported in the eCRF and interview the participants' parents/LARs if any additional information needs to be collected. Parents/LARs who don't have access to the eDiary will be requested to contact directly the investigation site to report any health event.

From D366 to D731, UK reconsented participants' parents/LARs will record in the memory aid any hospitalizations and emergency room visits that occurred. During the 18-month and 24-month phone calls, the Investigator or delegated site staff will interview parents/LARs to collect information reported in the memory aid and to assess the SAE relationship. Only the related SAE information will be collected in the eCRF.

8.2.1 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the participant is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the eCRF.

Collected information will be coded.

8.2.2 Clinical Examination

At Visit 01, the Investigator or a designee may perform a routine clinical examination. Information will be recorded in the source document.

The weight at enrollment will be measured for all participants and recorded in both the source document and in the eCRF and in the IRT.

For participants randomized in the nirsevimab group, pre-immunization temperature will be collected by the investigator as per routine practice and reported on the source document. Temperature of infants is taken to support ruling out of active infections.

If a participant needs medical attention or is hospitalized during the study, information collected in the participant's medical record will be reviewed, recorded in the eCRF, and the medical event assessed accordingly (ie, non-serious AEs within 30 days post-dosing/randomization, MAAEs, AESIs, and SAEs up to D366 for all participants or related SAEs from D366 to D731 for UK reconsented participants).

8.2.3 Collection and Reporting of Adverse Events (AEs)

<u>Immediate AEs</u>

Following immunization, parents or LARs of participants enrolled in the nirsevimab group will be requested to remain on site for the 30 minutes immediate surveillance of their infant.

Remote safety follow-up

During the visit, parents or LARs of all participants will be provided access to the eDiary application. They will be instructed to log in the eDiary application and answer questions in case a health-related event occurs in their infant. Depending on the time post-dosing/randomization at which the infant's health-related event occur, the investigator or designee will contact the infant's parents or LARs to collect additional information.

Detailed guidance and information on the handling of the eDiary, the monthly electronic contacts, the follow-up phone contacts, and on the completion of the eCRF are provided in the corresponding manuals included in the investigator site file or regulatory binder.

A memory aid will be provided to UK reconsented participants'parents or LARs to collect any hospitalizations and emergency room visits occurring from D366 to D731 post-dosing/randomization. During the 18-month and 24-month phone calls, the Investigator or delegated site staff will interview parents/LARs to collect information reported in the memory aid and to assess the SAE relationship. Only the related SAE information will be collected in the eCRF.

Hospitalization

As part of the safety follow-up, participants will be monitored for hospitalization through the eDiary during the first year of the study and through the memory aid during the second year of the study (only for UK reconsented participants). Parents or LARs will have to report hospitalization through the eDiary. Alternatively, parents or LARs can also directly contact the Investigator.

Upon hospitalization of their infant, parents or LARs will be asked to present the study card to medical personnel. The participant card will:

- Indicate participation in a clinical study
- Invite medical personnel to provide contact details of the host medical facility.
- Remind medical personnel that an RSV test should be conducted in case hospitalization is related to a respiratory illness.

Hospitalization due to respiratory illness

Hospitalization, RSV LRTI hospitalization, and very severe RSV LRTI are defined in Section 8.1.2.

Hospitalizations due respiratory illness (including cases of very severe RSV LRTI) will be reported in a specific eCRF page.

8.3 Adverse Events (AEs), Serious Adverse Events, and Other Safety Reporting

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.2.

When parents or LARs answer questions in the eDiary to report an health event in their infant, an investigation by the site or designee will be triggered to collect information on the AE in the eCRF.

The investigator and any designees are responsible for detecting through entries made by parents in the eDiary, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.2.

8.3.1 Exemption to the Reporting of LRTI Hospitalizations as SAEs

In this study, LRTI hospitalizations of any cause including RSV LRTI hospitalizations constitute the studied clinical outcome of interest; that is, they are constitutive of the efficacy endpoints. As a consequence, LRTI hospitalizations of any cause, including RSV LRTI hospitalizations, occurring during the study will not be considered and reported as SAEs.

It is to be noted that, during the first year of the study, this exemption does not apply in the situation where the Investigator would consider the LRTI hospitalization to be related to the investigational product or to any LRTI hospitalization with a Fatal outcome. During the second year of the study, this exemption does not apply in the situation where the Investigator would consider the LRTI hospitalization to be related to the investigational product. In these situations, the events are to be reported as SAEs and the Investigator is required to follow the protocol-specified process for reporting SAEs to the GPV Department (See Section 10.2.4).

8.3.2 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-immunization Observation Period

Participants enrolled in the nirsevimab group will be kept under observation for 30 minutes after immunization to ensure their safety. The post-immunization observation should be documented in the source document.

Non-serious Adverse Events

Non-serious adverse events will be collected from dosing/randomization (D01) until 30 days after immunization, ie, D31.

The intensity grading scale for non-serious adverse events is presented in Appendix 10.2.5.1.

Medically Attended Adverse Events (MAAEs)

MAAEs will be collected from dosing/randomization (D01) to D366 phone call.

Adverse Events of Special Interest (AESIs)

AESIs will be collected from dosing/randomization (D01) to D366 phone call

See Section 8.3.7 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from dosing/randomization (D01) until 12 months after immunization (D366) for all participants.

Information on related SAEs will be collected and assessed from D366 until D731 post-dosing/randomization for UK reconsented participants. Refer to Section 8.3.1 for the exemption of reporting LRTI hospitalizations as SAEs.

It is to be noted that, since this study is seeking real-world data, part of the participants' safety data will be collected retrospectively by the Investigator or designee. This means that, following the initial capture of information in the eDiary/memory aid by the parents or LARs, the Investigator or designee will be seeking additional or missing participant data from the medical facility where the medical visit or the hospitalization occurred to complete the corresponding eCRF.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.2. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.3.3 Method of Detecting AEs and SAEs

Individual eDiaries, specifically designed for this study by the Sponsor, will be made accessible to parents or LARs during Visit 01 at the study sites. The eDiaries will be used by parents or LARs to report health-related events occurring in participants, including unplanned medical visits and hospitalization. Individual memory aid will be provided to parents or LARs of UK reconsented participants to report any hospitalizations and emergency-room visits occurring from D366 to D731 post-dosing/randomization.

The Investigator or a designee may interview the parents or LARs to collect and clarify information recorded in the eDiary/memory aid. All clinical study information gathered by the study site and/or designee will be reported electronically by the Investigator or designee using a web-based eCRF. Any information that was not documented in the eDiary will first be captured in the source document and then reported electronically.

The 12-month follow-up will be done by interviewing by the investigator or delegated site staff all participants' parents or LARs over the telephone to capture SAEs, MAAEs, and AESIs, if applicable. The 18- and 24-month follow-up will be done by interviewing UK reconsented participants' parents or LARs over the telephone to capture related SAEs.

8.3.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator and/or delegated site staff is required to proactively follow each participant during subsequent contacts, unless parents or LARs refuse further contact. All AEs that are considered by the Investigator as serious or related to the study intervention administered, or AEs of special interest (as defined in Section 8.3.7), will be followed during the conduct of the study until resolution, stabilization, or the participant is lost to follow-up

(as defined in Section 7.3). For related SAEs ongoing at last study contact, such follow-up may need to continue after the end of the study.

Further information on follow-up procedures is provided in Appendix 10.2.

8.3.5 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.3.6 Pregnancy

Not applicable as the study does not include women of childbearing potential.

8.3.7 Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

The following AEs will be assessed as AESIs throughout the study:

- hypersensitivity, including anaphylaxis (56)
- immune complex disease (57)
- thrombocytopenia (58)

The designated Sponsor study representative will work with the investigator to ensure that all relevant information is provided and entered in the eCRF. If the event is considered serious, it must be reported to the Sponsor by the Investigator as an SAE, ie, no later than 24 hours of when she or he becomes aware of the event as an SAE (Appendix 10.2).

8.3.8 Medically Attended Adverse Events

MAAEs will be collected using the same process as other AEs.

See Appendix 10.2.1 for definition of MAAEs.

8.3.9 Health Measurement/Observation

Participants' parents or LARs will be able to report the occurrence of safety events in the eDiary during the first year of the study. In addition, and regardless of whether a safety event was captured during the month, there will be a monthly electronic contact with parents or LARs of the participant, via the eDiary application, to confirm that no health-related events went unreported during the month. The automated monthly electronic contacts will occur up to 6 months post-dosing/randomization. If parents or LARs of the participant confirm that a safety event occurred during the past month, a phone investigations by the site staff and/or designee will be triggered, and the data will be recorded in the eCRF.

At 12 months, a safety follow-up phone call will be made to the parents or LARs of the participant by the site personnel or designee.

Parents or LARs of UK reconsented participants will be able to report any hospitalizations and emergency room visits that occurred from D366 to D731 post-dosing/randomization in the memory aid.

8.4 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

No biomarkers are evaluated in this study.

8.7 Medical Resource Utilization

For participants who report LRTI hospitalizations during the study, the investigator or designee will collect data about health care resource utilization associated with medical encounters.

For each case of LRTI hospitalization, the data collected in the eCRF should:

- Include the RSV test result, the lowest rate of oxygen saturation recorded, the duration of hospital stay, the list of medical interventions leading to end of the hospitalization (eg, oxygen supplementation, intravenous fluid administration, admission to intensive care unit), and outcome, and
- Exclude procedures, tests, and encounters mandated by the protocol.

The sponsor may use the collected data to conduct economic analyses.

Medical Resource Utilization will be evaluated in this study as an exploratory objective to investigate the effectiveness of nirsevimab compared with no preventive intervention in reducing utilization of key medical resources. Data on medical resource utilization will be collected either directly (if the attending physician is the Investigator) or retrospectively from the host hospital and/or the attending physician (if the attending physician is not the Investigator) to identify and measure the impact on these key medical resources arising from RSV LRTI hospitalization in infants.

The evaluation of resource use will be based on RSV LRTI hospitalizations and duration of stay, utilization of oxygen supplementation, administration of intravenous fluid, and ICU admissions and duration of stay.

8.8 Immunogenicity Assessments

See Section 8.1.3.

9 Statistical Considerations

9.1 Statistical Hypotheses

The primary and key secondary efficacy objectives will be assessed in the Primary Analysis (see Section 9.4 for details of the Primary Analysis) by a hierarchical order. Details on statistical methods are provided in Section 9.4.

For the primary objective, a superiority approach will be used to assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization through the RSV season compared to no intervention in all 3 countries combined. Only if the superiority for the primary endpoint is demonstrated, a superiority approach will be used to assess the efficacy of nirsevimab in preventing very severe RSV LRTI through the RSV season compared to no intervention in all 3 countries combined, and no multiplicity adjustment is needed for this.

If the superiority for very severe RSV LRTI through the RSV season is demonstrated, a superiority approach will be used to assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization through RSV season compared to no intervention in each country separately. For this, Bonferroni adjustment of 2-sided α (ie, 0.05/3) is used to correct multiple testing in 3 countries in the sample size calculation and Bonferroni-Holm procedure will be used in the statistical analysis. For other secondary objectives and observational objectives, no hypotheses will be tested and the analyses will be descriptive.

9.2 Sample Size Determination

A total of 28 860 participants are expected to be enrolled of whom approximately 14 430 will receive nirsevimab and 14 430 will receive no intervention. This sample size is driven by the

demonstration of efficacy in preventing RSV LRTI hospitalization in each of 3 countries independently.

Based on the reported incidence rates of RSV LRTI hospitalization in France, Germany, and the UK (2) (51) (52), assuming a 1.1% incidence rate on average in the control group (ie, receiving no intervention), 9620 participants need to be enrolled in each of the 3 countries (which is equivalent to 74 events of RSV LRTI in each country) to ensure the 90% power to detect 60% efficacy in each country with a 2-sided α of 1.66% taking the multiplicity adjustment using Bonferroni approach into consideration.

The sample size of 28 860 participants has at least 99% power to detect 60% efficacy in preventing RSV LRTI hospitalizations in all 3 countries combined assuming an incidence rate of 0.86% in the control group (the lowest reported in the 3 countries) with a 2-sided α of 5%, and approximately 95% power to detect 60% efficacy in preventing very severe RSV LRTI defined in the protocol assuming an incidence rate of 0.4% in the control group (59) with a 2-sided α of 5%. To ensure at least 90% power for very severe RSV LRTI, at least 61 events are needed.

9.3 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Randomized	Participants who were randomly assigned to either the nirsevimab group or the control group
Safety Analysis Set (SafAS)	Participants who received nirsevimab in the study and all randomized participants if randomized to the control group and who did not receive nirsevimab inadvertently. All participants will have their safety analyzed according to the study intervention they actually received.
Per-Protocol Analysis Set (PPAS)	All randomized participants who did not have at least one of the following protocol deviations: - Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria - Participant did not receive nirsevimab or the correct dose of nirsevimab if randomized to nirsevimab - Participant received nirsevimab if randomized to no intervention - Administration of nirsevimab was not done as per-protocol - Participant did not have at least one contact for efficacy follow-up after dosing/randomization - Any other protocol deviations identified during the study conduct as relevant to the exclusion from the PPAS All participants will have their efficacy endpoints analyzed according to the group they were randomized to.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

There will be 3 planned main analyses for this study: the Primary Analysis, the First Year Analysis, and the Second Year Analysis. The Primary Analysis will be conducted when at least 61 events of RSV LRTI hospitalization in all 3 countries combined are observed, but no later than 30 April 2023. All available data collected up to the data cut-off date will be analyzed at the time of the Primary Analysis. The First Year Analysis will be conducted when all participants have completed the scheduled 12-month safety follow up. It will include all data and planned analyses. The Second Year Analysis will be conducted when all UK reconsented participants have completed the scheduled 24-month safety follow-up. It will include all data and planned analyses.

The efficacy analyses performed in the Primary Analysis will serve the purpose of evaluating the efficacy of nirsevimab in the study population. LRTI hospitalization will also be collected after the end of the RSV season and the efficacy will be calculated but only for descriptive purposes at the time of the First Year Analysis without the intention of a confirmatory conclusion. LRTI hospitalizations and wheezing episodes will also be collected at 24 months follow-up and at 12 and 24 months follow-up, respectively, in UK reconsented participants but only for descriptive purposes at the time of the Second Year Analysis (without the intention of a confirmatory conclusion for LRTI hospitalizations). Therefore, no multiplicity adjustment is needed for the 3 main analyses.

9.4.2 Primary Endpoint

The primary endpoint is the overall incidence of RSV LRTI hospitalization through the RSV season in healthy term and preterm infants in all 3 countries combined. The determination of RSV LRTI hospitalization is based on the criteria described in Section 8.1.2.2.

The efficacy of nirsevimab in preventing RSV LRTI hospitalization compared to no intervention will be estimated accounting for the follow-up time post-dosing/randomization up to the data cut-off date for the Primary Analysis as follows:

$(1- (CN / NN) / (CC / NC)) \times 100\%$

where:

- CN and CC are the numbers of RSV LRTI hospitalization through the RSV season in the nirsevimab and the control (ie, no intervention) groups, respectively.
- NN and NC are the total person-time contributed by participants randomized in the nirsevimab and the control groups, respectively.

The 95% CI for the efficacy will be calculated by an exact method assuming a binomial distribution of the number of RSV LRTI hospitalizations in the nirsevimab group conditional on the total number in both groups accounting for the follow-up time post-dosing/randomization.

The superior efficacy of nirsevimab in preventing RSV LRTI hospitalization will be concluded if the lower bound of the efficacy is > 0%. The primary efficacy analysis of the primary endpoint will be performed on all randomized participants.

If a participant experiences multiple occurrences of the same primary endpoint, only the first episode will be considered. The following rules will be applied in the calculation of the total person-time for the follow-up time:

- The start date for the follow-up will be the date of randomization for participants who are randomized to no intervention and the date of dosing for participants who are randomized to nirsevimab.
- For the participants who do not have the primary endpoint at the time of the Primary Analysis, the end date for the efficacy follow-up will be the end of the RSV season, or the last available date with confirmation of no RSV LRTI hospitalization for the Primary Analysis whichever is earlier. The efficacy follow-up will be censored at the end date.
- For the participants who have the primary endpoint at the time of the Primary Analysis, the end date for the efficacy follow-up will be the date of hospital admission.

The above-described analysis on the primary endpoint will also be conducted on the PPAS.

A sensitivity analysis using a Poisson regression model with robust variance will be performed on all randomized participants (60). The model contains the term of treatment group, and age group at randomization (ie, age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months) and country as covariates, adjusting for the log of the follow-up time as an offset. The efficacy of nirsevimab in preventing RSV LRTI hospitalization, defined as 1 minus Relative Risk, and its corresponding 2-sided 95% CI will be estimated from the model. The same rule used in the analysis for the primary endpoint as described above for the calculation of total follow-up time will be applied to the calculation of the follow-up time.

A Kaplan-Meier curve for time to first RSV LRTI hospitalization will be generated based on the observed events. The algorithm for time-to-event calculation is the same as that for follow-up time as above. Treatment group differences in time to first RSV LRTI hospitalization will be compared using the log-rank test stratified by country and age group at randomization. In addition, hazard ratio and the corresponding 95% CI will be obtained from the Cox proportional hazard model with age group at randomization and country as the covariates. The corresponding efficacy estimate is defined as (1-harzard ratio) × 100%.

The subgroup analysis of the primary endpoint will be conducted on the following in all randomized participants using the exact method described above in the primary efficacy analysis:

- Age group at randomization: age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months
- Weight at randomization: weight < 5 kg, weight ≥ 5 kg
- Gestational age: < 37 weeks, ≥ 37 weeks
- Gender: male, female
- Infants dosed in-season (dosed on or after the start date of RSV season) and before the start of the RSV season.

Note: please refer to Section 4.2 for a definition of the start and the end of RSV season

Additional analyses if deemed necessary will be detailed in the SAP.

9.4.3 Secondary Endpoints

9.4.3.1 Very severe RSV LRTI

If the efficacy of nirsevimab in preventing RSV LRTI hospitalization is demonstrated in the primary efficacy analysis, the very severe RSV LRTI through the RSV season will be compared between the nirsevimab and no intervention groups on all randomized participants using the same method for the primary efficacy analysis of the primary endpoint. The very severe RSV LRTI is a subset of RSV LRTI hospitalization with oxygen saturation < 90% (at any time during hospitalization) and oxygen supplementation. For participants with multiple very severe RSV LRTI episodes, only the first occurrence will be used in the analysis. If the lower bound of the 95% CI for the efficacy is > 0%, the superior efficacy of nirsevimab in preventing very severe RSV LRTI compared to the control group is demonstrated.

The above stated analysis on very severe RSV LRTI will be also conducted on the PPAS. The time to first very severe RSV LRTI will be analyzed using the Kaplan Meier curve and the Cox proportional hazard model, as described for the primary efficacy endpoint in Section 9.4.2, on all randomized participants.

Incidence of the very severe RSV LRTI will be summarized by the following subgroups:

- Age group at randomization: age ≤ 3.0 months, age > 3.0 to ≤ 6.0 months, age > 6.0 months
- Weight at randomization: weight < 5 kg, weight ≥ 5 kg
- Gestational age: < 37 weeks, ≥ 37 weeks
- Gender: male, female
- Infants dosed in-season (dosed on or after the start date of the RSV season) and before the start of the RSV season.
- Country

Note: please refer to Section 4.2 for a definition of the start and the end of RSV season

Additional analyses if deemed necessary will be detailed in the SAP.

9.4.3.2 RSV LRTI Hospitalization in each country

If the efficacy of nirsevimab in preventing very severe RSV LRTI compared to the control is concluded, RSV LRTI hospitalization will be evaluated in each of the 3 countries. The same analysis as described above in Section 9.4.2 the primary efficacy analysis for the primary endpoint with Bonferroni-Holm procedure based on the adjusted CIs for the multiplicity adjustment will be used to calculate the efficacy on all randomized participants in each country. The superior efficacy

of nirsevimab in preventing RSV LRTI hospitalization will be concluded for the country if the lower bound of the efficacy is > 0%.

Additional analyses if deemed necessary will be detailed in the SAP.

9.4.3.3 Other secondary efficacy endpoints

Efficacy and its 95% CIs for nirsevimab in reducing the following efficacy endpoints as compared to the control will be calculated using the exact method as described in the primary efficacy analysis for the exploratory purpose:

- Overall hospitalization for all-cause LRTI in all 3 countries combined throughout the RSV season
- RSV LRTI hospitalization through 150 days post-dosing/randomization (overall and in each country)
- Very severe RSV LRTI in all 3 countries combined through 150 days post-dosing/randomization
- Overall hospitalization for all-cause LRTI in all 3 countries combined through 150 days post-dosing/randomization
- RSV LRTI hospitalization through 180 days post-dosing/randomization (overall and in each country)
- Overall hospitalization for all-cause LRTI in all 3 countries combined through 180 days post-dosing/randomization
- Recurrent wheeze throughout the study period in UK reconsented participants

Analyses for the above efficacy endpoints through 150 days post-dosing/randomization and through 180 days post-dosing/randomization will be performed only at the First Year Analysis after all data are collected. Details of the analyses and additional analyses if deemed necessary will be described in the SAP.

Descriptive analyses of the incidence of RSV LRTI hospitalization and all-cause LRTI hospitalization and the incidence of recurrent wheeze with its 95% CIs for nirsevimab and the no intervention will be presented in UK reconsented participants.

9.4.4 Exploratory Endpoints

Efficacy and its 95% CIs for nirsevimab in reducing the following efficacy endpoints as compared to the control will be calculated using the exact method as described in the primary efficacy analysis for the exploratory purpose:

- Very severe RSV LRTI in all 3 countries combined through 180 days post-dosing/randomization

Analyses for the above efficacy endpoints through 180 days post-dosing/randomization will be performed only at the Final Analysis after all data are collected. Details of the analyses and additional analyses if deemed necessary will be described in the SAP.

For other exploratory endpoints, tabular summaries will be presented by the 2 arms. Categorical data will be summarized by the number and percentage of participants in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the SAP.

9.4.5 Safety Analysis

Safety endpoints will be analyzed based on the SafAS defined in Section 9.3. Safety of nirsevimab will be assessed by the occurrence of immediate AEs, non-serious AEs within 30 days post-dosing/randomization, and MAAEs, SAEs, and AESIs following 12 months post-dosing/randomization for all participants, related SAEs from D366 to D731 for UK reconsented participants. All AEs will be coded by MedDRA system organ class and preferred term. The type, incidence, and severity will be summarized by treatment group. Relationship to nirsevimab will also be summarized.

In addition, all AEs (including immediate AEs, non-serious AEs within 30 days post-dosing/randomization, and MAAEs, SAEs and AESIs) in neonates < 28 days of age at randomization will be summarized.

9.5 Interim Analyses

A Primary Analysis is planned prior to the formal completion of the study. The efficacy analyses planned in the Primary Analysis will serve the purpose of evaluating the efficacy of nirsevimab in the study population. Efficacy data analyzed in the First Year and Second Year Analyses are exploratory therefore a multiplicity adjustment is not needed. These analyses will be conducted at the timepoints described in Section 9.4.1.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term “participant” is used throughout this protocol. However, the term “subject” will be used in the eCRF in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements. Similarly, “legally acceptable representative” is used in the protocol whereas “guardian” is used in the eCRF.

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines

- Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])

- The protocol, informed consent form (ICF), Investigator Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
    - In case the participant's parents or LARs have decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial Disclosure

Information related to financial disclosure is described in the Investigator's contract.

10.1.3 Informed Consent Process

An electronic or email informed consent process can be implemented (if applicable per country regulations). Regardless of whether an eConsent, an email ICF or a paper ICF is used:

- The Investigator or her/his representative will explain the nature of the study to the parents or LARs of the participants and answer all questions regarding the study.
- The parents or LARs of the participants must be informed that the participation of their infant is voluntary. The parents or LARs of the participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant parents' or LARs' willingness to continue participation in the study, this will be communicated to the parents or LARs in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- The participants' parents or LARs must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the parents or LARs of the participant.

Recruitment Procedures

Infants will be recruited at hospitals, pediatric and general practice (GP) offices or other community-based clinics.

Pre-screening of infants to be born in season will start at 30 weeks of gestation (ie, before birth). Inclusion in the study (D01) will occur immediately after birth (up to their first scheduled visit after discharge) in participating sites. The final decision as to whether the newborn will be included in the study shall be with the attending physician who is also responsible for the appropriate documenting of inclusion. Infants will be randomly assigned to either the intervention or the no intervention arm of the study.

Recruitment of infants born out of season will be done at participating healthcare providers, eg, primary care offices or pediatric offices. Infants born out of season could also be enrolled at hospital if they are contacted by the hospital to schedule an appointment for enrolment. The date of inclusion (and dosing, for the nirsevimab arm) in the study (D01) is scheduled before or during the start of the RSV season. If possible, inclusion shall be done simultaneously with the mandatory health check-ups.

Infants born out of season will be recruited either prior to or during the RSV season. For the mothers of infants to be born in season, recruiting will start at 30 weeks gestation in women with an estimated delivery date during the RSV season. Participants will be randomly assigned in a 1:1 ratio to either the group that will be immunized with 1 dose of nirsevimab or the group that will receive no RSV preventative therapy.

10.1.4 Data Protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The parents or LARs of the participant must be informed that her/his personal study-related data will be used by the Sponsor in accordance with applicable data protection law. The level

of disclosure must also be explained to the participant's parents or LARs as described in the informed consent.

- The parents or LARs of the participant must be informed that her/his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The parents or LARs of the participant must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects.
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
    - Personnel within Sanofi or partners or service providers involved in the study
    - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
    - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
    - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.

- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to object to the processing, to request for access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees Structure

Participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study. The Sponsor's internal safety review committee, led by the PV representative and the RMO and designee(s), will be responsible for the unblinded review, assessment, and evaluation of safety data generated from this study. This committee is empowered to recommend a pause in recruitment and/or further immunization while it investigates any potential signal or concern.

This study will not include an early safety data review.

10.1.6 Dissemination of Clinical Study Data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical studies in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF and eDiary unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF/eDiary completion guidelines
- The investigator and designees must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, eDiary, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

Details on which clinical supplies are provided by the Sponsor or the site are described in the contract and vendor manuals included in the investigator site file or regulatory binder.

The study start date is considered the date of the first visit planned in the SoA of the first participant.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been either destroyed or returned to the Sponsor, the center study-site has all the documents necessary for archiving and a study-site closure visit has been performed

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- Information on the study intervention leads to doubt as to the benefit/risk ratio

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

Information related to publication policy is described in the Investigator's contract.

10.2 Appendix: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

LRTI hospitalizations of any cause, including RSV LRTI hospitalization, occurring at any time post-dosing/randomization, will not be considered and reported as SAEs (see Section 8.3.1 for more information).

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions
Adverse Reaction: An adverse reaction (AR) is any noxious and unintended response to a study intervention related to any dose. All AEs occurring at and around the IMP injection/administration site are to be considered by default as related to the IMP administered at that site and are therefore referred as injection/administration site ARs. All AEs which are not at and around the IMP injection/administration site, are referred as systemic AE. For each systemic AE, the investigator assesses the relationship to the IMP. Systemic AEs assessed as related to IMP are referred as systemic ARs. ***Immediate Event/Reaction:*** Immediate events are recorded to capture medically relevant AEs which occur within the first 30 minutes after immunization. ***Adverse Event of Special Interest (AESI):*** An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted. ***Medically Attended AE (MAAE)*** An MAAE is a new onset or a worsening of a condition that prompts the participant or participant's parent/legally acceptable representative to seek unplanned medical advice at a physician's office or Emergency Department. Physician contact made over the phone or by e-mail will be considered a physician office visit for the purpose of MAAE collection. This includes medical advice seeking during the study visit or routine medical care. This definition excludes pediatric check-ups, follow-up visits of chronic conditions with an onset prior to entry in the study.

10.2.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is other medically important event

- The term "Other medically important events" refers to events which do not meet any of the above seriousness criteria, but which are considered as serious based on investigator medical judgment

- Medical or scientific judgment should be exercised by the investigator in deciding whether expedited reporting is appropriate in other situations such as significant medical events that may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse, new-onset diabetes or autoimmune disease, or suspected transmission of any infectious agent via an authorized medicinal product.

Note: *Serious* and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.2.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the eCRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

By convention, all AEs reported at the injection site are considered to be related to the IMP (see definition in Section 6) and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

- Causal relationship of AEs and SAEs will be recorded as follows:
  - For non-serious AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the Investigator only.
  - For SAEs and non-serious AESIs, relationship to study intervention will be assessed by both the Investigator and the Sponsor (except for injection site reactions which will be related by default). Sponsor assessment is entered in the GPV database only.
  - For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
- The Investigator will assess the ***causal relationship*** between each AE and the study intervention administered as either ***not related*** or ***related***, based on the following definitions:
  - Not related – The AE is clearly / most probably caused by other etiologies such as participants' underlying condition, therapeutic intervention, or concomitant therapy; or the delay between immunization and the onset of the AE is incompatible with a causal relationship; or the AE started before the immunization (screening phase, if applicable)

- Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there are facts (evidence) or arguments to suggest a causal relationship

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always makes an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causal relationship in light of follow-up information and send an SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, when available the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- Serious adverse events likely to be related to the study intervention, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.2.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Details regarding SAE reporting can be found in the eCRF completion guidelines in the investigator site file or regulatory binder.

SAE Reporting to the Sponsor via Paper CRF

- The SAE paper CRF can be sent to the Sponsor by one of the following means:
  - By fax, to the following number: +33 (0) 1 60 49 70 70
  - In PDF format to the following e-mail address, using a method of transmission that includes password protection: CL-CPV-Receipt@sanofi.com

Safety Emergency Call

If, as per the Investigator's judgment, a participant experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on how to address any study-related medical question or problem. If the RMO is not available, then the Investigator may contact the RMO Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the contact sheet in the investigator site file or regulatory binder.

This process does not replace the need to report an SAE. The Investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department.

10.2.5 Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the “FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007”.

10.2.5.1 AE Intensity Grading Scale

All AEs will be classified according to the following intensity scale:

- Grade 1
  - eCRF: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - No grading in eDiary/memory aid
- Grade 2
  - eCRF: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - No grading in eDiary/memory aid
- Grade 3
  - eCRF: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - No grading in eDiary/memory aid

10.3 Appendix: Country-specific Requirements

10.4 Appendix: Risk-based Approach

ICH E6-R2 guideline for GCP is introducing the « risk-based approach » concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.5 Appendix: Abbreviations

AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
CRF	Case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	electronic CRF
eDiary	electronic Diary
FAS	Full analysis set
FVFS	First Visit First Subject
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPV	Global Pharmacovigilance
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IM	intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
IRT	interactive response technology
LAR	legally acceptable representative
LRTI	lower respiratory tract infection
LVFS	Last Visit First Subject
LVLS	Last Visit Last Subject
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-Investigational Medicinal Product
PPAS	Per-protocol analysis set
PV	pharmacovigilance

RMO	Responsible Medical Officer
RSV	respiratory syncytial virus
SAE	Serious adverse events
SafAS	Safety Analysis Set
SAP	Statistical analysis plan
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
WGA	weeks gestational age

10.6 Appendix: Protocol Amendment History

The Protocol Amendment Rationale for the current amendment is located directly before the Table of Contents.

Protocol update 1 – Version 2.0 (17 June 2022)

Overall Rational for the Protocol Update

VAS00006 protocol version 1.0 (dated 01 March 2022) was updated to extend the period during which LRTI hospitalizations are to be collected from 6 months to 12 months (ie, the entire study duration) post-dosing/randomization. This will help mitigate the variability of RSV seasonality and ensure that all LRTI hospitalizations occurring during next RSV season are captured.

This updated version of the protocol also provides some additional information on a number of operational matters. As this is a multicenter study taking place in three countries, it is important to ensure that operational procedures are clearly described to decrease the risk of deviation from the study protocol.

Among the clarifications brought with VAS00006 protocol version 2.0 are the following:

- The measurement method of the infant's temperature before dosing is to be performed as per routine practice.
- It has been made explicit that the collection of adverse events starts *after dosing/randomization* on the day of inclusion (Visit 1).
- The possibility to use an electronic Informed Consent process (applicable as per country regulations) was made explicit.
- It was made clearer that Informed Consent can take place before Visit 1 but inclusion/exclusion criteria verification and all other procedures must take place immediately before dosing/randomization.
- It was stated in the protocol that only infants born at ≥ 29 weeks gestational age would be included in the study. This requirement is now part of inclusion criterion I01 for more clarity.

Amendment 1 – Version 3.0 (19 July 2023)

Overall Rationale for the Amendment:

As a result of a post-marketing commitment to the United States Food and Drug Administration (FDA) to collect data for the evaluation of antibody-dependent enhancement of RSV disease in the second RSV season of neonates and infants who received nirsevimab prior to or during their first RSV season, the follow-up of HARMONIE participants is being extended to 24 months.

To address this commitment, the HARMONIE study design was updated with the addition of a 12-month follow-up period, including 2 phone calls at D546 and D731 post-dosing/randomization, in United Kingdom (UK) participants only. At the end of the first-year follow-up, all UK participants' parents/LARs still in the study will be informed of the study extension and their consent will be asked.

In order to minimize the burden on sites, families and participants while still answering the objectives of this protocol amendment, it was decided to invite in this study extension only the UK participants, who represent 50% of the study population. Only UK participants whose parents/LARs have given consent (called reconsented participants hereafter) will participate in the study extension.

The 12-month extension period is also used as the opportunity to retrospectively collect information on wheeze at D366 and D731 post-dosing/randomization in UK reconsented participants only.

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12 Sponsor Signature Page

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