Clinical Study Protocol

Protocol Title:

Phase II, randomized, observer-blind, placebo-controlled, multi-center study of a live-attenuated Respiratory Syncytial Virus vaccine to assess the vaccine virus' transmissibility in household or daycare center settings, shedding, and genetic stability, and to describe the immunogenicity and safety of the vaccine in infants and toddlers 6 to < 24 months of age

Study Code: VAD00014

Amendment Number: 2

Compound: Live-Attenuated Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L vaccine (RSVt vaccine)

Brief Title:

Study on a live-attenuated Respiratory Syncytial Virus vaccine for assessment of safety, transmissibility, and genetic stability of the vaccine virus among close contacts in infants and toddlers 6 to < 24 months of age

Study Phase: II

Sponsor Name and Legal Registered Address:

Sanofi Pasteur Inc.
Discovery Drive, Swiftwater, PA 18370-0187, USA

Manufacturer: Same as Sponsor

Regulatory Agency Identifier Number:

WHO UTN: U1111-1278-3910

Protocol Version Number: 4.0

Approval Date: 28 September 2023

Responsible medical officer (RMO) and pharmacovigilance (PV) representative names and contact information will be provided separately.

The study centers, the investigators at each center, and the coordinating investigator(s) are also listed in a separate document.

Document History

Previous Version	Date	Comments
1.0	01 August 2022	Version not submitted
2.0	13 October 2022	First version used in the study
3.0	26 June 2023	Amendment 1

IEC: Independent Ethics Committee; IRB: Institutional Review Board

* Versions in bold font have been approved by the IEC(s) / IRB(s) and used in the study.

Overall Rationale for the Amendment:

The amendment of protocol version 3.0 to protocol version 4.0 (Amendment 2) included administrative changes and the following changes:

- An update of the endpoint of the 3rd primary objective to clarify that the sequencing is not limited to the NS2 region
- An additional exploratory objective and endpoint for infectivity, and a clarification to the exploratory objective for [redacted]
- Clarification that the first interim analysis is planned in Q4 2023 on available participant data irrespective of recruitment completion and the second interim analysis is planned for all participants
- Addition of symptoms of RSV medically attended acute respiratory illness and the corresponding grading scale
- Addition of a description of RSV B green fluorescent protein microneutralization assay
- Addition of height and weight measurements of pediatric participants at enrollment

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

Phase II, randomized, observer-blind, placebo-controlled, multi-center study of a live-attenuated Respiratory Syncytial Virus vaccine to assess the vaccine virus' transmissibility in household or daycare center settings, shedding, and genetic stability, and to describe the immunogenicity and safety of the vaccine in infants and toddlers 6 to < 24 months of age

Brief Title:

Study on a live-attenuated Respiratory Syncytial Virus vaccine for assessment of safety, transmissibility, and genetic stability of the vaccine virus among close contacts in infants and toddlers 6 to < 24 months of age

Rationale:

In the context of intranasal administration of a live attenuated RSV vaccine and to demonstrate that a large-scale study with the RSVt vaccine can be conducted safely, both the transmission rate and the genetic stability of the vaccine virus will be determined. In addition, the vaccine virus shedding will be described in the RSVt vaccinees at regular timepoints and the clinical safety in their close contacts will be assessed.

Data generated in the VAD00014 study will provide insights into the transmission of the RSVt vaccine virus and genetic stability, along with the safety and immunogenic profile of the RSVt vaccine candidate, and may support the next steps of the development, including the planned large-scale Phase III efficacy study.

Objectives, Endpoints:

Objectives	Endpoints
Primary	
• To describe the vaccine virus transmission in pediatric participants receiving placebo after the first study intervention administration	• Presence of vaccine virus in day (D)01, D04, D08, D11, D15, D18, and D22 nasal swabs, detected by RSVt quantitative reverse transcription polymerase chain reaction (RSVt qRT-PCR) Assay in pediatric participants receiving placebo.
• To describe the vaccine virus shedding in all pediatric participants with detected vaccine virus after each administration	• Titer of vaccine virus shedding in D01, D04, D08, D11, D15, D18, D22, D64, and D71 nasal swabs, quantified by RSVt qRT-PCR Assay in all pediatric participants.

Objectives	Endpoints
• To describe the vaccine virus stability in pediatric participants receiving placebo and ad-hoc close contact participants	• Difference in genetic sequence of mutated vaccine virus segments compared to the reference strain vaccine virus isolates in the vaccine virus positive swabs from pediatric participants receiving placebo and ad-hoc close contact participants
Secondary	
Immunogenicity • To evaluate the RSV A serum neutralizing and RSV serum anti-F immunoglobulin G (IgG) antibody responses to the study intervention after each study intervention administration in all pediatric participants	**Immunogenicity** • RSV A serum neutralizing antibody titers up to 28 days after the second administration (D01, D57, and D85) • RSV serum anti-F IgG enzyme-linked immunosorbent assay (ELISA) antibody titers up to 28 days after the second administration (D01, D57, and D85)
Safety • To assess the safety profile of the RSVt vaccine after each and any study intervention administration in pediatric participants	**Safety** • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each study intervention administration • Presence of any solicited (ie, pre-listed in the participant's diary card [DC] and in the case report book [CRB]) administration site and systemic reactions within 21 days after each study intervention administration • Presence of any unsolicited (spontaneously reported) AEs within 28 days after each study intervention administration • Presence of any adverse events of special interest (AESIs) within 28 days after each study intervention administration • Presence of any medically attended adverse events (MAAEs) within 28 days after each study intervention administration • Presence of any serious adverse events (SAEs) throughout the study
Transmission and virus shedding • To describe the vaccine virus transmission in pediatric participants receiving placebo after the second study intervention administration	**Transmission and virus shedding** • Presence of vaccine virus in D64 and D71 nasal swabs, detected by RSVt qRT-PCR Assay in the pediatric participants receiving placebo

Overall Design:

Type of design	Parallel, multi-center
Phase	II
Control method	Placebo-controlled
Study population	• Pediatric participants: Healthy infants / toddlers 6 to < 24 months of age in close contact with other infants / toddlers 6 to < 24 months of age who participate in the study • Ad-hoc close contact participants: ad-hoc close contact children and adults who experience acute respiratory illness (ARI) in the 28 days following the administration of the study intervention to the close contact pediatric participant
Countries	United States and Puerto Rico
Level and method of blinding	Observer-blind: • Blinding for vaccine group assignment: participants, parents or legally acceptable representative (LAR), outcome assessors, investigators, laboratory personnel, Sponsor study staff • No blinding for study staff who prepare and administer the study interventions
Study intervention assignment method	Pediatric participants will be screened for eligibility criteria at the time of inclusion and randomized to receive either RSVt vaccine or placebo in a 1:1 ratio

Brief Summary:

The primary purpose of the VAD00014 study is to assess the shedding, transmission, and genetic stability of the live-attenuated RSVt vaccine after each intranasal vaccination (56 days apart) in infants and toddlers 6 to < 24 months of age. Study details include:

The study duration will be:

- up to 8 months, including the 6 months safety follow-up phone call after the second study intervention administration for the pediatric participants

The treatment administration for the pediatric participants will be on D01 and D57 (1 intranasal administration each).

The visit frequency will be twice a week after D01 (ie, first administration of study intervention) up to D22 for a total of 7 visits (D01, D04, D08, D11, D15, D18, and D22), and 7, 14, and 28 days after D57 (second administration) at D64, D71, and D85. Some of these visits may be managed as home visits or daycare center visits.

Additional illness visits may occur during the study intervention phase (D01-D85) in case of acute respiratory symptoms.

Number of Participants:

A total of 100 pediatric participants are expected to be randomized (50 participants in each study intervention group).

Intervention Groups and Duration:

Eligible pediatric participants will be randomized in a 1:1 ratio to receive 2 intranasal administrations (56 days apart) of either the RSVt vaccine or placebo at D01 and D57.

Eligible ad-hoc close contacts will be enrolled if they develop ARI symptoms and will not receive any study intervention.

The duration of participation will be approximately 8 months for each pediatric participant. The duration of participation of the ad-hoc close contacts is limited to the illness Visit(s).

Study interventions:

Investigational medicinal product 1: RSVt vaccine [redacted]

- Form: Suspension of virus
- Composition: Each [redacted] dose of RSVt vaccine will contain the live-attenuated RSV with *i)* [redacted] approximately [redacted] to be delivered [redacted]
- Route of administration: intranasal

Statistical considerations:

All analysis will be descriptive. No statistical hypothesis will be tested.

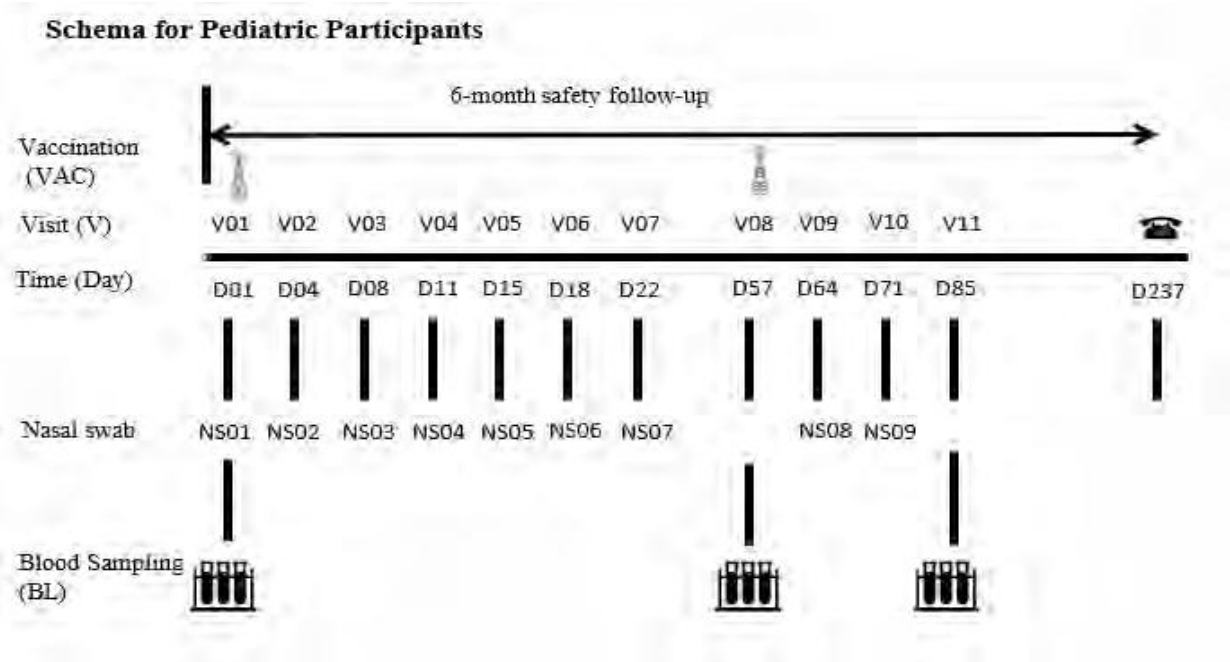
All endpoints will be summarized by study intervention group. For the main parameters, 95% confidence interval (CI) of point estimate will be calculated.

Data Monitoring/Other Committee: No

1.2 Schema

The graphical design of VAD00014 study for pediatric participants is presented in Figure 1.

Figure 1: Graphical study design for pediatric participants



1.3 Schedule of Activities (SoA)

Table 1.1: Schedule of activities for pediatric participants

Phase II Study, 11 Planned Visits, 2 Vaccinations, 3 Blood Samples, 9 Planned Nasal Swabs, One 6-Month Safety Follow-up Phone Call, approximately 8 Months' Duration Per Pediatric Participant

Visit/Contact*	***Collection of information in the CRF***	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**Safety follow-up phone call**	**Illness Visit‡‡**
Study timelines days (D)		D01	D04	D08	D11	D15	D18	D22	D57	D64	D71	D85	D237	
Visit Interval			V01 + 3d	V01 + 7d	V01 + 10d	V01 + 14d	V01 + 17d	V01 + 21d	V01 + 56d	V08 + 7d	V08 + 14d	V08 + 28d	V08 + 6 months	
Time windows (days)		NA	[+1]	[+1]	[+1]	[+1]	[+1]	[+1]	[+7]	[+1]	[+1]	[+7]	[+14]	
Visit procedures:														
Informed consent	X	X												
Inclusion/exclusion criteria	X	X												
Collection of demographic data	X													
Collection of medical history	X Significant Medical History	X												
Physical examination	X	X							X					
Vital signs†	X	X							X					
Rapid COVID-19 test	X	X							X					

Visit/Contact*	***Collection of information in the CRF***	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**Safety follow-up phone call**	**Illness Visit‡‡**
Study timelines days (D)		D01	D04	D08	D11	D15	D18	D22	D57	D64	D71	D85	D237	
Visit Interval			V01 + 3d	V01 + 7d	V01 + 10d	V01 + 14d	V01 + 17d	V01 + 21d	V01 + 56d	V08 + 7d	V08 + 14d	V08 + 28d	V08 + 6 months	
Time windows (days)		NA	[+1]	[+1]	[+1]	[+1]	[+1]	[+1]	[+7]	[+1]	[+1]	[+7]	[+14]	
Collection of reportable concomitant medications/vaccinations	X								X					X
Randomization/allocation of participant number	X	X												
Dose number	X	X							X					
Blood sampling (BL) [5 mL]	X	BL0001 Pre-vac1							BL0002 Pre-vac2			BL0003		
Nasal swab (NS)‡	X	NS0001 Pre-vac1	NS0002	NS0003	NS0004	NS0005	NS0006	NS0007		NS0008	NS0009			UN0001 to UN000X
Vaccination (vac)	X	VAC1							VAC2					
Immediate surveillance (30 min)§	X	X							X					
DC provided**		DC1							DC2					
DC reviewed††			DC1	DC1	DC1	DC1	DC1	DC1	DC1	DC2	DC2	DC2		
DC collected									DC1			DC2		
MA provided												MA		
MA reviewed													MA	
Collection of solicited administration site and systemic reactions	X	From D01 to D22							From D57 to D78					
Collection of unsolicited AEs	X	From D01 to D29							From D57 to D85					

Visit/Contact*	*Collection of information in the CRF*	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	Safety follow-up phone call	Illness Visit‡‡
Study timelines days (D)		D01	D04	D08	D11	D15	D18	D22	D57	D64	D71	D85	D237	
Visit Interval			V01 + 3d	V01 + 7d	V01 + 10d	V01 + 14d	V01 + 17d	V01 + 21d	V01 + 56d	V08 + 7d	V08 + 14d	V08 + 28d	V08 + 6 months	
Time windows (days)		NA	[+1]	[+1]	[+1]	[+1]	[+1]	[+1]	[+7]	[+1]	[+1]	[+7]	[+14]	
Collection of AESIs and MAAEs	X	From D01 to D29							From D57 to D85					
Collection of SAEs	X	Throughout the study												
Phone Call													X	
Collection of End of Study Intervention Phase status	X											X		
Collection of 6-Month Follow-up-End of Study status	X												X	

Abbreviations: AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; CRF, case report form; DC: diary card; LAR, legally acceptable representatives; MA, memory aid; MAAE, medically-attended adverse event; NA, not applicable; SAE, serious adverse event.

* Additional unscheduled visits may be performed for safety reasons; information will be reported in the source documents.

† Vital signs will be collected in the eCRF.

‡ All pediatric participants will provide a nasal swab sample for detection of vaccine virus shedding / transmission at specified visits. The same nasal swab specimen may also be tested for respiratory pathogens (including COVID-19), if the pediatric participant is ill at the time of the visit. If needed, home visits (including Illness Visit) may be conducted by a clinical site nurse to perform the nasal swabs, except for V07, which should be done at the clinical site (as a physician should review the diary card).

§ Any unsolicited systemic adverse events occurring within the 30 minutes from study intervention administration will be recorded as immediate unsolicited systemic AE in the case report book.

** The investigator or a designee will remind the parents / LAR to bring back the DC at the next visit and will answer any questions.

The parent / LAR will record information in the DC about solicited reactions from D01 to D22, and unsolicited AEs and AESIs from D01 to D29 after each study intervention administration.

†† The investigator or a designee will interview the parents / LAR to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear. In case of home visit(s) done by a clinical site nurse, the DC will be reviewed by a physician at the next clinical site visit.

‡‡ Illness Visits: Additional nasal swab specimens for the detection of RSV and respiratory pathogens" (including COVID-19) will also be collected from pediatric participants in case of acute respiratory illness. All the nasal swab specimens will be collected in the recommended viral transport media tube and will be stored between -60°C and -80°C until ready to ship.

Table 1.2: Schedule of activities for ad-hoc close contact participants

Phase II Study, at least 1 Unplanned Illness Visit, at least 1 Unplanned Nasal Swab, Duration is limited to the Illness Visit(s)

Visit (V) / Contact*	***Collection of information in the CRF***	**Illness Visit(s)**
Study timelines - Days(D)		**Not applicable**
Visit Interval		**ARI** symptoms during the 28 days following any administration of the study intervention to the close contact pediatric participant**
Time windows (days)		**Not applicable**
Informed consent†	X	X
Collection of demographic data†	X	X
Allocation of participant number†	X	X
Nasal swab (NS)‡	X	UN0001 to UN000X§
Collection of End of Study status	X	At the end of the study intervention phase for the pediatric participant in close contact to ad-hoc participant

Abbreviations: CRF, case report form; ARI, acute respiratory illness

* Additional unscheduled visits may be performed for safety reasons; information will be reported in the source documents.

† To be collected during the first illness visit.

‡ Illness Visits: All the nasal swab specimens will be collected in the recommended viral transport media tube and will be stored between -60°C and -80°C until ready to ship.

§ Ad-hoc close contact participants will provide a nasal swab sample for detection of vaccine virus transmission. The same nasal swab specimen may also be tested for respiratory pathogens (including COVID-19).

** Acute respiratory illness includes upper and lower respiratory illness.

2 Introduction

2.1 Study Rationale

In the context of intranasal administration of a live attenuated RSV vaccine and to demonstrate that a large-scale study with the RSVt vaccine can be conducted safely, both the transmission rate and the genetic stability of the vaccine virus will be determined. In addition, the vaccine virus shedding will be described in the RSVt vaccinees at regular timepoints and the clinical safety in their close contacts will be assessed.

Data generated in the VAD00014 study will provide insights into the transmission of the RSVt vaccine virus and genetic stability, along with the safety and immunogenic profile of the RSVt vaccine candidate, and may support the next steps of the development, including the planned large scale Phase III efficacy study.

2.2 Background

Respiratory syncytial virus (RSV) is the most important cause of severe acute lower respiratory illness (LRI) in infants and children (1) (2) and the most common cause of severe pneumonia requiring hospital admission in children worldwide (3). According to global estimates, RSV caused approximately 33 million cases of LRI and approximately 118 000 deaths in children < 5 years of age in 2015 (2).

Live attenuated intranasal RSV vaccines are an attractive option for pediatric immunization because they mimic mild natural infections and induce durable cellular, humoral, and both local and systemic immunity. Several studies of live attenuated RSV vaccine candidates have indicated that these vaccines do not cause the vaccine-associated enhanced RSV disease observed in children who received formalin-inactivated RSV (4) (5) (6) (7) (8) (9) (10) (11) (12). Progress has been made in the understanding of the RSV gene function, and the use of reverse genetic systems to engineer rationally-designed attenuated RSV strains, including strains attenuated through deletion of the nonstructural (NS) 2 gene like the live attenuated RSV ΔNS2/Δ1313/I1314L vaccine candidate (13) (14). RSV NS2 is a virally-encoded type I and III interferon antagonist that interferes with interferon induction and signaling (15) (16) (17). The increased interferon response to infection may enhance the adaptive immune response, as has been demonstrated for bovine RSV with NS1 or NS2 deletion in calves (18). NS2 also functions as a pathogenicity factor, promoting epithelial cell shedding in vitro and in the hamster model, and its deletion may potentially reduce small airways obstruction, thus improving the safety profile of such vaccine candidates (19).

Live Attenuated Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L Vaccine Candidate

The investigational RSV ΔNS2/Δ1313/I1314L vaccine (hereafter referred to as the NIH RSV ΔNS2/Δ1313/I1314L vaccine), developed at the Laboratory of Infectious Diseases at the National Institute of Allergy and Infectious Diseases, is based on reverse genetics approaches used to create

deletions of the gene encoding the RSV interferon / apoptosis antagonist NS2 protein (ΔNS2). Deletion of NS2 gene attenuates the virus and may enhance immunogenicity. RSV ΔNS2/Δ1313/I1314L vaccine additionally contains a genetically stabilized attenuating and temperature sensitivity mutation in the L protein (codon deletion Δ1313, as well as a missense mutation I1314L that prevents a de-attenuating mutation that otherwise can occur at position 1314). The RSV ΔNS2/Δ1313/I1314L temperature sensitivity translates into a shut-off of virus replication at 38ºC-39°C.

Prior to RSV ΔNS2/Δ1313/I1314L vaccine, three RSV vaccine viruses with the NS2 gene deletion (rA2cpΔNS2, rA2cp248/404ΔNS2, and rA2cp530/1009ΔNS2) had been evaluated in clinical studies (6). The rA2cpΔNS2 candidate was over-attenuated for adults but under-attenuated for use in young children, whereas both rA2cp248/404ΔNS2 and rA2cp530/1009ΔNS2 were over-attenuated and insufficiently immunogenic in seronegative children.

Sanofi's investigational RSV ΔNS2/Δ1313/I1314L vaccine (hereafter referred to as RSVt vaccine) is the same construct as the NIH RSV ΔNS2/Δ1313/I1314L vaccine. The vaccines differ in formulation and mode of intranasal administration. The RSVt vaccine is being developed for the pediatric population.

Phase I Clinical Data (NIH RSV ΔNS2/Δ1313/I1314L)

A Phase Ia study was conducted by the National Institutes of Health (NIH) in RSV seronegative children aged 6 to 24 months (n=20) who received NIH RSV ΔNS2/Δ1313/I1314L vaccine at the 10^6 PFU dose level. This study showed that the 10^6 PFU dose level was safe, had good infectivity (100% of vaccinated participants infected) and immunogenicity (80% of participants with a $\geq$ 4-fold rise in neutralizing antibody titers), and primed for a strong anamnestic response to wildtype (WT) RSV infection in the post-RSV season surveillance (20).

Another study aiming at describing the safety and immunogenicity of the NIH RSV ΔNS2/Δ1313/I1314L vaccine in RSV-seronegative children (IMPAACT 2018, NCT03227029 / NCT03422237) confirm the previous results such as the good safety profile, high infectivity (88%) and genetic stability of the candidate (21).

This vaccine candidate is presently being evaluated in infants 4 to 6 months of age (unscreened for RSV antibodies at baseline) by the NIH at the Center for Immunization Research, Johns Hopkins University (NCT01893554) (22). In this younger age cohort, 15 participants have been enrolled to date and have completed the post-vaccination acute and post-acute-phase follow-up to date, without any safety signals.

Based on these Phase I study data, RSVt vaccine appears to be safe and immunogenic, and it is currently being evaluated by Sanofi for further clinical development.

Phase I/II Clinical Study (RSVt Vaccine)

The ongoing Sanofi Phase I/II study (VAD00001) is a randomized, observer-blind, placebo-controlled, multi-center, dose-finding study to evaluate the safety, immunogenicity, infectivity, and vaccine virus shedding after 1 or 2 administrations of the Sanofi RSVt vaccine in infants and toddlers 6 to 18 months of age in the United States and Latin America (Chile and Honduras). A total of 259 infants and toddlers 6 to18 months of age have been randomized to receive 1 or 2

intranasal administrations of RSVt vaccine (at either an investigational dose level of [redacted]

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 RSVt vaccine may be found in the Investigator's Brochure (IB) and Investigational Directions for Use (IDFU) for a device product.

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 Vaccine: RSVt Vaccine		
Anaphylaxis	All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine.	Exclusion criterion E02 for those at increased risk. Observation period after vaccination for early detection and treatment. Each site must have measures to treat Anaphylaxis available at the time of vaccination
Upper or lower respiratory tract illness	If a live-attenuated RSV vaccine is insufficiently attenuated, participants could experience upper or lower respiratory tract illness	Medical surveillance with qualified medical personnel to provide care if needed
Study Procedures		
Vasovagal reactions (syncope), or psychogenic reactions to needle (blood sampling)	Anxiety-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection or blood draw, and may be accompanied by several neurological signs such as transient visual disturbance, paresthesia or seizure-like activity	Observation period after vaccination for early detection and treatment.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Infection in rare instances at the blood draw site		Early detection, observation, and appropriate treatment.
Use of topical anesthetic cream include temporary skin discoloration, skin irritation, rash, hives, and rarely dizziness or drowsiness		Early detection, observation, and appropriate treatment.
Other		
Risks occasionally associated with nasal swabs include pain or discomfort and occasionally epistaxis. Nasal swabs are not standard care in pediatric population.		Study personnel performing nasal swab will receive appropriate training to perform the procedure

2.3.2 Benefits from Study Participation

Pediatric participants randomized in the group to receive the RSVt vaccine may benefit from coverage against respiratory syncytial virus and may be less likely to develop RSV associated pneumonia or RSV related severe illness and/or hospitalization.

However, as with all vaccines, vaccination with the investigational vaccine may not protect individuals 100%.

2.3.3 Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to participants enrolled in this study, the anticipated benefits, that may be afforded, outweigh the potential risks that may result from study participation.

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 describe the vaccine virus transmission in pediatric participants receiving placebo after the first study intervention administration	• Presence of vaccine virus in day (D)01, D04, D08, D11, D15, D18, and D22 nasal swabs, detected by RSVt quantitative reverse transcription polymerase chain reaction (qRT-PCR) Assay in pediatric participants receiving placebo
• To describe the vaccine virus shedding in all pediatric participants with detected vaccine virus after each administration	• Titer of vaccine virus shedding in D01, D04, D08, D11, D15, D18, D22, D64, and D71 nasal swabs, quantified by RSVt qRT-PCR Assay in all pediatric participants
• To describe the vaccine virus stability in pediatric participants receiving placebo and ad-hoc close contact participants	• Difference in genetic sequence of mutated vaccine virus segments compared to the reference strain vaccine virus isolates in the vaccine virus positive swabs from pediatric participants receiving placebo and ad-hoc close contact participants
Secondary	
Immunogenicity • To evaluate the RSV A serum neutralizing and RSV serum anti-F immunoglobulin G (IgG) antibody responses to the study intervention after each study intervention administration in all pediatric participants	**Immunogenicity** • RSV A serum neutralizing antibody titers up to 28 days after the second administration (D01, D57, and D85) • RSV serum anti-F IgG ELISA antibody titers up to 28 days after the second administration (D01, D57, and D85)
Safety • To assess the safety profile of the RSVt vaccine after each and any study intervention administration in pediatric participants.	**Safety** • Presence of any unsolicited systemic AEs reported in the 30 minutes after each study intervention administration • Presence of any solicited (ie, pre-listed in the participant's diary card [DC] and in the case report book [CRB]) administration site and systemic reactions within 21 days after each study intervention administration

Objectives	Endpoints
	• Presence of any unsolicited (spontaneously reported) AEs within 28 days after each study intervention administration • Presence of any AESIs within 28 days after each study intervention administration • Presence of any MAAEs within 28 days after each study intervention administration • Presence of any SAEs throughout the study
Transmission and virus shedding • To describe the vaccine virus transmission in pediatric participants receiving placebo after the second study intervention administration	**Transmission and virus shedding** • Presence of vaccine virus in D64 and D71 nasal swabs, detected by RSVt qRT-PCR in the pediatric participants receiving placebo
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]

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	Parallel, multi-center
Phase	II
Control method	Placebo-controlled
Study population	• Pediatric participants: Healthy infants / toddlers 6 to < 24 months of age in close contact with other infants / toddlers 6 to < 24 months of age who will participate in the study • Ad-hoc close contact participants: Ad-hoc close contact children and adults who experience ARI in the 28 days following the administration of the study intervention to the close contact pediatric participant
Level and method of blinding	Observer-blind: • Blinding for study intervention group assignment: participants, parents or LAR, outcome assessors, investigators, laboratory personnel, Sponsor study staff • No blinding for study staff who prepare and administer the study interventions
Study intervention assignment method	Pediatric participants will be screened for eligibility criteria at the time of inclusion and randomized to receive either RSVt vaccine or placebo in a 1:1 ratio. Randomization will be stratified by contact group (the household /group attended in daycare center) and by age group (< 12 months / ≥ 12 months)
Number of participants	100 pediatric participants 6 to < 24 months of age
Intervention groups	Eligible pediatric participants will be randomized in a 1:1 ratio to receive 2 intranasal administrations (56 days apart) of either the RSVt vaccine or placebo at D01 and D57
Total duration of study participation	Approximately 8 months for each pediatric participant. The duration of the ad-hoc close contacts will be limited to the Illness Visit.
Countries	United States and Puerto Rico
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	NO

VAD00014 study is planned to enroll a convenience sample of 100 children aged 6 to < 24 months (hereafter referred as pediatric participants) at least by pairs or larger groups of children, living in a context in which the probability of transmission is maximized, ie, group of children attending daycare centers, twins, and children living with siblings of similar age. The pediatric participants will be randomized to receive either the RSVt vaccine or placebo (the placebo group will allow to assess the transmissibility and safety of the RSVt vaccine in a blinded way).

VAD00014 study will be randomized, observer-blind, placebo-controlled, and will include 2 administrations, 56 days apart (ie, at Day (D)01 and D57). Pediatric participants will be randomized in 1:1 ratio and are planned to be enrolled in pairs or in small groups (ie, siblings or attending the same daycare center) to ensure that transmissibility from pediatric participants receiving the RSVt vaccine to pediatric participants receiving the placebo can be evaluated. Shedding, transmissibility, and genetic stability of the vaccine virus will be assessed through the collection of nasal swabs at regular intervals after each study intervention administration. As RSVt vaccine will be administered by intranasal route, vaccine virus shedding is then expected in the nose. Therefore, nasal swabs are commonly used for shedding assessment, especially in the infant population in which nasal washes are more invasive.

In addition, pediatric participant's close contacts who experience an ARI in the 28 days following the study intervention administration may be asked to provide a nasal swab. The pediatric participant's close contacts are any persons who are in the same room as the pediatric participant for more than 4 hours a day for at least 3 days a week. These may include children attending the same daycare center, daycare center staff in contact with pediatric participants, or household members of pediatric participants. They are hereafter referred to as the ad-hoc close contact participants.

Each pediatric participant will provide a blood sample at baseline, and after each study intervention administration, ie, 56 days after the first administration (D57, pre-administration 2) and 28 days after the second administration (D85). The blood sample collected at Visit 01 will be used to determine the pediatric participant's RSV serostatus at baseline. The blood samples collected at Visit 08 and Visit 11 will be used to assess the pediatric participants' immune response after each administration. The RSVt vaccine immunogenicity will be evaluated using an RSV A microneutralization assay and an RSV anti-F IgG ELISA.

The safety profile of the study interventions will be assessed in all pediatric participants after each administration with the collection of:

- immediate AEs occurring within 30 minutes
- solicited administration site and systemic reactions within 21 days after each study intervention administration
- unsolicited AEs, AESIs, and MAAEs within 28 days after each study intervention administration
- serious AEs (SAEs) throughout the study

For the ad-hoc close contact participants, MAAEs related to study procedures will be followed up to 28 days after each study procedure and collected in source documents.

The following AESIs will be collected:

[redacted]

4.2 Scientific Rationale for Study Design

Rationale for enrolling pediatric participants

It is expected that infants who already had RSV infection or who are seropositive present a lower virus shedding and thus a lower probability of vaccine virus transmission to their close contacts (23). In VAD00014 study, potential pediatric participants will not be screened based on their RSV baseline serostatus. Therefore, in order to maximize the probability of transmission during the study, enrolling a higher proportion of children aged 6 to 12 months may help to increase the proportion of seronegative participants and thereby increase the probability of transmission to pediatric participants receiving the placebo and / or to ad-hoc close contact participants. Some efforts will be made to enroll twins, to optimize the probability of transmission, and to limit the possible impact of age difference between the RSVt vaccine and placebo recipients. Stratification by age group could also be a way to control for the age distribution among RSVt vaccine and placebo recipients (eg, to ensure that for siblings, some younger and older children will receive RSVt vaccine).

Evaluation of Vaccine Virus Transmission

Transmission of the vaccine virus will be defined as presence of detected vaccine virus in the pediatric participants placebo-recipients and ad-hoc close contact participants, by RSVt qRT-PCR assay. Planned nasal swabs will be collected on all pediatric participants (ie, vaccinees and placebo recipients) on D01, D04, D08, D11, D15, D18, D22, D64, and D71. Nasal swabs will not be collected on D57 or D85 since vaccine virus shedding is not expected to last so long after the first administration and is expected to be lower after the second administration.

Based on an NIH study conducted with the same vaccine construct and on the same target population (20), it is expected that the probability of transmission from vaccinees to other persons will be higher when the virus shedding in the vaccinees is the highest (between 4 and 9 days after vaccine administration), so that nasal swabs will be collected regularly after the first administration to be able to detect vaccine virus. Vaccine virus shedding is expected to be lower after the second administration (8), justifying the collection of fewer nasal swabs after the second administration, and performing the interim analysis of the primary objective of transmission after the first dose.

[redacted]

[redacted]

Illness Visit(s)

For any pediatric participants presenting clinical symptoms of ARI during the intervention phase (D1 to D85), an additional nasal swab may be collected to identify potential WT RSV infection with Multiplex RT-PCR. Some of the regular nasal swabs from symptomatic children in which no vaccine virus was detected may also be tested for WT RSV strain. If ARI is diagnosed < 2 days before or after a scheduled nasal swab, then the planned nasal swab will be used for WT RT-PCR testing. The ad-hoc close contact participants with any clinical symptoms of ARI within 28 days after study intervention administration of the close contact pediatric participant should have an illness visit.

Consideration of the RSV Season

The VAD00014 study is planned to start during Quarter (Q)4 2022, regardless of the actual start of the RSV season. In the Northern Hemisphere, the RSV season usually begins in late Q3 or early Q4 and lasts about 5 months. However, due to the increased variability in the RSV epidemiology since the beginning of the SARS-CoV-2 pandemic, it is difficult to evaluate the extent to which the RSV season will impact the clinical study. To mitigate the impact of the RSV season during the study, ARI will be followed up to 28 days after the second study intervention administration for all pediatric participants. Baseline blood sample will be used as an indication of possible previous RSV exposure.

Non-exclusion of pregnant women participants

Ad-hoc close contact participants can include pregnant females as they will only provide nasal swabs and will not receive any study intervention. Thus, VAD00014 study can be considered a safety surveillance study for the ad-hoc close contact participants and therefore pregnant women are not excluded from participating in the study.

4.3 Justification for Dose

Justification for 2 doses administration schedule

There are several published studies evaluating 2 or 3 administrations of attenuated RSV or parainfluenza virus type 3 (PIV3) candidate vaccines (4) (5) (8) (24) (25) (26) (27) (28) (29). Generally, there was a high level of restriction of the second administration, and limited serum immune responses. The main effect was vaccine infectivity in the individuals who did not respond to the first administration. Two administrations of RSV ΔNS2/Δ1313/I1314L may improve the infectivity of either dose.

Justification for vaccine dose

The vaccine dose has been selected based on benefit/risk assessment based on results obtained the first Phase I/II VAD00001 study conducted in infants and toddlers 6 to 18 months of age receiving 2 doses of RSVt vaccine at concentration of [redacted]

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed the last visit or contact planned in the SoA.

The end of the study is defined as the date of the last visit or 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

5.1.1 Inclusion Criteria

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

AGE

I01. Aged 6 months to < 24 months on the day of inclusion[1]

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS

I02. Participants who are healthy as determined by medical evaluation including medical history.

I03. Born at full term of pregnancy (≥ 37 weeks) or born after a gestation period of 27 through 36 weeks and medically stable as assessed by the investigator, based on the following definition: "Medically stable" refers to the condition of premature infants who do not require significant medical support or ongoing management for debilitating disease and who have demonstrated a clinical course of sustained recovery by the time they receive the first dose of study intervention

I04. Attends a daycare facility at least 3 days per week and 4 hours per day at which the participant would be in a contact group/playroom of at least one other child 6 to < 24 months of age who will participate in this study or is a member of a household, which includes at least one other child 6 to < 24 months of age who will participate in this study

INFORMED CONSENT

I05. Informed consent form has been signed and dated by the parent(s) or other legally acceptable representative (and by an independent witness if required by local regulations)

OTHER INCLUSIONS

I06. Participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

[1] "**6 months to < 24 months**" means from the day of the 6 months after birth to the day before the 2nd birthday

5.2 Exclusion Criteria

Pediatric 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. 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[2]

E03. Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[3]

E04. Any acute febrile illness in the past 48 hours that according to investigator judgment is significant enough to interfere with successful inoculation on the day of vaccination. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided.

E05. Probable or confirmed ongoing case of COVID-19 at the time of enrollment

E06. Member of a household that contains an immunocompromised individual, including, but not limited to:

- a person who is HIV infected
- a person who has received chemotherapy within the 12 months prior to study enrollment
- a person who has received (within the past 6 months) or is receiving (at the time of enrollment) immunosuppressant agents
- a person living with a solid organ or bone marrow transplant

E07. Member of a household that includes, or will include, an infant who is less than 6 months of age at the time of enrollment

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

[3] Chronic illness may include, but is not limited to, cardiac disorders, lung disease (including any history of reactive airway disease, receipt of bronchodilator or inhaled steroid therapy, or medically diagnosed wheezing), atopy, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases

E08. Attends a daycare facility and shares a daycare room with infants less than 6 months of age, and parent/legally acceptable representative is unable or unwilling to suspend attendance at the daycare facility for 28 days following study intervention administration

E09. Any need of supplemental oxygen therapy in a home or hospital setting at the time of enrollment.

PRIOR/CONCOMITANT THERAPY

E10. Participant's mother previous receipt or planned administration of an investigational RSV vaccine or any monoclonal antibody (such as Infliximab) during pregnancy and/or breastfeeding.

E11. Receipt or planned receipt of any of the following vaccines prior to or after the first study intervention administration:

- any influenza vaccine within 7 days prior to and after, or
- any COVID-19 or inactivated vaccine or live-attenuated rotavirus vaccine within 14 days prior to and after, or
- any live vaccine, other than rotavirus vaccine, within 28 days prior to and after

E12. Previous receipt of an investigational RSV vaccine or receiving any anti-RSV product (such as ribavirin or RSV IG or RSV monoclonal antibody) at the time of enrollment.

E13. Receipt of immune globulins, blood or blood-derived products in the past 3 months

E14. Receipt of intranasal and intra-ocular medications within 3 days prior to study enrollment

E15. Receipt at the time of enrollment or previous receipt of salicylate (aspirin) or salicylate-containing products

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

E16. Participation at the time of study enrollment (or in the 6 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

OTHER EXCLUSIONS

E17. Deprived of freedom in an emergency setting, or hospitalized involuntarily

E18. Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

If the participant has a primary physician who is not the investigator, the site should contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.3 Lifestyle Considerations

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study 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.

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

The Sponsor may decide to temporarily delay the enrollment/randomization/administration of study intervention in case of occurrence of an event requiring further investigation and until the Sponsor's governance decision on further steps.

Temporary intervention discontinuation may be considered by the investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency. For all temporary intervention discontinuations, duration should be recorded by the investigator in the source documents.

6 Study Interventions 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: Vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the CRF as reportable medications (see Section 6.8). Study procedures (eg, blood sampling) are also not considered as study interventions.

6.1 Study Interventions Administered

Study interventions are described in Table 6.1.

Table 6.1: Study Interventions Administered

Intervention Name	RSVt Vaccine [redacted]	Placebo
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Type	Vaccine	Vaccine
Dose Form	Nasal spray suspension	Nasal spray suspension
Unit Dose Strength	Each [redacted] dose of RSVt vaccine will contain the live-attenuated RSV with [redacted] dose.	Same formulation buffer as RSVt vaccine
Excipients/Diluent	[redacted]	Same formulation buffer as RSVt vaccine
Dosage Level(s)	[redacted]	[redacted]
Number of Doses / Dosing Interval	2 doses 56 days apart for pediatric participants	2 doses 56 days apart for pediatric participants
Route of Administration	Intranasal	Intranasal

Site of Administration	Each nostril	Each nostril
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	The investigational and placebo products in single-dose vials will be supplied with investigational labeling and packaging according to national regulations. Each single dose of investigational or placebo product will be identified by a unique number on the primary label and on the outer carton label. The carton label will also have a detachable label for the sites to attach to the source documents.	
Current/Former Name(s) or Alias(es)	Not applicable	Not applicable
Batch Number	TBD	TBD
Storage Conditions	Study interventions will be stored in a freezer at ≤ -60°C (≤ -76°F) and will be protected from the light.	

IMP: Investigational Medicinal Product; NIMP: Non-Investigational Medicinal Product; TBD: to be determined

Table 6.2 summarizes the study interventions per arm.

Table 6.2: Study Arms

Arm title	Group 1 RSVt	Group 2 Control
Arm type	Experimental	Placebo
Associated study interventions	RSVt vaccine	Placebo

6.1.1 Medical Devices

Medical device (not manufactured by the Sponsor) provided for use in this study is the [redacted]

Instructions for medical device use are provided in the product insert.

[redacted]

[redacted]

[redacted]

In vitro device performance characterization:

[redacted]

6.2 Preparation, Handling, Storage, and Accountability

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 will be provided to the study personnel.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

Site staff will connect to the Interactive Response Technology (IRT), enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. For all participants, the IRT will assign a participant number. For pediatric participants, the IRT will then provide the group assignment and have the site staff confirm it. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

Participant 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).

The first digit of the 5-digit participant identifier will correspond to the participant group (ie, 0 for pediatric participants and 1 for ad-hoc close contact participants). For the pediatric participants only, the 2nd and 3rd digits of the participant identifier will correspond to the group of contact identifier. For example, Participant 630000101235 is the 35th participant enrolled in Center Number 1 (630 being Puerto Rico country code) and is part of Contact Group Number 12;

Participant 630000110024 is the 24th ad-hoc close contact participant enrolled in Center Number 1.

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT and an internal system.

6.3.2 Blinding and Code-breaking Procedures

The study will be performed in a modified double-blind fashion:

- Participants, participants' parents or legally acceptable representative, Investigators and study staff who conduct the safety and immunogenicity assessments will not know which study intervention is administered
- Only the study staff who prepare and administer the study intervention and are not involved with the safety evaluation will know which study intervention is administered

The Investigator responsible for safety assessment will not attend the vaccination session but will be available in case of emergency (anaphylactic shock).

Treatment ID numbers will be used to identify each vaccine dose for the purpose of randomization, vaccination, and the recording of the study intervention administered. Treatment numbers will be randomly assigned to study interventions. The IRT vendor will be responsible for assigning the treatment group identification and treatment number to be received by the enrolled pediatric participant. The participant, the participant's parent(s)/legally acceptable representative, the Investigator, and the study staff members who collect the safety data and laboratory personnel who analyze the blood samples will all be blinded to the group assignment. The individual responsible for preparing / administering study intervention will not be authorized to collect any safety / serology data.

The code may be broken in the event of an AE only when the identification of the study intervention received could influence the treatment of the participant. Code-breaking should be limited to the pediatric participant(s) experiencing the AE.

The blind can be broken by the investigator or a designee through the IRT system. Once the emergency has been addressed by the site, the investigator or a designee must notify the Sponsor's RMO if a participant's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking case report form (CRF) is to be completed.

The Independent Ethics Committees (IEC) / Institutional Review Boards (IRB) must be notified of the code-breaking, in accordance with local regulations. All documentation pertaining to the event must be retained in the site's study records and in the Sponsor's files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

A request for the code to be broken may also be made:

- by the Global Pharmacovigilance (GPV) Department through an internal system for reporting to Health Authorities in the case of an unexpected SAE considered causally related, as described in International Council for Harmonisation (ICH) E2A. In this case,

the code will be broken only for the participant(s) in question. The information resulting from code-breaking (ie, the participant's study intervention or group assignment) will not be communicated to either the investigator or the immediate team working on the study, except for the GPV representative.

An unblinded interim analysis will be performed in Q4, 2023 on available data collected from D01 (V01) to D22 (V07), irrespective of study enrollment status. An additional unblinded interim analysis will be performed once all data collected from D01 (V01) to D22 (V07) from all participants is available. The interim analyses will include baseline immunogenicity, safety, and shedding / transmission up to 21 days after the first administration, in order to share preliminary data to Health Authorities.

Randomization code will be broken for the Sponsor but blinding will be maintained at sites and participants/parents levels.

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:

- All study interventions will be administered 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(s) 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 should:

1) Contact the RMO immediately.
2) Evaluate the participant to determine, in consultation with the RMO, whether study intervention should be interrupted
3) Closely monitor the participant for any AE/SAE.
4) Document the quantity of the excess of the overdose in the source documents.

6.8 Concomitant Therapy

Reportable medications include medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an adverse event) or may interfere with the development or measurement of the immune response (eg, the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays and intranasal and ophthalmic medications in the context of this intranasal vaccine). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

This may include medications of interest that were started prior to the day of vaccination, and even stopped prior to enrollment if there is a reasonable possibility that they may have an impact on safety and / or immune assessment during study participation.

The following reportable medications are defined:

- Medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, intranasal/intraocular medications, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids)
- Medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Sponsor's laboratory or other testing laboratories, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as deoxyribonucleic acid [DNA] synthesis inhibitors)
- Medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

Reportable medications will be collected in the CRF until the end of the unsolicited follow-up period.

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical (other than intranasal and intraocular) and ear treatments will not be recorded.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication Form of the CRF unless the medication(s) received belong(s) to the reportable medications list. Medications will be coded using the WHODrug dictionary.

The following medications will be prohibited during the study period for pediatric participants: intranasal and intraocular medications, and salicylate or salicylate-containing products.

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, vasovagal, or other immediate allergic reaction.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 10.1.

7.1 Discontinuation of Study Intervention

7.1.1 Temporary Contraindications

Should a participant experience one of the conditions listed below, the investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the SoA.

If the postponement occurs out of the timeframe for vaccination, the participant will be permanently discontinued from study intervention but will continue to be followed for safety

TCI01: Any acute febrile illness in the past 48 hours that according to investigator judgment is significant enough to interfere with successful inoculation on the day of vaccination. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

TCI02: Receipt or planned receipt of any of the following vaccines prior to or after the first study intervention administration:

- any influenza vaccine within 7 days prior to and after, or
- any COVID-19 or inactivated vaccine or live-attenuated rotavirus vaccine within 14 days prior to and after, or
- any live vaccine, other than rotavirus vaccine, within 28 days prior to and after

Temporary intervention discontinuation may be considered by the investigator because of suspected AEs. For all temporary intervention discontinuations, duration should be recorded by the investigator in the source documents.

7.1.2 Definitive Contraindications

Participants will permanently discontinue (definitive discontinuation) study intervention for the reasons listed below. These participants must not receive any additional dose of study intervention but should continue to be followed for safety and immunogenicity.

Should a participant experience at least one of the conditions listed below, the investigator will discontinue vaccination:

DCI01: An anaphylactic or other significant allergic reaction to the previous dose of vaccine

DCI02: Probable or confirmed ongoing case of COVID-19 at the time of enrollment

DCI03: Serious AE assessed as related to the study vaccine following the previous dose of vaccine, based on Investigator’s judgment

In the event of a local or national immunization program with a pandemic influenza vaccine or any other vaccine as needed, participants who receive pandemic influenza vaccine or any other vaccine as needed at any time during the study will not be withdrawn from the study.

7.1.3 Other Reasons

A participant may discontinue from study intervention at any time at his/her own parent/LAR request, or at the discretion of the investigator for safety, behavioral, or compliance reasons.

Participants should continue to be followed for safety.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own parent/LAR 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 CRF.
- The participant will be permanently discontinued from the study intervention and the study at that time. However, the site should attempt to contact them 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.
- If the participant withdraws consent for disclosure of future information, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent, he/she may request destruction of any biological samples taken (unless local law requires not to destroy them), and the investigator must document this in the site study records.
- Withdrawn participants will not be replaced. However, in specific situations, if judged necessary and according to the number of withdrawn participants, the sample size may be increased to maintain the number of evaluable participants of the study. Participants' numbers will not be reassigned.

7.3 Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the site for a required study visit or cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit

schedule, and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (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 participant continue to be unreachable, he/she will be considered lost to follow-up.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Safety/laboratory results that could unblind the study will not be reported to sites or other blinded personnel until the study has been unblinded at the site level.

Blood and nasal samples will be collected as described in the SoA tables (Section 1.3).

The maximum amount of blood collected from each pediatric participant over the duration of the study, including any extra assessments that may be required, will not exceed 15 mL (approximately 5 mL for each blood sampling). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The volume for each pediatric participant nasal swab must be 4 mL of nasal swab specimen collected in viral transport media ([redacted]).

Guidance and information for the sample collection, preparation, storage, and shipment will be provided to the study personnel.

8.1 Efficacy and Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA.

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Transmission and Vaccine Virus Shedding Assessments

Assays will be performed by the Sponsor's laboratory (Sanofi, USA) or by an external testing laboratory under the Sponsor's laboratory responsibility.

8.1.2.1 Vaccine virus shedding

Shedding of the attenuated RSV vaccine strain in nasal swab samples will be evaluated by RSVt qRT-PCR assay in all the nasal swabs collected, from planned and unplanned visits, in pediatric and ad-hoc close contact participants.

[redacted]

8.1.2.2 [redacted]

[redacted]

[redacted]

The above ARI episodes will be graded following the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 - July 2017; (30) except for [redacted] and fever.

Table 8.1: DAIDS severity scale for RSV MAARI

Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**		**Grade 4 Potentially Life-Threatening**
Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated		Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

All deaths related to an RSV MAARI are to be classified as Grade 5.

[redacted]

[redacted]

Table 8.2 Targets Detected by the ePlex Respiratory Pathogen Panel 2 Assay

[redacted]

8.1.3 Immunogenicity Assessments

8.1.3.1 Immunogenicity Assessment Methods

Assays will be performed by the Sponsor's laboratory (Sanofi, USA) or an external testing laboratory under the Sponsor's laboratory responsibility.

8.1.3.1.1 RSV A and RSV B serum neutralizing antibody titers

RSV A and RSV B serum neutralizing antibody titers will be evaluated by Microneutralization (MN) assay.

[redacted]

[redacted]

8.1.3.1.2 RSV Serum Anti-F IgG ELISA

Assays will be performed by the Sponsor's laboratory (Sanofi, USA) or an external testing laboratory under the Sponsor's laboratory responsibility.

The ELISA method to be used is summarized below. The method is currently in development and a detailed procedure will be submitted prior to the start of clinical testing. Method will be qualified for Phase I and II studies and will be validated prior to Phase III clinical testing.

[redacted]

8.1.3.1.3 RSV Serum Anti-F IgA ELISA

The anti-RSV F IgA ELISA will be performed at Sanofi HEXIM, Orlando, Florida.

The ELISA method to be used is summarized below. The method is currently in development and a detailed procedure will be submitted prior to the start of clinical testing. Method will be characterized for Phase I and II studies and will be validated prior to Phase III clinical testing.

[redacted]

8.2 Safety Assessments

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

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

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 CRF. Collected information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

8.2.2 Physical Examinations

At Visit 1 and Visit 8, the investigator or a designee will perform a clinical physical examination. Information will be recorded in the source document and in the CRF.

8.2.3 Vital Signs

Rectal pre-vaccination temperature will be systematically collected by the investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used.

Height and weight will be collected at enrollment.

8.2.4 Clinical Safety Laboratory Tests

Not applicable.

8.2.5 Pregnancy Testing

Not applicable.

8.2.6 Viremia/Vaccinemia

Virus shedding will be evaluated and described in all pediatric participants at D01, D04, D08, D11, D15, D18, D22, D64, and D71. Presence of vaccine virus will be assessed in the ad-hoc close contact participants at the illness visit. Shedding of the attenuated RSV vaccine strain in nasal swab samples will be evaluated by RSVt qRT-PCR assay (as described in Section 8.1.2).

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.

AEs will be reported by the participants' parents / legally acceptable representatives to the investigator, then by the investigator to the Sponsor.

The investigator and any qualified designees are responsible for detecting, 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 intervention (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 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

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

Reactogenicity

Solicited administration site reactions will be collected from the day of vaccination until 21 days after each vaccination (D01 to D22 and D57 to D78).

Solicited systemic reactions will be collected from the day of vaccination until 21 days after each vaccination (D01 to D22 and D57 to D78).

The solicited administration site reactions and systemic reactions that are pre-listed in the diary cards and CRF, together with the intensity scales, are presented in Appendix 10.2.5.1.1.

Reactogenicity is to be reported only for IMPs. Refer to Table 6.1 to know which study interventions are considered as IMPs.

Unsolicited Non-serious Adverse Events

Unsolicited non-serious adverse events will be collected from the day of vaccination until 28 days after each vaccination (D01 to D29 and D57 to D85).

The intensity grading scale for unsolicited non-serious adverse events is presented in Appendix 10.2.5.1.2.

Medically Attended Adverse Events (MAAEs)

MAAEs will be collected from the day of vaccination until 28 days after each vaccination (D01 to D29 and D57 to D85).

Adverse Events of Special Interest (AESIs)

AESIs will be collected from the day of vaccination until 28 days after each vaccination (D01 to D29 and D57 to D85).

See Section 8.3.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from D01 until 180 days after the last vaccination. However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the CRF.

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.

8.3.2 Method of Detecting AEs and SAEs

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants' parents / legally acceptable representatives for the recording of daily safety information. These diary cards will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants' Parents / LARs] will also be provided with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct participants' parents / LARs on how to correctly use these tools.

At specified intervals, the investigator or a designee will interview the participants' parents / legally acceptable representatives to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the investigator or designee using a web-based CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

The 6-month follow-up should be done at least 180 days after the last vaccination for all participants having received at least one dose of the study intervention, by interviewing participants' parents / legally acceptable representatives either during a visit or over the telephone using a questionnaire to capture SAEs and AESIs, if applicable.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participant's parents / legally acceptable representatives refuse further contact. All AEs that are considered by the investigator as serious, or related to the study intervention administered, or that led to study or vaccination discontinuation, or AEs of special interest (as defined in Section 8.3.6), 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 visit, 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.

8.3.4 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, IRB/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 (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

Not applicable as women of childbearing age will not receive the study intervention.

8.3.6 Adverse Events of Special Interest

The following AESIs will be collected:

8.3.7 Medically Attended Adverse Events

MAAEs will be collected using the same process as other AEs. See Appendix 10.2.1 for definition of MAAEs.

8.4 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) are evaluated in this study. The blood samples and nasal swabs collected during the study can be used to measure other immunogenicity assessments.

8.7 Immunogenicity Assessments

See Section 8.1.2.

8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9 Leftover Biological Samples

Any unused part of the biological samples collected for this study (blood sample and nasal swab) are being retained in long-term storage (for up to 25 years after the end of the study) to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results. The biological samples will be securely stored at the Sponsor's laboratory.

The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health during the study are dedicated for immediate use. If any of these biological samples are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

8.10 Use of Biological Samples And Data For Future Research

Future research may help further the understanding of disease and the development of new vaccines/medicines. Reuse of coded data and biological samples (leftover) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study intervention to the Sponsor or which is co-developing the study intervention with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participants, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of samples will not be included in the local informed consent form [ICF]). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover samples.

Data protection – Processing of coded clinical data

The study participants will be provided with all mandatory details of the data processing in Part 2 of the ICF. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples for future research

Remaining leftover samples will be used only after the study ends, ie end of study as defined in the study protocol. Additional nasal swab can be collected and used during the study conduct at a given timepoint (eg, illness visit) as defined in the study protocol.

The study participants will be provided with all mandatory details of the use of their biological samples (leftover) in Part 2 of the ICF.

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study.

Any samples remaining at the end of the retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

9 Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock and it 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.

9.1 Statistical Hypotheses

All analyses will be descriptive, no hypothesis will be tested.

9.2 Analysis Sets

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

Participant Analysis Set	Description
Randomized	Pediatric participants for whom a study intervention group has been allocated.
Safety Analysis Set (SafAS)	Pediatric participants who have received at least one study intervention administration. All pediatric participants will have their safety analyzed after each study intervention administration according to the study intervention they actually received, and after any study intervention administration according to the study intervention received at the first study intervention administration. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full Analysis Set (FAS)	Subset of randomized pediatric participants who received at least one study intervention administration Pediatric participants will be analyzed according to the study intervention to which they were randomized.
Per-protocol analysis set (PPAS)	The PPAS is a subset of the FAS. The pediatric participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: • Pediatric participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Pediatric participant did not receive first study intervention administration at D01 • Pediatric participant received a study intervention at D01 other than the one that he / she was randomized to receive • Preparation and / or administration of study intervention at D01 not done as per-protocol • Pediatric participant NOT having at least 4 nasal swabs (with a valid result) between D08 and D22, with a maximum of 5 days' time interval

	between 2 consecutive nasal swabs • Pediatric participant received a protocol-prohibited therapy before collection of nasal swabs between D08 and D22 • Pediatric participant with an emergency unblinding performed by the investigator before collection of nasal swab at D22 • Pediatric participant who was RSV exposed before study intervention administration at D01
Other analysis set	An analysis set will be used to document transmission of vaccine virus in the ad-hoc close contact participants

9.3 Statistical Analyses

The SAP will be finalized prior to database lock and it 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.

9.3.1 General Considerations

The statistical methodology will be based on the use of two-sided 95% CIs.

All endpoints will be summarized by study intervention group. For the main parameters, 95% CI of point estimates will be calculated using the normal approximation for quantitative data and using the exact binomial distribution (Clopper-Pearson method) for proportions.

For immunogenicity data, assuming that log10 transformation of the titers/titer ratio follows a normal distribution, first, the mean and 95% CIs will be calculated on log10 (titers/titers ratio) using the usual calculation for normal distribution. Then, antilog transformations will be applied to the results of calculations, to compute geometric mean titers (GMTs) and geometric mean titer ratios (GMTRs) and their 95% CIs.

Viral shedding, vaccine virus stability (pediatric participants receiving placebo and ad-hoc close contact participants), and safety analyses will be performed on the SafAS. Immunogenicity analyses will be presented on the FAS. Transmissibility analyses will be performed on the SafAS and PPAS as well as on other analysis set (ad-hoc close contact participants).

9.3.2 Primary Endpoints

Vaccine virus transmission

Presence of vaccine virus detected by RSVt qRT-PCR in nasal swabs after the first study intervention administration (D01, D04, D08, D11, D15, D18, and D22) will be summarized in pediatric participants receiving placebo with 95% CIs:

- Number and percentage of participants with vaccine virus detected at each timepoint
- Number and percentage of participants with vaccine virus detected in at least one nasal swab

Vaccine virus shedding

Titer of vaccine virus shedding quantified by RSVt qRT-PCR in nasal swabs after each study intervention administration will be summarized at each timepoint (D01, D04, D08, D11, D15, D18, D22, D64, and D71) in pediatric participants by study intervention group with 95% CIs.

Vaccine virus stability

Presence of any vaccine virus mutation will be described in pediatric participants receiving placebo and ad-hoc close contact participants and may be described as well in a subset of pediatric participants receiving RSVt vaccine. Further details will be provided in the SAP.

9.3.3 Secondary Endpoints

Immunogenicity

The following immunogenicity endpoints will be summarized at each timepoint (D01, D57, and D85) in pediatric participants by study intervention group with 95% CIs: RSV A serum neutralizing antibody titers and RSV serum anti-F IgG antibody titers. The 95% CIs for the GMTs and GMTRs will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method.

Safety

The safety parameters, including frequencies of immediate reactions, solicited reactions, unsolicited AEs, AESIs, MAAEs, and SAEs will be described after each and any study intervention administration in pediatric participants by study intervention group with the 95% CIs of point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions.

Vaccine virus transmission

Presence of vaccine virus detected by RSVt qRT-PCR in nasal swabs after the second study intervention administration (D64 and D71) will be summarized in pediatric participants receiving placebo with 95% CIs:

- Number and percentage of participants with vaccine virus detected at each timepoint
- Number and percentage of participants with vaccine virus detected in at least one nasal swab

9.3.4 Exploratory Endpoints

[redacted]

[redacted]

9.3.5 Other Analysis

As exploratory analysis, probability of transmission of vaccine virus will be calculated for the pediatric participants using Greenwood / Reed-Frost models after each administration of study intervention.

9.4 Interim Analyses

An unblinded interim analysis will be performed in Q4, 2023 on available data collected from D01 (V01) to D22 (V07), irrespective of study enrollment status. An additional unblinded interim analysis will be performed once all data collected from D01 (V01) to D22 (V07) from all participants is available. The interim analyses will include baseline immunogenicity, safety, and shedding / transmission up to 21 days after the first administration, in order to share preliminary data to Health Authorities.

Randomization code will be broken for the Sponsor but blinding will be maintained at sites and participants/parents levels.

No statistical adjustment is necessary because no hypotheses will be tested.

This study will not include an early safety data review.

The SAP will describe the planned interim analyses in greater detail.

9.5 Sample Size Determination

No sample size calculation was done as there are no statistical hypotheses in this study. A total of 100 pediatric participants (ie, 50 per study intervention group) are planned to be enrolled, based on clinical feasibility.

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 CRF 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 CRF.

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, ICFs, 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, if applicable
  - 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 has 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

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participants or the participants' parents / legally acceptable representatives and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants and participants' parents / legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines,

privacy and data protection requirements including those of the GDPR and of the French law, where applicable, and the IRB/IEC or study center.

- Depending on local legal and regulatory requirements, a separate assent form signed by the participant may be required for minor ad-hoc close contact participants. The assent form is in addition to, not in place of, an ICF that is signed by the parent / legally acceptable representative (and by an independent witness if required).
- 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's or parents' / legally acceptable representatives' willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- Participants/ parent/LAR must be reconsented to the most current version of the ICF(s) during their participation in the study. Where participants are not in the study anymore, the Sponsor must define if those participants must or not re-consent or be informed of the revision (eg, if the processing of personal data is modified, if the Sponsor changes).
- A copy of the ICF(s) must be provided to the participant or participants' parents / legally acceptable representatives.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones) and future research. Each option is subject to an independent consent and must be confirmed by ticking checkboxes in ICF Part 3, each checkbox corresponding to a specific use: consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research, and consent for performance of genetic analyses on biological samples. The investigator or authorized designee will explain to each participant why data and samples are important for future research. Participants / parent/LAR will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Recruitment Procedures

Participants will be recruited from the general population. Before start of the study, the investigator will contact parents/LARs of an appropriate pool of potential participants and invite them to participate in the study. The sites will ensure that any advertisements used to recruit participants (letters, pamphlets, posters, etc) are submitted to Sanofi prior to submission to the IEC / IRB for approval. Detailed guidance and information will be provided separately.

Emphasis will be placed on trying to enroll twin pediatric participants.

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 personal 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' race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on African-American population for the FDA).

- 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 participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her 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.
- Participants must be informed that their study-related data will be used for the whole "product development program", ie, for this study 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. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).

- 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 blinded review, assessment, and evaluation of safety data generated from this study. This committee is empowered to recommend a pause in recruitment and/or further vaccination while it investigates any potential signal or concern.

10.1.6 Dissemination of Clinical Study Data

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

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 trials in patients 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 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 Organizations".

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRFs 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 CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Instructions.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact patient safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy including definition of study critical data items and processes (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.
- The protocol will be signed by the RMO, and a Protocol Investigator Agreement Form (PIAF) will be signed by all investigators. The clinical study report will be signed by the RMO and the coordinating investigator. In case no coordinating investigator has been designated, it will be the responsibility of the RMO or designee(s) to identify the signatory investigator.

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, diary cards, 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 CRF 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 CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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

Study personnel will be informed of which clinical supplies will be provided by the Sponsor or the site.

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, all samples are shipped to the appropriate laboratories, the center study-site has all the documents necessary for archiving and a study-site closure visit has been performed along with a Site Close Out Form submitted to the IRB, as required.

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 Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, 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 condition 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
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs which occur within the first 30 minutes after vaccination.

Reactogenicity / Solicited Reactions:

The **reactogenicity** of a vaccine refers to the property of such vaccine to be able to produce common "expected" adverse reactions (either systemic or at the injection site) and its associated signs and symptoms.

A solicited reaction is an “expected” adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF (eg, nasal congestion occurring between the day of vaccination and the next 21 days).

By definition, solicited reactions are considered as being related to the corresponding IMP administered.

For injectable vaccines, solicited reactions can either be solicited injection/administration site reactions or solicited systemic reactions

Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site of the IMP. Injection/administration site reactions are commonly inflammatory reactions.

Solicited injection / administration site reactions are reactions at and around the injection / administration site of the IMP observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. It is considered by default as being related to the IMP administered at that site.

Note: « Administration site reaction » term is only to be used for vaccines that are not intended to be administered by injection.

Systemic AR:

Systemic ARs are all ARs that are not injection or administration site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the injection or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Solicited systemic reactions are systemic AEs observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. Solicited systemic reactions occurring

during the specified collection period are always considered related to the IMP even if there is evidence of alternative etiology.

Unsolicited AE/AR:

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (eg, headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to an IMP.

Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

All unsolicited 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 unsolicited injection/administration site ARs.

All unsolicited AEs which are not at and around the IMP injection/administration site, are referred as systemic unsolicited AE. For each unsolicited systemic AE, the investigator assesses the relationship to the IMP. Systemic AEs assessed as related to IMP are referred as systemic ARs.

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, and solicited reactions.

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) that 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 authorised 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 CRF 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 (either solicited or unsolicited) and all solicited systemic AEs 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 unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic 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 unsolicited systemic 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 vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the first vaccination (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).

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: +33 160 497 070
  - In PDF format to the following e-mail address, using a method of transmission that includes password protection: CL-CPV-Receipt@sanofi.com
  - By express mail, to the following address: Global Pharmacovigilance, Sanofi Pasteur, Discovery Drive, Swiftwater, PA 18370

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 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 Sponsor contact, as needed. The toll-free contact information for the Call Center will be provided separately.

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.

In case of emergency code-breaking, the investigator is required to follow the code-breaking procedures described in Section 6.3.2.

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 Tables for Clinical Abnormalities

10.2.5.1.1 Solicited AR Intensity Grading Scale

Table 10.1: [redacted]

Table 10.2: Solicited systemic reactions: terminology, definitions, and intensity scales – Infants and toddlers aged ≤ 23 months

CRF term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Vomiting does not include spitting up	Inconsolable crying without a determined reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale*	**Grade 1:** ≥ 38.0°C to ≤ 38.5°C **or** ≥ 100.4°F to ≤ 101.3°F **Grade 2:** > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F	**Grade 1:** CRF and DC: 1 episode per 24 hours **Grade 2:** CRF and DC: 2–5 episodes per 24 hours	**Grade 1:** CRF and DC: < 1 hour **Grade 2:** CRF and DC: 1–3 hours	**Grade 1:** CRF and DC: Sleepier than usual or less interested in surroundings **Grade 2:** CRF and DC: Not interested in surroundings or did not wake up for a feed / meal	**Grade 1:** CRF and DC: Eating less than normal **Grade 2:** CRF and DC: Missed 1 or 2 feeds / meals completely	**Grade 1:** CRF and DC: Easily consolable **Grade 2:** CRF and DC: Requiring increased attention

CRF term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
	Grade 3: > 39.5°C **or** > 103.1°F	**Grade 3** CRF: ≥ 6 episodes per 24 hours or requiring parenteral hydration DC: at least 6 episodes per 24 hours or requiring intravenous hydration (fluids administered in the arm or leg)	**Grade 3:** CRF and DC: > 3 hours	**Grade 3:** CRF and DC: Sleeping most of the time or difficult to wake up	**Grade 3:** CRF and DC: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	**Grade 3:** CRF: Inconsolable DC: Inconsolable (cannot be comforted)

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, the body temperature will be recorded, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

Participants' parents / legally acceptable representatives are to measure body temperature once per day, preferably always at the same time, and using the same standard unit of the considered country (Celsius or Fahrenheit) consistently. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card / memory aid, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is rectal.

10.2.5.1.2 Serious and Non-serious Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.2.5.1.1).

All other unsolicited AEs, including SAEs, will be classified according to the following intensity scale:

[redacted]

10.3 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.

10.4 Appendix: Protocol Amendment History

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

Protocol Update from Version 1.0 (01 August 2022) to Version 2.0 (13 October 2022):

The updates of protocol version 1.0 to protocol version 2.0 were administrative with the purpose of correction of errors, harmonization of text, and updating information.

Protocol Amendment 1: from Version 2.0 (13 October 2022) to Version 3.0 (26 June 2023):

The updates of protocol version 2.0 to protocol version 3.0 were administrative with the purpose of including clinical sites in the United States in addition to sites in Puerto Rico.

10.5 Appendix: Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ARI	acute respiratory illness
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRB	case report book
CRF	case report form
DC	diary card
DNA	deoxyribonucleic acid
ELISA	Enzyme-linked Immuno-adsorbant Assay
FAS	full analysis set
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GPV	Global Pharmacovigilance
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDFU	investigational directions for use
IEC	Independent Ethics Committees
IMP	investigational medicinal product
IR	Investigator Registry
IRB	Institutional Review Boards
IRT	Interactive Response Technology
LAR	legally acceptable representative
LRI	lower respiratory infection

MAAE	medically attended adverse event
MAARI	medically attended acute respiratory illness
MedDRA	Medical Dictionary for Regulatory Activities
NC	negative control
NIH	National Institutes of Health
NIMP	non-investigational medicinal product
NS	nasal swab
PFU	plaque forming units
PIAF	Protocol Investigator Agreement Form
PPAS	per-protocol analysis set
PV	pharmacovigilance
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
QTL	quality tolerance limit
RMO	Responsible Medical Officer
RNA	ribonucleic acid
RSV	Respiratory Syncytial Virus
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SIP	Shared Investigator Platform
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reactions
TBD	to be determined
URI	upper respiratory infection
VTM	Viral Transport Media
WT	wild type

10.6 References

1. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588-98.

2. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946-58.

3. O'Brien K, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Higdon MM, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019;394(10200):757-79.

4. Wright PF, Karron RA, Belshe RB, Thompson J, Crowe JE, Jr., Boyce TG, et al. Evaluation of a live, cold-passaged, temperature-sensitive, respiratory syncytial virus vaccine candidate in infancy. J Infect Dis. 2000;182(5):1331-42.

5. Karron RA, Wright PF, Belshe RB, Thumar B, Casey R, Newman F, et al. Identification of a recombinant live attenuated respiratory syncytial virus vaccine candidate that is highly attenuated in infants. J Infect Dis. 2005;191(7):1093-104.

6. Wright PF, Karron RA, Madhi SA, Treanor JJ, King JC, O'Shea A, et al. The interferon antagonist NS2 protein of respiratory syncytial virus is an important virulence determinant for humans. J Infect Dis. 2006;193(4):573-81.

7. Wright PF, Karron RA, Belshe RB, Shi JR, Randolph VB, Collins PL, et al. The absence of enhanced disease with wild type respiratory syncytial virus infection occurring after receipt of live, attenuated, respiratory syncytial virus vaccines. Vaccine. 2007;25(42):7372-8.

8. Malkin E, Yogev R, Abughali N, Sliman J, Wang CK, Zuo F, et al. Safety and immunogenicity of a live attenuated RSV vaccine in healthy RSV-seronegative children 5 to 24 months of age. PLoS One. 2013;8(10):e77104.

9. Karron RA, Luongo C, Thumar B, Loehr KM, Englund JA, Collins PL, et al. A gene deletion that up-regulates viral gene expression yields an attenuated RSV vaccine with improved antibody responses in children. Sci Transl Med. 2015;7(312):312ra175.

10. Buchholz UJ, Cunningham CK, Muresan P, Gnanashanmugam D, Sato P, Siberry GK, et al. Live respiratory syncytial virus (RSV) vaccine candidate containing stabilized temperature-sensitivity mutations is highly attenuated in RSV-seronegative infants and children. J Infect Dis. 2018;217(9):1338-46.

11. McFarland EJ, Karron RA, Muresan P, Cunningham CK, Valentine ME, Perlowski C, et al. Live-Attenuated Respiratory Syncytial Virus Vaccine Candidate With Deletion of RNA Synthesis Regulatory Protein M2-2 is Highly Immunogenic in Children. J Infect Dis. 2018;217(9):1347-55.

12. Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969;89(4):422-34.

13. Collins PL, Melero JA. Progress in understanding and controlling respiratory syncytial virus: still crazy after all these years. Virus Res. 2011;162(1-2):80-99.

14. Collins PL, Hill MG, Camargo E, Grosfeld H, Chanock RM, Murphy BR. Production of infectious human respiratory syncytial virus from cloned cDNA confirms an essential role for the transcription elongation factor from the 5' proximal open reading frame of the M2 mRNA in gene expression and provides a capability for vaccine development. Proc Natl Acad Sci U S A. 1995;92(25):11563-7.

15. Ramaswamy M, Shi L, Varga SM, Barik S, Behlke MA, Look DC. Respiratory syncytial virus nonstructural protein 2 specifically inhibits type I interferon signal transduction. Virology. 2006;344(2):328-39.

16. Lo MS, Brazas RM, Holtzman MJ. Respiratory syncytial virus nonstructural proteins NS1 and NS2 mediate inhibition of Stat2 expression and alpha/beta interferon responsiveness. J Virol. 2005;79(14):9315-9.

17. Spann KM, Tran KC, Chi B, Rabin RL, Collins PL. Suppression of the induction of alpha, beta, and lambda interferons by the NS1 and NS2 proteins of human respiratory syncytial virus in human epithelial cells and macrophages [corrected]. J Virol. 2004;78(8):4363-9.

18. Valarcher JF, Furze J, Wyld S, Cook R, Conzelmann KK, Taylor G. Role of alpha/beta interferons in the attenuation and immunogenicity of recombinant bovine respiratory syncytial viruses lacking NS proteins. J Virol. 2003;77(15):8426-39.

19. Liesman RM, Buchholz UJ, Luongo CL, Yang L, Proia AD, DeVincenzo JP, et al. RSV-encoded NS2 promotes epithelial cell shedding and distal airway obstruction. J Clin Invest. 2014;124(5):2219-33.

20. Karron RA, Luongo C, Mateo JS, Wanionek K, Collins PL, Buchholz UJ. Safety and Immunogenicity of the Respiratory Syncytial Virus Vaccine RSV/ΔNS2/Δ1313/I1314L in RSV-Seronegative Children. J Infect Dis. 2020;222(1):82-91.

21. The National Institute of Health. The U.S. National Library of Medicine. Evaluating the Infectivity, Safety, and Immunogenicity of Recombinant Live-Attenuated RSV Vaccines RSV ΔNS2/Δ1313/I1314L or RSV 276 in RSV-Seronegative Infants 6 to 24 Months of Age. [Internet]. [cited 2022 May 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT03227029?term=NCT03227029&cond=RSV+Infection&draw=2&rank=1.

22. The National Institute of Health. The U.S. National Library of Medicine. Evaluating the Safety and Immune Response to a Single Dose of a Respiratory Syncytial Virus (RSV) Vaccine in Infants and Children. [Internet]. [cited 2022 May 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT01893554.

23. Karron RA, Wright PF, Crowe JE, Jr., Clements-Mann ML, Thompson J, Makhene M, et al. Evaluation of two live, cold-passaged, temperature-sensitive respiratory syncytial virus vaccines in chimpanzees and in human adults, infants, and children. J Infect Dis. 1997;176(6):1428-36.

24. Karron RA, Belshe RB, Wright PF, Thumar B, Burns B, Newman F, et al. A live human parainfluenza type 3 virus vaccine is attenuated and immunogenic in young infants. Pediatr Infect Dis J. 2003;22(5):394-405.

25. Karron RA, Casey R, Thumar B, Surman S, Murphy BR, Collins PL, et al. The cDNA-derived investigational human parainfluenza virus type 3 vaccine rcp45 is well tolerated, infectious, and immunogenic in infants and young children. Pediatr Infect Dis J. 2011;30(10):e186-91.

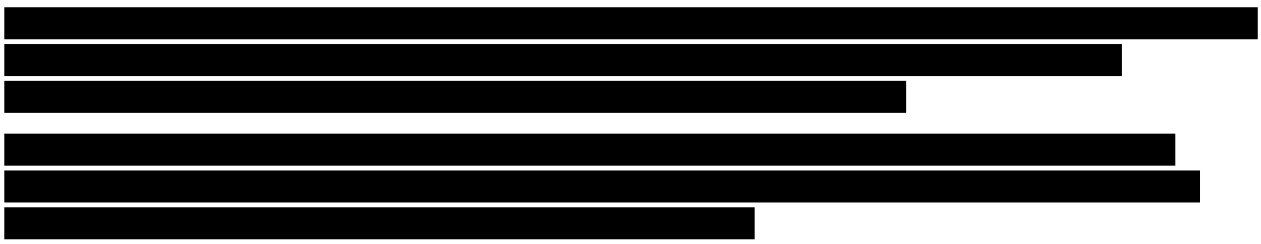
26. Englund JA, Karron RA, Cunningham CK, Larussa P, Melvin A, Yogev R, et al. Safety and infectivity of two doses of live-attenuated recombinant cold-passaged human parainfluenza type 3 virus vaccine rHPIV3cp45 in HPIV3-seronegative young children. Vaccine. 2013;31(48):5706-12.

27. Greenberg DP, Walker RE, Lee MS, Reisinger KS, Ward JI, Yogev R, et al. A bovine parainfluenza virus type 3 vaccine is safe and immunogenic in early infancy. J Infect Dis. 2005;191(7):1116-22.

28. Bernstein DI, Falloon J, Yi T. A randomized, double-blind, placebo-controlled, phase 1/2a study of the safety and immunogenicity of a live, attenuated human parainfluenza virus type 3 vaccine in healthy infants. Vaccine. 2011;29(40):7042-8.

29. Bernstein DI, Malkin E, Abughali N, Falloon J, Yi T, Dubovsky F. Phase 1 study of the safety and immunogenicity of a live, attenuated respiratory syncytial virus and parainfluenza virus type 3 vaccine in seronegative children. Pediatr Infect Dis J. 2012;31(2):109-14.

30. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1. July 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.



11 Sponsor Signature Page

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