Clinical Study Protocol

Protocol Title:

A parallel group, Phase III, randomized, observer blind, placebo controlled, multi-center, multinational, multi-arm study to demonstrate non-inferiority of the immune response of a low dose compared to the standard dose and to evaluate the safety of a respiratory syncytial virus vaccine in infants and toddlers (OPAL)

Study Code: VAD00015

Amendment Number: 3

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

Brief Title: A study on the immunogenicity and safety of 3 different dose concentrations of a respiratory syncytial virus vaccine in infants and toddlers

Study Phase: 3

Acronym: OPAL

Sponsor Name and Legal Registered Address:

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Manufacturer:

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Regulatory Agency Identifier Numbers:

Registry	ID
World Health Organization (WHO) universal trial number	U1111-1298-7338
US Investigational New Drug (IND) number	[redacted]
US National Clinical Trial number	NCT06705140

Protocol Version Number: 7.0

Approval Date: 24 September 2025

Medical Monitor Name and Function:

Responsible Medical Officer (RMO): [redacted] MD, PhD - Global Clinical Development Strategy Expert.

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

Document History and Protocol Amendment Rationale

Previous Version	Date	Comments
1.0	14 February 2024	IEC/IRB-approved version not used in the study
2.0	06 June 2024	IEC/IRB-approved version not used in the study
3.0	23 September 2024	First version used in the study
4.0	21 October 2024	Internal version not submitted
5.0	31 January 2025	Version for submission in the US
6.0	20 February 2025	Version for submission in the US

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.

Amendment 3 (24-September-2025) - Overall Rationale for the Amendment:

The main reasons for updating protocol version 6.0 (Amendment 2) to protocol version 7.0 (Amendment 3) are to increase the number of participants to be included in the Mucosal Immunity Subset and to update the exclusion criteria to incorporate a new licensed monoclonal antibody for RSV.

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Abbreviations and Definitions of terms

Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ARD	acute respiratory disease
AxMP	auxiliary medicinal product
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CRF	case report form
CTA	clinical trial application
D	day
DRMP	development risk management plan
EC	ethics committee
[redacted]	
EDSR	early date safety review
[redacted]	
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMO	Genetically Modified Organism
GMT	geometric mean titer
HA	health authority
HD	high dose
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IRB	Institutional Review Board
LAR	legally acceptable representative
LAV	live attenuated vaccine
LD	low dose
LLOQ	lower limit of quantitation
LRTD	lower respiratory tract disease
MA	memory aid
mAb	monoclonal antibody
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
NI	non-inferiority
NIH	National Institute of Health
NS	nasal sample
NO	nasosorption sample
NSS	nasal spray system
PFU	plaque forming unit
PPAS	per-protocol analysis set
[redacted]	
PV	Pharmacovigilance
qRT-PCR	quantitative real time-polymerase chain reaction
QTL	quality tolerance limit
[redacted]	
RMO	Responsible Medical Officer
RSV	respiratory syncytial virus
SADE	serious adverse device effect
SAE	serious adverse event
SafAS	safety analysis set
[redacted]	
SAP	statistical analysis plan

SMT	safety management team
SoA	schedule of activities
URTD	upper respiratory tract disease
TBD	to be determined

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title:

A parallel group, Phase III, randomized, observer-blind, placebo-controlled, multi-center, multi-national, multi-arm study to demonstrate non-inferiority of the immune response of a low dose compared to the standard dose and to evaluate the safety of a respiratory syncytial virus vaccine in infants and toddlers (OPAL)

Brief Title:

A study on the immunogenicity and safety of 3 different dose concentrations of a respiratory syncytial virus vaccine in infants and toddlers

Regulatory Agency Identifier Numbers:

Registry	**ID**
World Health Organization (WHO) universal trial number	U1111-1298-7338
US Investigational New Drug (IND) number	[redacted]
US National Clinical Trial number	NCT06705140

Rationale:

To complement the [redacted] studies of the RSVt vaccine in the context of the vaccine's [redacted] the VAD00015 study will investigate 3 vaccine dose concentrations for immunogenicity and safety (ie, low [LD: target [redacted] PFU/dose], standard [SD: target [redacted] PFU/dose], and high dose [HD: target [redacted] PFU/dose]). Thus, the aim of the study is to evaluate whether the LD (ie, [redacted]) is non-inferior to the SD (ie, [redacted]) as assessed by RSV A and RSV B serum neutralizing antibodies 28 days after the second vaccination (Day 85). The goal is to show that the LD will generate an immune response non-inferior to the SD. In addition, the study aims to investigate if the vaccine is safe in infants and toddlers born at term (ie, ≥ 37 weeks of gestation) and born preterm (ie, 28 through 36 weeks of gestation).

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands and Estimators	
		Population Level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
Primary			
Immunogenicity To demonstrate the non-inferiority of 2 administrations of the LD RSVt vaccine antibody levels to RSV A and RSV B compared to the SD RSVt vaccine (Cohort 2)	• RSV A and RSV B serum neutralizing antibody titers at 28 days post-dose 2 (D85)	Ratio of GMTs between groups (LD RSVt / SD RSVt) of each RSV antibody (A and B) Success criteria: The non-inferiority of LD RSVt versus SD RSVt will be demonstrated if the lower limit (LL) of the 2-sided 95% CI of the ratio of GMTs is > 2/3 for both RSV antibodies (A and B)	Immunogenicity will be estimated in the setting where participants do receive the full vaccination schedule and do not deviate from protocol requirements potentially impacting immunogenicity, as defined in the Per-Protocol Analysis set* (PPAS) (Principal Stratum Strategy, see Section 9.2). Other intercurrent events will be handled as per Treatment Policy Strategy. Missing data will not be imputed unless specified in the SAP.
Safety 1. To assess the safety profile of the SD and HD RSVt vaccine after each and any administration in medically stable participants born preterm (Cohort 1) 2. To assess the safety profile of the	• Presence of unsolicited systemic AEs reported in the 30 minutes after each vaccination • Presence of solicited administration site reactions within 21 days after each vaccination • Presence of solicited systemic reactions within 21 days after each vaccination	The main parameters for the safety endpoints will be described by number of participants, percentage, and 95% CI using the exact binomial distribution (Clopper Pearson method) for single proportion.	Safety will be estimated in the setting where participants received at least one study intervention administration as defined in the Safety Analysis Set**. Any relevant intercurrent event will be handled according to treatment policy

Objectives	Endpoints	Estimands and Estimators	
		Population Level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
LD/SD/HD RSVt vaccine after each and any administration in Cohort 2 participants	• Presence of unsolicited AEs within 28 days after each vaccination • Presence of MAAEs throughout the study • Presence of SAEs throughout the study • Presence of AESIs throughout the study		strategy. Missing data will not be imputed unless specified in the SAP.
Secondary			
Immunogenicity 1. To describe the RSVt vaccine humoral immune responses in Cohort 1 participants 2. To describe the RSVt vaccine humoral immune responses in Cohort 2 participants	• RSV A and RSV B serum neutralizing antibody titers at baseline (D01) and D85 • RSV serum anti-F IgA, anti-F IgG, and anti-G IgG antibody titers at D01 and D85		

Objectives	Endpoints	Estimands and Estimators	
		Population Level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
Vaccine Virus Shedding To describe the vaccine virus shedding in all participants with detected vaccine virus after each administration (Cohort 1 and Cohort 2)	• Presence of RSVt vaccine virus viral shedding in D08 and D64 nasal samples measured by qRT PCR • Titer of vaccine virus shedding in D08 and D64 nasal samples quantified by qRT-PCR		

Preterm=born after a gestation period of 28 through 36 weeks. At term= born after a gestation period of ≥ 37 weeks.
LD=target [redacted] PFU; SD=target [redacted] PFU; HD=target [redacted] PFU
Abbreviations: Ab, antibody; AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; D, day; GMTs, geometric mean titers HD, high dose; LD, low dose; LL, lower limit; MAAE, medically attended adverse event; PFU, plaque forming units; qRT-PCR, quantitative real time-polymerase chain reaction; SAE, serious adverse event; SD, standard dose; RSV, respiratory syncytial virus.
*The primary population of interest for immunogenicity is defined as participants meeting the inclusion and exclusion criteria at the time of enrollment, receiving full vaccination schedule, and not deviating from protocol requirements potentially impacting immunogenicity.
**The primary population of interest for safety is defined as participants receiving at least one dose of study vaccine.

The exploratory objectives are presented in the Section "Objectives and Endpoints/Estimands" of the protocol main text.

Overall Design:

Type of design	Parallel, multinational, multi-center
Phase	3
Control method	Placebo-controlled
Study population	Healthy infants and toddlers aged 6 months to < 22 months. **Cohort 1**: Participants born after a gestation period of 28 through 36 completed weeks and medically stable. **Cohort 2**: Participants born after a gestation period of ≥ 37 weeks. Contingent upon an acceptable safety profile of the HD in preterm participants, enrolment in Cohort 2 will proceed to include participants born preterm. Cohort 1 and Cohort 2 participants will be enrolled in parallel.
Regions	Latin America and North America
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 *Generally, safety data review during the study will be performed in a blinded manner by the Sponsor Safety Management Team (SMT). Safety data for Cohort 1 participants will be reviewed in an unblinded manner at the predefined time-points, involving pause of enrollment.

Investigational intervention assignment method	**Cohort 1**: (1:1 randomization) Group 1 (N=10): 2 administrations of SD RSVt Group 2 (N=10): 2 administrations of placebo (2:1 randomization) Group 3 (N=10): 2 administrations of HD RSVt Group 4 (N=5): 2 administrations of placebo Group 1 and 2 participants will be enrolled first and will be randomized to receive either SD RSVt vaccine or placebo. Based on the acceptable safety profile up to 28 days after the first vaccination, enrolment of participants into Groups 3 and 4 will proceed. Respectively, enrollment of pre-term participants in Cohort 2 will initiate, based on the acceptable safety profile up to 28 days after the first vaccination of Groups 3 and 4. **Cohort 2 (2:2:2:1 randomization):** Group 1 (N=304): 2 administrations of LD RSVt Group 2 (N=304): 2 administrations of SD RSVt Group 3 (N= 304): 2 administrations of HD RSVt Group 4 (N=152): 2 administrations of placebo Cohort 2 participants will be randomized to receive either LD, SD, or HD RSVt vaccine or placebo. Randomization will be stratified by study country, age group (< 12 months and ≥ 12 months), and potential RSV seropositivity (based on maternal immunization, and previous receipt of RSV mAb). Cohorts 1 and 2 will enroll in parallel.

Inclusion/Exclusion Criteria

Inclusion criteria

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

AGE

I01. Aged 6 months to < 22 months on the day of inclusion[a]

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS

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

For Cohort 1 and Cohort 2 (contingent upon satisfactory safety profile of the RSVt vaccine in Cohort 1)**:**

I03. Participant born 28 through 36 weeks of gestation 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

For Cohort 2:

I04. Participant born at full term of pregnancy (≥ 37 weeks of gestation)

INFORMED CONSENT

I05. Informed consent form has been signed and dated by the parent(s)/LAR(s) (and by an independent witness if required by local regulations)

OTHER INCLUSIONS

I06. Participant and parent(s)/LAR are able to attend all scheduled visits and to comply with all study procedures

Exclusion criteria

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

MEDICAL CONDITIONS

E01. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within

[a] "**6 months to < 22 months**" means from the day of the 6-month birthday to the day before the 22-month birthday. The second vaccine administration should be administered before the study participant has turned 24 months of age.

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[b]

E03. Chronic illness that, in the opinion of the investigator based on medical history or physical examination, is at a stage where it might interfere with study conduct or completion. Chronic illness may include, but is not limited to, cardiac disorders, lung disease (including any history of reactive airway disease or receipt of bronchodilator or inhaled steroid therapy), atopy, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and congenital or genetic diseases.

E04. History of medically diagnosed wheezing: Children with a history of recurrent wheezing will be excluded. Children with a previous single episode of wheezing may be included if that episode of wheezing was not associated with hospitalization or if the child does not have a family history of wheezing.

E05. 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.

E06. Probable or confirmed ongoing case of viral respiratory infection (including COVID-19, influenza, rhinovirus, etc.) at the time of enrollment. A prospective participant should not be included in the study until the respiratory infection has resolved.

E07. Member of a household that contains an immunocompromised individual, including, but not limited to:

- a person who is human immunodeficiency virus (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

Potential close contact with other immunocompromised individual within 30 days after each vaccination as per investigator's discretion

[b] The components of study intervention are listed in the Investigator's Brochure.

PRIOR/CONCOMITANT THERAPY

E08. Participant's biological mother previous receipt or planned administration of an investigational RSV vaccine during pregnancy and/or breastfeeding.

E09. Receipt or planned receipt of any of the following vaccines prior to enrollment or after the first study intervention administration:

- Any other intranasal live attenuated vaccine within the 28 days prior to and after the first study intervention administration
- Unless given on the day of the first study intervention administration, any other injectable live attenuated vaccines within the 28 days prior to and after. Concomitant receipt on the day of the first study intervention administration is allowed.

E10. Planned receipt of any monoclonal antibody for RSV (such as Nirsevimab, Clesrovimab, or Palivizumab) for the duration of the study

E11. Previous receipt of an investigational RSV vaccine or receiving any anti-RSV product (such as ribavirin or RSV immune globulin) at the time of enrollment. Previous receipt of Nirsevimab or Clesrovimab within 6 months or Palivizumab within 3 months prior to the first study vaccine administration

E12. Receipt of immune globulins, blood or blood-derived products in the past 3 months

E13. Receipt of intranasal and intra-ocular medications within 3 days prior to study enrollment

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

E14. Participation at the time of study enrollment or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.

OTHER EXCLUSIONS

E15. Being in an emergency setting

E16. Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.

Brief Summary:

VAD00015 will be a Phase 3, parallel group, randomized, observer-blind, placebo-controlled, multi-national, multi center, multi-arm study to be conducted in 1099 healthy children enrolled at 6 to < 22 months of age. The purpose of the study is to evaluate the non-inferiority of the immune response of the LD when compared to the SD RSVt vaccine and the safety of the SD and HD vaccine in preterm born children and of the HD vaccine in full term born children administered by intranasal route and compared to placebo.

Study details include:

- The study duration will be approximately 8 months for each participant, including the 6 months safety follow-up phone call after the second study intervention administration.
- [redacted]
- Visit frequency will be as shown in Table 1 for the Main Set of participants [redacted]
- The study intervention administration for the participants will be on D01 (V1) and 56 days after (1 intranasal administration in each nostril at each timepoint).
- Each participant will provide a blood sample at baseline (Day 1 [D01] pre-administration of dose 1) and 28 days (D85) after the administration of dose 2 for the measurement of post vaccination serum neutralizing antibodies (Ab) titers to RSV A and RSV B.
  Baseline blood samples will be used also as an indicator of possible previous RSV exposure or passive immunity conferred by receipt of RSV monoclonal antibody or maternal vaccination.
- Nasal samples will be collected 7 days after each vaccination for vaccine virus shedding determination (Table 1[redacted]).

[redacted]

- Safety data will be collected during all study visits, as well as at designated timepoints via contacts with the parents/ legally acceptable representative (LAR) of the study participants.

Table 1: Main set of participants - visit frequency

Cohort 1 and 2	Visit 1 (V1)	Visit 2 (V1 + 7 days)	Visit 3 (V1+56 days)	Visit 4 (V3+ 7 days)	Visit 5 (V3+ 28 days)
Main set*	BL VAC	NS	VAC	NS	BL

Abbreviations: BL, blood sampling; NS; nasal sample; V, visit; VAC, vaccination (ie, study intervention administration)
*Participants from Cohort 1 and Cohort 2 not included in the subset.

[redacted]

Number of Participants:

A total of 1099 participants are expected to be randomized: 35 in Cohort 1 and 1064 in Cohort 2.

Study Arms and Duration:

In each study group (RSVt vaccine and placebo groups), eligible participants will be randomized to receive 2 intranasal administrations (56 days apart, ie, at D01 and D57) of either dose of the RSVt vaccine or placebo.

Study arms will be as follows:

Cohort 1 participants (born prematurely) enrollment will be done in a sequential /stepwise approach. Step 1: the first 20 participants will be randomized 1:1 to receive SD RSVt or placebo.

Step 2: based on the acceptability of the safety profile (up to 28 days after the first vaccination), 15 additional participants will be randomized 2:1 to HD RSVt or placebo.

Step 1:

- Group 1 (N=10): 2 administrations of SD RSVt (target [redacted] PFU/dose)
- Group 2 (N=10): 2 administrations of placebo

Contingent upon safety of SD RSVt:

Step 2:

- Group 3 (N=10): 2 administrations of HD RSVt (target [redacted] PFU/dose)
- Group 4 (N=5): 2 administrations of placebo

Contingent upon an acceptable safety profile of the HD in Cohort 1, enrolment in Cohort 2 will open to participants born preterm.

Cohort 2 participants will be randomized at a 2:2:2:1 ratio for Groups 1 to 4, respectively.
Group 1 (N=304): 2 administrations of LD RSVt (target [redacted] PFU/dose)
Group 2 (N=304): 2 administrations of SD RSVt (target [redacted] PFU/dose)
Group 3 (N=304): 2 administrations of HD RSVt (target [redacted] PFU/dose)
Group 4 (N=152): 2 administrations of placebo

Cohorts 1 and 2 will enroll in parallel.

At each vaccination visit, [redacted] mL of RSVt vaccine or placebo will be administered in each nostril with the use of an investigational device.

Study duration will be approximately 8 months for each participant.

Study intervention(s):

Investigational medicinal product 1: LD RSVt Vaccine (target [redacted] PFU/[redacted] mL)

- Form: Liquid for nasal spray
- Composition: Each [redacted] mL dose of RSVt vaccine will contain the live-attenuated RSV with [redacted]
- Route of administration: intranasal

Investigational medicinal product 2: SD RSVt Vaccine (target [redacted] mL)

- Same form, composition, and route of administration as for product 1.

Investigational medicinal product 3: HD RSVt Vaccine (target [redacted] PFU/[redacted] mL)

- Same form, composition, and route of administration as for product 1.

Investigational medicinal product 4: Placebo

- Form: Liquid for nasal spray
- Composition: buffer, same [redacted] formulation buffer as that used for the RSVt vaccine, to be delivered as approximately [redacted] mL per nostril
- Route of administration: intranasal

Statistical considerations:

Statistical Hypotheses

Primary Immunogenicity Objective

Twenty-eight days after the second administration of the RSVt vaccine to Cohort 2 participants, the geometric mean titers (GMTs) of neutralizing RSV (A and B) antibodies of the LD RSVt group will be compared to SD RSVt group. The following hypotheses will be tested for each RSV antibody:

$$H_0 : \text{GMT(rsv, LD)/GMT(rsv, SD)} \leq 2/3$$
$$H_1 : \text{GMT(rsv, LD)/GMT(rsv, SD)} > 2/3$$

where GMT(rsv, LD) and GMT(rsv, SD) are GMTs of RSV antibodies (A and B) in LD RSVt and SD RSVt from Cohort 2, respectively.

If the lower limit of the 2-sided 95% CI of the ratio of the GMTs between LD RSVt and SD RSVt groups is > 2/3 for both neutralizing RSV antibodies (A and B), the inferiority null-hypothesis will be rejected and non-inferiority (NI) of LD RSVt compared to SD RSVt will be demonstrated.

Statistical Analyses

All endpoints will be summarized at each timepoint by study intervention group. For the analysis of Cohort 1, Group 2 and Group 4 (ie, placebo groups) may be pooled. Results will be presented separately for each cohort.

In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs and GMTRs, 95% CIs of point estimates will be calculated using normal approximation, assuming they are log10-normally distributed.

The immunogenicity analyses for primary endpoints will be performed on the Per-Protocol Analysis Set (PPAS) and will be confirmed on the Full Analysis Set (FAS). For other immunogenicity endpoints, analyses will be performed on the PPAS and may be confirmed on the FAS if the difference between the number of participants in the PPAS and the number of participants in the FAS is not less than 10%.

Safety analyses will be performed on the Safety Analysis Set (SafAS).

Primary Endpoints

Immunogenicity Analysis

The 2-sided 95% CIs of the ratio of GMTs between LD RSVt group and SD RSVt group from Cohort 2 will be calculated assuming that log10 transformation of the titers follows a normal distribution. If the lower limits of the 2-sided 95% CIs are greater than 2/3 for both RSV A and RSV B antibodies, the inferiority null hypothesis will be rejected.

Safety Analysis

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

Sequence of Analyses

An unblinded primary completion analysis will be performed on data collected up to 28 days post-dose 2 for immunogenicity and safety in all participants for each cohort. Randomization code will be broken for the sponsor, but blinding will be maintained at sites and at the participants/parents level.

Sample Size Determination

[redacted]

[redacted]

For Primary Immunogenicity Objective

[redacted].

For Primary Safety Objective

The sample size of 304 participants in the HD RSVt group will provide a probability of 95% to observe an event that has a true incidence of 1% and will provide a probability of 78% to observe an event that has a true incidence of 0.5%.

Safety Management Team

Participant safety will also be continuously monitored by the Sponsor's internal safety management team (SMT), which includes safety signal detection at any time during the study. This committee, led by the Patient Safety and Pharmacovigilance (PSPV) representative and the Responsible Medical Officer (RMO), will be responsible for the 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.

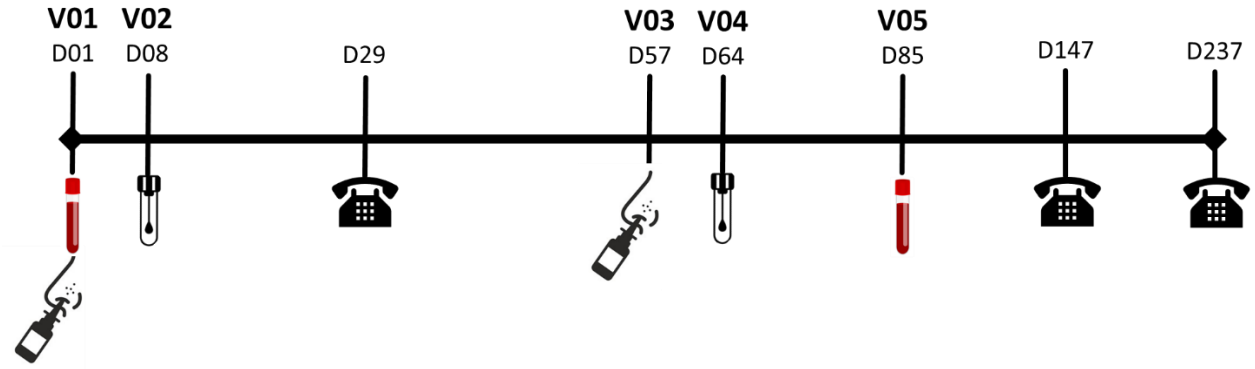
Independent Data Monitoring Committee

A Phase 3 program-based Independent Data Monitoring Committee (IDMC) will be appointed and including the oversight of study VAD00015. The IDMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for harms or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. The membership composition, specific responsibilities of members, timing of reviews, objectives for review, and decision criteria will be documented in the IDMC Charter.

1.2 SCHEMA

The graphical design of VAD00015 study is presented in Figure 1 and in [redacted].

Figure 1: Graphical study design – Main set of participants



Legend:



Abbreviations: D=day; V=visit

RSVt vaccine (low-, standard-, or high-dose) or placebo to be administered intranasally at V01 and V03.
Blood samples will be collected at V01 (pre-vaccination) and V05 for immunogenicity assessments.
Nasal samples will be collected 7 days post vaccination at V02 and V04 for vaccine viral shedding determination.

[redacted]

1.3 SCHEDULE OF ACTIVITIES (SOA)

The study procedures should follow the order listed in the SoA.

Table 3: Schedule of activities for the Main Set of participants

Phase 3 Study, 5 Planned Visits, 3 Phone Calls, 2 Vaccinations, 2 Blood Samples, 2 Nasal Samples, approximately 8 Months' Duration Per Participant

Visit/Contact	***Collection of information in the CRF***	**Visit 1 (V01)**	**Visit 2**	**Phone Call**	**Visit 3**	**Visit 4**	**Visit 5**	**Phone Call**	**Phone Call**
Study timelines - days(D)		D01	D08	D29	D57	D64	D85	D147	D237
Visit Interval (V0X + days)		NA	V01+7	V01+28	V01+56	V03+7	V03+28	V03+3 months	V03+6 months
Time windows (days)		NA	[+2]	[+2]	[+14]	[+2]	[+7]	[+14]	[+14]
Age (months)		**6 to < 22**			**8 to < 24**				
Informed consent	X	X							
Inclusion/exclusion criteria	X	X							
Collection of demographic data	X	X							
Collection of medical history[*]	X Significant Medical History	X							
Physical examination[†]		X			X				
Pre-vaccination temperature[‡]		X			X				
Vital signs[§]	X	X			X				

[*] Including participant past RSV illness, maternal RSV vaccination and RSV disease during pregnancy. Participant's growth curve should also be reviewed.

[†] Including but not limited to a cardiopulmonary exam. Physical examination is mandatory prior to vaccination at vaccination visits. For other visits, it may be performed, if necessary, based on the health status of the participant.

[‡] Axillary pre-vaccination body temperature will be collected during vaccination visits and reported in the source document.

[redacted]

Visit/Contact	*Collection of information in the CRF*	Visit 1 (V01)	Visit 2	Phone Call	Visit 3	Visit 4	Visit 5	Phone Call	Phone Call
Study timelines - days(D)		D01	D08	D29	D57	D64	D85	D147	D237
Visit Interval (V0X + days)		NA	V01+7	V01+28	V01+56	V03+7	V03+28	V03+3 months	V03+6 months
Time windows (days)		NA	[+2]	[+2]	[+14]	[+2]	[+7]	[+14]	[+14]
Age (months)		**6 to < 22**			**8 to < 24**				
Collection of reportable concomitant medications/vaccinations (including participant RSV mAb receipt)	X	X	X	X	X	X	X		
Randomization/allocation of participant number	X	X							
Dose number	X	X			X				
Blood sampling (BL) [5 mL]	X	**BL0001**					**BL0002**		
Nasal sample (NS)	X		**NS0001**			**NS0002**			
Vaccination (VAC)	X	**VAC1**			**VAC2**				
Immediate surveillance (30 min)[**]	X	X			X				
Participant diary or Memory Aid (MA) provided[††]		X			X		X		
Participant diary or MA reviewed[‡‡]			X	X	X	X	X	X	X
Participant diary or MA collected (if applicable)					X		X		
Collection of solicited administration site and systemic reactions[§§]	X	X	X		X	X			

[**] Any unsolicited systemic adverse events occurring within the 30 minutes from study intervention administration will be recorded as immediate unsolicited systemic AE in the CRF.

[††] At each visit the investigator will remind the participants' parents/LARs to fill out the participant diary or MA if applicable and will answer any questions.

[‡‡] At each phone call, the investigator will interview the participants' parents/LARs to review the information recorded in the participant diary or MA and will attempt to clarify anything that is incomplete or unclear. The paper participant diary will be collected and archived on site as described in the table.

Visit/Contact	***Collection of information in the CRF***	**Visit 1 (V01)**	**Visit 2**	**Phone Call**	**Visit 3**	**Visit 4**	**Visit 5**	**Phone Call**	**Phone Call**
Study timelines - days(D)		D01	D08	D29	D57	D64	D85	D147	D237
Visit Interval (V0X + days)		NA	V01+7	V01+28	V01+56	V03+7	V03+28	V03+3 months	V03+6 months
Time windows (days)		NA	[+2]	[+2]	[+14]	[+2]	[+7]	[+14]	[+14]
Age (months)		**6 to < 22**			**8 to < 24**				
Collection of unsolicited AEs[***]	X	X	X	X	X	X	X		
Collection of SAEs, AESIs, and MAAEs (throughout the study)	X	X	X	X	X	X	X	X	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; CRF, case report form; LAR, legally acceptable representatives; MA, memory aid; MAAE, medically attended adverse event; SAE, serious adverse event

[§§] Solicited administration site and systemic reactions will be collected for 21 days after each vaccine administration.

[***] Unsolicited AEs will be collected for 28 days after each vaccine administration.

[†††] In case of participant discontinuation at a visit, all the CRF forms related to this visit will be completed with available information.

[‡‡‡] A phone call will be made at least 6 months after the last study intervention received for all the participants, including early terminated participants.

Table 4: [redacted]

[redacted]





2 INTRODUCTION

Sanofi's live-attenuated respiratory syncytial virus (RSV) ΔNS2/Δ1313/I1314L vaccine (hereafter referred to as RSVt vaccine) is being developed for active immunization against RSV infection in the pediatric population – infants and toddlers. Results from Phase 1 and Phase 2 studies (VAD00001, VAD00012, and VAD00014), conducted by Sanofi, showed acceptable safety and immunogenicity profiles for the RSVt vaccine candidate. Results also showed good infectivity and no transmission of vaccine virus to close contacts of RSVt recipients. Following these studies, VAD00015 (also known as OPAL) is initiated as part of the Phase 3 development of the RSVt vaccine.

2.1 STUDY RATIONALE

The aim of the present study is to evaluate 3 formulations of the RSVt vaccine (low [LD], standard [SD], and high [HD]) in terms of immunogenicity and safety in children aged 6 to < 22 months at enrollment. The objective of study VAD00015 is to evaluate the clinical non-inferiority of the LD [redacted] when compared to the SD ([redacted]) and to describe the clinical safety of the HD in children born at full term (ie, ≥ 37 weeks of gestation), and of the SD and HD in prematurely born children (ie, 28 through 36 weeks of gestation).

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 101 400 deaths in children < 5 years of age in 2019 (2).

There are 2 subtypes of RSV (A and B) and multiple genotypes that can circulate simultaneously. The seasonal nature of RSV transmission varies globally. In temperate climates, RSV rates increase during late autumn, winter, and/or spring, whereas tropical and arctic climates observe RSV cases year-round (4,5).

Natural immunity to RSV is incomplete and reinfection occurs throughout life. Although a definitive correlate of protection against RSV infection remains elusive, cell mediated immunity, mucosal immunoglobulin (Ig) A, and neutralizing antibodies (Abs) have been associated with protection from RSV infection (6).

[redacted]

RSVt Vaccine Candidate

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 (7,8,9,10,11,12,13).

The US National Institutes of Health (NIH) developed a live-attenuated RSV vaccine (ie, ΔNS2/Δ1313/I1314L vaccine) by deleting the gene encoding the RSV interferon / apoptosis antagonist nonstructural (NS)2 protein (14,15,16,17,18).Deletion of the NS2 gene (ΔNS2) attenuates the virus by decreasing pathogenicity (19,20).and enhancing immunogenicity (21). This 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 temperature sensitivity, which translates into a shut-off of virus replication at 38ºC-39°C, is thought to restrict vaccine virus replication to the upper respiratory tract, increasing vaccine safety (11).The NIH vaccine has been shown to be safe and immunogenic in RSV-seronegative children in Phase I studies (22,23). Further research is ongoing in RSV-seropositive children (24).

Sanofi's investigational RSVt vaccine is the same construct (ie, ΔNS2/Δ1313/I1314L) as the NIH RSV vaccine. The vaccines differ in formulation and mode of intranasal administration.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks, reasonably expected adverse events (AEs), the potential risks, and uncertainties of the RSVt vaccine may be found in the Investigator's Brochure (IB). Medical device-related risk considerations are discussed in Section 6.1.1.2.

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 5.

Table 5: Potential risks of clinical significance and risk mitigation / management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Mitigation / Management
Investigated Vaccine: RSVt Vaccine		
Anaphylaxis	Important potential risk: 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.
Acute Wheeze	Vaccine associated wheeze is considered a potential risk with live attenuated vaccines administered by the nasal route.	Observation period after vaccination for early detection and treatment Medical surveillance with qualified medical personnel to provide care if needed
Vaccine Associated Enhanced Disease	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. Unlike other pathogens, RSV does not display enhanced disease, and thus enhanced disease is only an artifact of vaccination with no replicating approaches, however, this theoretical risk remains.	Medical surveillance with qualified medical personnel to provide care if needed
[redacted]	[redacted]	[redacted]

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Mitigation / Management
	[redacted]	[redacted]
Study Procedures		
Possible reactions to blood draw	Risks occasionally associated with venipuncture include pain and bruising at the site of the blood draw. Venipuncture, lightheadedness, infection, and syncope (rarely). Infection in rare instances at the blood draw site may occur.	Early detection, observation, and appropriate treatment
Possible reactions to nasal sample procedure	Risks occasionally associated with nasal samples include pain or discomfort and occasionally epistaxis. Nasal samples are not standard care in the pediatric population.	Appropriate training for study personnel to perform nasal samples.
Possible reactions to topical anesthetic cream (used for blood draw procedure)	Reactions to the 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		
Not applicable	Not applicable	Not applicable

Appropriate medical equipment and routine emergency medications must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction. This equipment is not provided by the Sponsor.

2.3.2 Benefits from Study Participation

Participants randomized in any of the groups to receive the RSVt vaccine may benefit from coverage against RSV and may be less likely to develop RSV associated acute respiratory disease (ARD), lower tract respiratory disease (LRTD), or RSV-related severe illness and/or hospitalization. However, as with all vaccines, vaccination with the investigational vaccine may not protect individuals 100%.

Placebo recipients will not receive any direct benefit from enrollment in this study.

Even if participants do not directly benefit, this study will contribute to the development of a vaccine that may help children as well as other people in the future.

2.3.3 Overall Benefit-Risk Conclusion

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

3 OBJECTIVES AND ENDPOINTS/ESTIMANDS

The study objectives and the corresponding endpoints are described in Table 6.

Table 6: Objectives and endpoints

Objectives	Endpoints	Estimands and Estimators	
		Population Level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
Primary			
Immunogenicity To demonstrate the non-inferiority of 2 administrations of the LD RSVt vaccine antibody levels to RSV A and RSV B compared to the SD RSVt vaccine (Cohort 2)	• RSV A and RSV B serum neutralizing antibody titers at 28 days post-dose 2 (D85)	Ratio of GMTs between groups (LD RSVt / SD RSVt) of each RSV antibody (A and B) Success criteria: The non-inferiority of LD RSVt versus SD RSVt will be demonstrated if the lower limit (LL) of the 2-sided 95% CI of the ratio of GMTs is > 2/3 for both RSV antibodies (A and B)	Immunogenicity will be estimated in the setting where participants do receive the full vaccination schedule and do not deviate from protocol requirements potentially impacting immunogenicity, as defined in the Per-Protocol Analysis set* (PPAS) (Principal Stratum Strategy, see Section 9.2). Other intercurrent events will be handled as per Treatment Policy Strategy. Missing data will not be imputed unless specified in the SAP.
Safety 1. To assess the safety profile of the SD and HD RSVt vaccine after each and any administration in medically stable participants born preterm (Cohort 1)	• Presence of unsolicited systemic AEs reported in the 30 minutes after each vaccination • Presence of solicited administration site reactions within 21 days after each vaccination	The main parameters for the safety endpoints will be described by number of participants, percentage, and 95% CI using the exact binomial distribution (Clopper Pearson method) for single proportion.	Safety will be estimated in the setting where participants received at least one study intervention administration as defined in the Safety Analysis Set**.

Objectives	Endpoints	Estimands and Estimators	
		Population Level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
2. To assess the safety profile of the LD/SD/HD RSVt vaccine after each and any administration in Cohort 2 participants	• Presence of solicited systemic reactions within 21 days after each vaccination • Presence of unsolicited AEs within 28 days after each vaccination • Presence of MAAEs throughout the study • Presence of SAEs throughout the study • Presence of AESIs throughout the study		Any relevant intercurrent event will be handled according to treatment policy strategy. Missing data will not be imputed unless specified in the SAP.
Secondary			
Immunogenicity 1. To describe the RSVt vaccine humoral immune responses in Cohort 1 participants 2. To describe the RSVt vaccine humoral immune responses in Cohort 2 participants	• RSV A and RSV B serum neutralizing antibody titers at baseline (D01) and D85 • RSV serum anti-F IgA, anti-F IgG, and anti-G IgG antibody titers at D01 and D85		

Objectives	Endpoints	Estimands and Estimators	
		Population Level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
Vaccine Virus Shedding To describe the vaccine virus shedding in all participants with detected vaccine virus after each administration (Cohort 1 and Cohort 2)	• Presence of RSVt vaccine virus viral shedding in D08 and D64 nasal samples measured by qRT PCR • Titer of vaccine virus shedding in D08 and D64 nasal samples quantified by qRT-PCR		
[redacted]			

Preterm=born after a gestation period of 28 through 36 weeks. At term= born after a gestation period of ≥ 37 weeks.
LD=target [redacted] PFU; SD=target [redacted] PFU; HD=target [redacted] PFU
Abbreviations: Ab, antibody; AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; D, day; GMTs, geometric mean titers HD, high dose; LD, low dose; LL, lower limit; MAAE, medically attended adverse event; PFU, plaque forming units; qRT-PCR, quantitative real time-polymerase chain reaction; SAE, serious adverse event; SD, standard dose; RSV, respiratory syncytial virus.
*The primary population of interest for immunogenicity is defined as participants meeting the inclusion and exclusion criteria at the time of enrollment, receiving full vaccination schedule, and not deviating from protocol requirements potentially impacting immunogenicity.
**The primary population of interest for safety is defined as participants receiving at least one dose of study vaccine.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The design of the study is summarized in Table 7.

Table 7: Overall design

Type of design	Parallel, multinational, multi-center
Phase	3
Control method	Placebo-controlled
Study population	Healthy infants and toddlers aged 6 months to < 22 months. **Cohort 1**: Participants born after a gestation period of 28 through 36 completed weeks and medically stable. **Cohort 2**: Participants born after a gestation period of ≥ 37 weeks. Contingent upon an acceptable safety profile of the HD in preterm participants, enrolment in Cohort 2 will proceed to include participants born preterm. Cohort 1 and Cohort 2 participants will be enrolled in parallel.
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 *Generally, safety data review during the study will be performed in a blinded manner by the Sponsor Safety Management Team (SMT). Safety data for Cohort 1 participants will be reviewed in an unblinded manner at the predefined time-points, involving pause of enrollment.

Investigational intervention assignment method	**Cohort 1**: (1:1 randomization) Group 1 (N=10): 2 administrations of SD RSVt (target [redacted] PFU) Group 2 (N=10): 2 administrations of placebo (2:1 randomization) Group 3 (N=10): 2 administrations of HD RSVt (target [redacted] PFU) Group 4 (N=5): 2 administrations of placebo Group 1 and 2 participants will be enrolled first and will be randomized to receive either SD RSVt vaccine or placebo. Based on the acceptable safety profile up to 28 days after the first vaccination, enrolment of participants into Groups 3 and 4 will proceed. Respectively, enrollment of pre-term participants in Cohort 2 will initiate, based on the acceptable safety profile up to 28 days after the first vaccination of Groups 3 and 4 (Section 8.4.10) **Cohort 2 (2:2:2:1 randomization):** Group 1 (N= 304): 2 administrations of LD RSVt (target [redacted] PFU) Group 2 (N= 304): 2 administrations of SD RSVt (target [redacted] PFU) Group 3 (N= 304): 2 administrations of HD RSVt (target [redacted] PFU) Group 4 (N= 152): 2 administrations of placebo Cohort 2 participants will be randomized to receive either LD, SD, or HD RSVt vaccine or placebo. Randomization will be stratified by study country, age group (< 12 months and ≥ 12 months), and potential RSV seropositivity (based on maternal immunization and previous receipt of RSV mAb). Cohorts 1 and 2 will enroll in parallel.
Number of participants	A total of 1099 participants are expected to be randomized: 35 in Cohort 1 and 1064 in Cohort 2.
Intervention groups	RSVt vaccine groups (LD, SD, and HD) and placebo
Total duration of study participation	Approximately 8 months for each participant, including the 6 months safety follow-up phone call after the second study intervention administration.

Regions	Latin America and North America
Use of an Independent Data Monitoring Committee (IDMC) or similar review group	An IDMC will be used. Further details are provided in Section 10.1.5

Brief Summary:

VAD00015 will be a Phase 3, parallel group, randomized, observer-blind, placebo-controlled, multi-national, multi center, multi-arm study to be conducted in 1099 infants and toddlers 6 months to < 22 months of age. The purpose of the study is to evaluate the non-inferiority of the immune response of the LD when compared to the SD RSVt vaccine (Cohort 2) and the safety of the SD and HD vaccine in preterm born participants (Cohort 1) and of the HD vaccine in full term born participants (Cohort 2) administered by intranasal route and compared to placebo.

Study details include:

- Study intervention administration for the participants will be on D01 (V1) and 56 days after (1 intranasal administration in each nostril [mL] at each timepoint).
- [redacted]
- Visit frequency will be as shown in Table 8 for the Main Set of participants [redacted]
- Each participant will provide a blood sample at baseline (Day 1 [D01] pre-administration of dose 1) and 28 days (D85) after the administration of dose 2 for the measurement of post vaccination serum neutralizing Ab titers to RSV A and RSV B.
  Baseline blood samples will be used also as an indicator of possible previous RSV exposure or passive immunity conferred by receipt of RSV monoclonal antibody or maternal vaccination (as defined in Section 8.2.2).
- Nasal samples will be collected 7 days after each vaccination for vaccine virus shedding determination (Table 8 and [redacted]).
- [redacted]
- Safety data will be collected during all study visits, as well as at designated timepoints via contacts with the parents/LARs of the study participants.

Table 8: Main set of participants visit frequency

Cohort 1 and 2	Visit 1 (V1)	Visit 2 (V1 + 7 days)	Visit 3 (V1+56 days)	Visit 4 (V3+ 7 days)	Visit 5 (V3+ 28 days)
Main set*	BL VAC	NS	VAC	NS	BL

Abbreviations: BL, blood sampling; NS; nasal sample; V, visit; VAC, vaccination (ie, study intervention administration)
*Participants from Cohort 1 and Cohort 2 not included in the subset.

[redacted]

Safety:

The safety profile of the study interventions will be assessed in all 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 within 28 days after each study intervention administration.
- SAEs, MAAEs, and AESIs (ie, [redacted]) - throughout the study.

The safety of the RSVt vaccine will be continuously monitored by the Safety Management Team (SMT) (see Section 8.4.10).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Justification for the primary immunogenicity and safety endpoints

The objective of study VAD00015 is to evaluate the clinical non-inferiority of the low [redacted] and to describe the clinical safety of the high end of the operative range in infants and toddlers born prematurely (ie, 28 through 36 weeks of gestation) and at full term (ie, ≥ 37 weeks of gestation).

Therefore, this study intends to generate evidence that vaccine potency [redacted] is still above a clinically justified limit, ie, that the target [redacted] PFU (LD RSVt vaccine) immune response is non-inferior compared to the target [redacted] (SD RSVt vaccine) to be administered in the pivotal Phase 3 efficacy study (VAD00004).

Additionally, the study will evaluate the safety of the SD and HD (target [redacted] PFU) RSVt vaccines in premature and at term children. The LD and SD RSVt vaccines have been administered in infants born at term in the first-in-human clinical study VAD00001 with no safety concerns. There is no clinical safety data available for the HD yet.

Rationale for placebo

Placebo will be used for safety and immunogenicity comparisons to vaccine groups. The inclusion of a placebo group will maintain the study blind and will allow for an unbiased evaluation of the study endpoints.

Dosing interval

To allow some flexibility with the administration of the second dose, the interval between the 2 doses will be 2-2.5 months (ie, the visit window around dose 2 will be + 14 days). This will also offer a better fit with existent well-child or vaccination visits, in different countries, for the targeted age range. The broader window for dose 2 administration is not anticipated to impact meaningfully immunogenicity.

Justification for observer-blind during the entire study

Since RSVt vaccine has a different appearance than the placebo, VAD00015 study will be an observer-blind study in which a designated unblinded preparator and administrator at each study site will know which study intervention has been administered. The Investigator/Sub-Investigator/staff involved in the safety assessment will be blinded to decrease the risk of potential bias in safety and immunogenicity assessments.

Study location

The study will be conducted in Northern and Southern Hemisphere countries. The list of countries will secure diversity of population and healthcare settings.

Intranasal delivery

The intranasal route aims to mimic the natural exposure and to elicit a robust mucosal immunity to block RSV infection at the point of entry. This administration route protects from upper and lower respiratory illness caused by RSV. Additionally, administration via this route translates into fewer childhood injections and increased vaccination acceptance.

4.3 JUSTIFICATION FOR DOSE

Justification for 2-dose administration schedule

Among several published studies evaluating 2 or 3 administrations of attenuated RSV or parainfluenza virus type 3 candidate vaccines (7,8,9,25,26,27,28,29,30), 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. Results from the Phase 1/2 VAD00001 study conducted in infants and toddlers 6 to 18 months of age, who received 2 doses of RSVt vaccine, showed that the proportion of RSV-naïve recipients who had a 4-fold rise in neutralizing antibody titers was higher after the second administration compared to the first administration. Thus, 2 administrations of RSVt vaccine would improve its infectivity and resulting immune response.

Justification for vaccine dose levels

The vaccine dose levels have been selected based on benefit/risk assessment from data obtained in the Phase 1/2 VAD00001 study in which participants received the RSVt vaccine at a concentration of [redacted] PFU or [redacted] PFU per dose. A similar safety profile was observed at both dose levels. The vaccine virus shedding showed marked vaccine take at both dose levels and the percentages of RSV-naïve recipients who attained a 4-fold or more response in serum neutralizing antibody responses post the second vaccine administration were similar for both dose levels. The results of VAD00001 study support a wide operative range for the candidate RSVt

vaccine in terms of safety and immunogenicity that could include doses from target [redacted] to target [redacted] PFU (ie, LD to HD), which fall within the planned release [redacted]. The SD (target [redacted] PFU) has been selected for Phase 3 clinical development.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if the participant has completed the last applicable visit/contact planned in the SoA (Section 1.3).

The end of the study is defined as the date that the last test results have been released for samples collected at Visit 5 for the Main Set of participants and [redacted] related to primary and secondary endpoints. The end of study must be achieved no later than 9 months after the last visit/contact of the last participant in the study.

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

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

I01: Aged 6 months to < 22 months on the day of inclusion[a]

Type of participant and disease characteristics

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

For Cohort 1 and Cohort 2 (contingent upon satisfactory safety profile of the RSVt vaccine in Cohort 1)**:**

I03: Participant born 28 through 36 weeks of gestation 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

For Cohort 2:

I04: Participant born at full term of pregnancy (≥ 37 weeks of gestation)

Informed Consent

I05: Informed consent form has been signed and dated by the parent(s)/LAR(s) (and by an independent witness if required by local regulations).

[a] "**6 months to < 22 months**" means from the day of the 6-month birthday to the day before the 22-month birthday. The second vaccine administration should be administered before the study participant has turned 24 months of age.

Other Inclusions

I06: Participant and parent(s)/LAR(s) are able to attend all scheduled visits and to comply with all study procedures.

5.2 EXCLUSION CRITERIA

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

Medical conditions

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

E02. 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[b]

E03. Chronic illness that, in the opinion of the investigator based on medical history or physical examination, is at a stage where it might interfere with study conduct or completion. Chronic illness may include, but is not limited to, cardiac disorders, lung disease (including any history of reactive airway disease or receipt of bronchodilator or inhaled steroid therapy), atopy, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and congenital or genetic diseases.

E04. History of medically diagnosed wheezing: Children with a history of recurrent wheezing will be excluded. Children with a previous single episode of wheezing may be included if that episode of wheezing was not associated with hospitalization or if the child does not have a family history of wheezing.

E05. 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.

E06. Probable or confirmed ongoing case of viral respiratory infection (including COVID-19, influenza, rhinovirus, etc.) at the time of enrollment. A prospective participant should not be included in the study until the respiratory infection has resolved.

[b] The components of study intervention are listed in the Investigator's Brochure.

E07. Member of a household that contains an immunocompromised individual, including, but not limited to:

- a person who is human immunodeficiency virus (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

Potential close contact with other immunocompromised individual within 30 days after each vaccination as per investigator's discretion

Prior/concomitant therapy

E08. Participant's biological mother previous receipt or planned administration of an investigational RSV vaccine during pregnancy and/or breastfeeding.

E09. Receipt or planned receipt of any of the following vaccines prior to enrollment or after the first study intervention administration:

- Any other intranasal live attenuated vaccine within the 28 days prior to and after the first study intervention administration
- Unless given on the day of the first study intervention administration, any other injectable live attenuated vaccines within the 28 days prior to and after. Concomitant receipt on the day of the first study intervention administration is allowed.

E10. Planned receipt of any monoclonal antibody for RSV (such as Nirsevimab, Clesrovimab, or Palivizumab) for the duration of the study

E11. Previous receipt of an investigational RSV vaccine or receiving any anti-RSV product (such as ribavirin or RSV immune globulin) at the time of enrollment. Previous receipt of Nirsevimab or Clesrovimab within 6 months or Palivizumab within 3 months prior to the first study vaccine administration

E12. Receipt of immune globulins, blood or blood-derived products in the past 3 months

E13. Receipt of intranasal and intra-ocular medications within 3 days prior to study enrollment.

Prior/concurrent clinical study experience

E14. Participation at the time of study enrollment or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.

Other exclusions

E15. Being in an emergency setting.

E16. Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.

As applicable per local regulations: If the participant has a primary physician who is not the investigator, the site should contact this physician with the participant's parent(s) / LAR(s) consent to inform this physician 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 has consented to participate in the clinical study is not subsequently assigned to study intervention/entered in the study. 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 and considered for the study if all inclusion and exclusion criteria are met at a later time-point.

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 study 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 interventions are all pre-specified, investigational and auxiliary medicinal products (ie, IMP and AxMP), medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

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 6.9). Study procedures (eg, blood sampling) are also not considered as study interventions.

An IMP is "a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical study". An AxMP is "a medicinal product used for the needs of a clinical study as described in the protocol, but not as an investigational medicinal product".

6.1 STUDY INTERVENTIONS ADMINISTERED

Study interventions are described in Table 10.

Table 10: Study interventions administered

Intervention name	Low Dose (LD) RSVt Vaccine	Standard Dose (SD) RSVt Vaccine	High Dose (HD) RSVt Vaccine	Placebo
Intervention description	Live attenuated virus	Live attenuated virus	Live attenuated virus	Same formulation buffer as RSVt vaccine
Marketing authorization status	Not approved	Not approved	Not approved	Not applicable
Use	Experimental	Experimental	Experimental	Placebo
IMP or AxMP	IMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine	Vaccine
Dosage form	Liquid for nasal spray	Liquid for nasal spray	Liquid for nasal spray	Liquid for nasal spray
Unit dose strength	[redacted] PFU/dose	[redacted] PFU/dose	[redacted] PFU/dose	Same formulation buffer as RSVt

Intervention name	Low Dose (LD) RSVt Vaccine	Standard Dose (SD) RSVt Vaccine	High Dose (HD) RSVt Vaccine	Placebo
	corresponding to a target of [redacted] PFU/dose Each dose ([redacted]mL) of RSVt vaccine will contain the live-attenuated RSV with [redacted]	corresponding to a target of [redacted] PFU/dose Each dose ([redacted] mL) of RSVt vaccine will contain the live-attenuated RSV with [redacted]	corresponding to a target of [redacted] PFU/dose. Each dose ([redacted] mL) of RSVt vaccine will contain the live-attenuated RSV with [redacted]	vaccine
Excipients/diluent	[redacted] formulation buffer	[redacted] formulation buffer	[redacted] formulation buffer	[redacted]
Dosage level	[redacted] mL per dose (corresponding to [redacted] mL per nostril)	[redacted] mL per dose (corresponding to [redacted] mL per nostril)	[redacted] mL per dose (corresponding to [redacted] mL per nostril)	[redacted] mL per dose (corresponding to [redacted] mL per nostril)
Number of doses / dosing interval	2 doses 56 days apart	2 doses 56 days apart	2 doses 56 days apart	2 doses 56 days apart

Intervention name	Low Dose (LD) RSVt Vaccine	Standard Dose (SD) RSVt Vaccine	High Dose (HD) RSVt Vaccine	Placebo
Route of administration	Intranasal	Intranasal	Intranasal	Intranasal
Site of administration	Each nostril	Each nostril	Each nostril	Each nostril
Sourcing	Provided by the Sponsor	Provided by the Sponsor	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.			
Current/former name or alias	Not applicable (NA)	NA	NA	NA
Storage conditions	Study interventions will be stored in a freezer at ≤ -60°C (≤ -76°F).			

Abbreviations: AxMP, auxiliary medicinal product; IMP, investigational medicinal product.

Table 11 summarized the study interventions per arm.

Table 11: Study arms

	Cohort 1			
Arm title	Group 1 (SD RSVt vaccine)	Group 2 (Control)	Group 3 (HD RSVt vaccine)	Group 4 (Control)
Arm type	Experimental	Placebo	Experimental	Placebo
Arm description	2 administrations of target [redacted] PFU	2 administrations of placebo	2 administrations of target [redacted] PFU	2 administrations of placebo

	Cohort 2			
Arm title	Group 1 (LD RSVt vaccine)	Group 2 (SD RSVt vaccine)	Group 3 (HD RSVt vaccine)	Group 4 (Control)
Arm type	Experimental	Experimental	Experimental	Placebo
Arm description	2 administrations of target [redacted] PFU	2 administrations of target [redacted] PFU	2 administrations of target [redacted] PFU	2 administrations of placebo

6.1.1 Medical Device

6.1.1.1 Intranasal administration device description

The Intranasal device kit / Nasal Spray System (NSS) is intended for intranasal use and will consist of the following components:

[redacted]

The syringe and transfer needle are commercially available medical devices in US, EU, and some additional regions globally. [redacted]

[redacted] Detailed instructions for preparation and administration using the intranasal device are provided in the Pharmacy Manual.

6.1.1.2 Risk Management and Clinical Risks and Benefits of the Medical Device

Risk management is conducted throughout the design and development process for the RSVt NSS in accordance with the process outlined in ISO 14971 Application of risk management to medical devices. System level risk analyses are performed to evaluate known and anticipated use-related risks and hazards, design risks, and assembly process risks, as appropriate based upon the configuration of the device. Following the identification of any risks, risk control measures are developed and implemented to eliminate or reduce the identified use, design, and process risks. The risk evaluation and risk control activities are iterated such that any risks that are found to be unacceptable are controlled or reduced such that the overall residual risk is acceptable in relation to the benefit of the treatment.

Nasal spray has been selected as an appropriate method for administration of the RSVt vaccine as it can be used to deliver the live attenuated vaccine rapidly, painlessly, and efficiently. This route of immunization is intended to mimic the natural route of RSV infection and thus elicit mucosal immunity in a safe and effective manner. Mucosal immunity has been shown to correlate with protection against upper and lower respiratory tract disease (31). This route of immunization is therefore key to achieving prophylaxis against RSV disease throughout the respiratory tract (LRTD and ARD).

The NSS proposed to be used in this clinical investigation is considered low-risk[redacted] Identified hazards are considered to have low severity or low probability of occurrence. No safety concerns have been observed related to the nasal spray device during prior clinical experience; however, the use of the nasal spray device may lead to minor undesirable effects or discomfort.

It is anticipated that fluid contact with the mucosal membrane will facilitate the immune response. This route of administration has been shown in previous clinical studies via spray or drops to be an effective route for live attenuated vaccine candidates (22). Furthermore, delivery into both nostrils is considered a risk mitigation to increase the likelihood of achieving an immune response should there be an obstruction in one nostril, but equivalent dosing in each nostril is not a requirement for the vaccine. [redacted]

[redacted]

Preclinical evaluation provides evidence that the NSS is designed to meet key safety and performance requirements. Initial formative human factors studies support the appropriateness of this administration method, as well as administration with the NSS from a user perspective.

There are no contraindications associated with use of the NSS. Based on the benefit-risk discussion above, it can be concluded that the benefits of using the NSS in the proposed investigation outweigh the associated risks.

6.1.1.3 Assessment of Intranasal Device

All medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 10.4) and appropriately managed by the Sponsor.

The NSS is not the subject of the clinical investigation and there are no device-related endpoints evaluated as part of the clinical investigation. The study is not intended to address or assess risks and clinical benefits of the device.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1) The investigator must confirm appropriate conditions (eg, temperature) 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, prepare, or administer study intervention.
3) The preparation of the study interventions using the NSS will be described separately.
4) 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.
5) The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
6) Further guidance and information for the final disposition of unused study interventions will be provided to the study personnel.

6.3 ASSIGNMENT TO STUDY INTERVENTION

On the day of enrollment, participants who meet all the inclusion criteria but none of the exclusion criteria and whose parent(s)/ LAR(s) sign/s the informed consent form (ICF) will be randomly assigned to a study group with their Cohort.

Cohort 1

For Groups 1 and 2, participants will be randomly assigned to Group 1 or Group 2 in a 1:1 ratio.

For Groups 3 and 4, participants will be randomly assigned to Group 3 or Group 4 in a 2:1 ratio.

Randomization will not be stratified for participants in Cohort 1.

Cohort 2

Participants will be randomly assigned to Groups 1 through 4 in a 2:2:2:1 ratio. Randomization will be stratified by study country, age group (infants/toddlers; < 12 months and ≥ 12 months), and potential RSV seropositivity (based on maternal immunization and previous receipt of RSV mAb).

Distribution of study participants will be as follows, based on age at inclusion:

- Infants (< 12 months): N=50-70%
- Toddlers (≥ 12 months): N=30-50%

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. 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 for the last 5-digit participant identifier will indicate the cohort (eg, 1 for Cohort 1, 2 for Cohort 2). The second digit for the last 5-digit participant identifier will indicate the subset (eg, 1 for [redacted] and 0 for the Main Set. For example, Participant 340000110005 is the fifth participant enrolled in Center Number 1 in Honduras (340 being the Honduras country code) of the Cohort 1 and is part of the Main Set. Other examples: Participant 340000121004 is the fourth participant enrolled in Center Number 1 in Honduras of the Cohort 2 and is part of the [redacted]. Participant 340000120124 is the one hundred twenty-fourth participant enrolled in Center Number 1 in Honduras of the Cohort 2 and is part of the Main Set.

The randomization codes will be kept securely in the IRT.

6.4 BLINDING

Description of the level of blinding

The study will be blinded to the following through the end of the study:

- Investigators and study site staff who conduct the safety assessment*, laboratory personnel, and participants' parents/LAR will not know which study intervention is administered.
- Sponsor laboratory personnel will be blinded for assays related with primary/secondary/exploratory endpoints.

The study will be unblinded for:

- Study staff preparing/administering the study interventions.

*Generally, safety data review during the study will be performed in a blinded manner by the Sponsor Safety Management Team (SMT). Safety data for Cohort 1 participants will be reviewed in an unblinded manner at the predefined time-points, involving pause of enrollment.

The Independent Data Monitoring Committee will have access to unblinded data as defined in the IDMC Charter.

Code breaking procedures in case of AE

The code may be broken by the investigator 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 participant(s) experiencing the AE.

The blind can be broken by the investigator through the IRT system. Once the emergency has been addressed by the site, the investigator must notify the Sponsor's Responsible Medical Officer (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 IEC/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 Pharmacovigilance (PV) 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[c]. 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 PV representative.

- In case of potential safety issues, as recommended by the Sponsor's safety governance or IDMC, case unblinding will be communicated to dedicated Sponsor staff for unblinded safety evaluation

An unblinded primary completion analysis will be performed on data collected up to 28 days post-dose 2 for immunogenicity and safety in all participants for each cohort. Randomization code will be broken for the sponsor, but blinding will be maintained at sites and at participants/parents level.

[c] All unexpected and related SAEs submitted to European Union competent authorities must be unblinded.

6.5 STUDY INTERVENTION COMPLIANCE

The following measures will ensure that the study intervention is administered as planned (see Table 10), 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

6.6 DOSE MODIFICATION

Not applicable.

6.7 CONTINUED ACCESS TO STUDY INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.8 TREATMENT OF OVERDOSE

Since the study intervention is administered by a health care professional, it is unlikely that overdose by administration 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 and in the CRF.

See also Section 8.4.8 for the reporting.

6.9 PRIOR AND CONCOMITANT THERAPY

Prior and concomitant therapy collected includes medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an AE) 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). 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.

Reportable medications and protocol-prohibited concomitant therapies are described hereafter. Protocol-permitted concomitant therapies are all those which are not protocol-prohibited concomitant therapies.

6.9.1 Reportable medications

The following reportable medications are defined:

- Medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, 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, any RSV monoclonal antibody, RSV immunoglobulin, or ribavirin taken before or during the study, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids).

The following medications are not to be reported: homeopathic medication, topical treatment (except topical analgesics applied at the site of study intervention), inhaled steroids, and ear treatments.

Reportable medications and vaccines will be collected in the CRF from D01 until the end of the solicited and unsolicited follow-up period after the second study vaccination from all participants.

Reason for treatment, route, dose, frequency will not be recorded in the CRF.

Medications given in response to an AE will be captured in the “Action Taken with Adverse Event” 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 WHO Drug dictionary.

6.9.2 Protocol-prohibited concomitant therapies

Protocol-prohibited therapy will lead to exclusion from the PPAS. Prohibited therapies preceding and following study vaccination are listed in Section 5.2 (E08 to E13).

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 10.1.9.

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 should still be within the timeframe for vaccination indicated in the SoA.

If the postponement occurs out of the timeframe for vaccination, the participant can continue to receive study intervention but will be excluded from the PPAS (see Section 9.2).

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: Probable or confirmed ongoing case of viral respiratory infection (including COVID-19, influenza, rhinovirus, etc.) at the time of vaccination. A prospective participant should not be vaccinated until the respiratory infection has resolved

TCI03: Receipt or planned receipt of any of the following vaccines:

- Any other intranasal live attenuated vaccine within the 28 days prior to and after study intervention administration
- Unless given on the day of study intervention administration, any other injectable live attenuated vaccines within the 28 days prior to and after concomitant receipt on the day of study intervention administration is allowed.

TCI04: Receipt of intranasal and intra-ocular medications within 3 days prior to vaccination

TCI05: Becomes a 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 vaccination
- 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

Potential close contact with other immunocompromised individual within 30 days after each vaccination as per investigator's discretion

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.

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: SAE 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 or any other vaccine, as needed, participants who receive the respective vaccine~~,~~ at any time during the study will not be withdrawn from the study. The Sponsor should be notified immediately when knowledge of such a local or national immunization program is available.

7.1.3 Other Reasons

A participant may discontinue from study intervention at any time at the participant's parent(s)/LAR(s) request, for any reason (or without providing any reason).

A participant may discontinue from study intervention at any time 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 the participant's parent(s)/LAR(s) request, for any reason (or without providing any reason).
- A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- 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 the participant's parent(s)/LAR(s) and complete all scheduled safety follow-ups, except if the participant's parent(s)/LAR(s) specified that they do not want to be contacted again and it is documented in the source document.

- If the participant's parent(s)/LAR(s) withdraw consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant's parent(s)/LAR(s) withdraw their child from the study, the participant's parent(s)/LAR(s) may request destruction of any samples taken and not tested (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. Participants' numbers will not be reassigned.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and the participant's parent(s)/LAR(s) are 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 if the participant's parent(s)/LAR(s) cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant's parent(s)/LAR(s) and reschedule the missed visit as soon as possible, counsel the participant's parent(s)/LAR(s) on the importance of maintaining the assigned visit schedule, and ascertain whether the participant's parent(s)/LAR(s) wish(es) their child to continue in the study and/or ascertain whether the participant should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator must make every effort to regain contact with the participant's parent(s)/LAR(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's parent(s)/LAR(s) last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant's parent(s)/LAR(s) continue to be unreachable, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Safety/laboratory results that could unblind the study will not be reported to sites or other blinded personnel until the study has been unblinded.

8.1 ADMINISTRATIVE AND GENERAL PROCEDURES

8.1.1 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. Growth curve should be reviewed. 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). Prior history suggestive of significant probable or confirmed RSV illness will also be documented. Participants gestational age at birth will also be captured.

8.1.2 Sample Collection

Blood, nasal, [redacted] samples will be collected as described in the SoA tables (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 10 mL (5 mL for each blood sampling or as required by local regulations), see Table 12. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 12: Blood sampling volume (mL) per visit

Visit Number(V)	V01	V05/V06
Study Timelines (Days/Months)	D01	D85
Time Windows (Days)	NA	+14
Immunogenicity assessments	5 mL	5 mL

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

8.2 EFFICACY AND IMMUNOGENICITY ASSESSMENTS

Planned timepoints for immunogenicity and vaccine virus shedding assessments are provided in the SoA tables.

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

8.2.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.2.2 Immunogenicity Assessments

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

Immunogenicity of the RSVt vaccine will be evaluated in blood/serum samples collected from participants at D01 and D85. [redacted]

8.2.2.1 Baseline Serostatus

The baseline serostatus will be determined on blood samples collected before first study intervention administration (D01; V01).

The results for the baseline serostatus will not be available at the time of the first study intervention administration and will be used for statistical analyses.

Study participants will be categorized as either RSV-naïve participants or RSV-exposed participants with the following definitions:

- RSV-Naïve participants: participants with no prior exposure to RSV infection defined as: [redacted]

- RSV-exposed participants: participants with prior exposure to RSV infection defined as:

- Otherwise, baseline serostatus will be defined as Undetermined.

Baseline blood samples may also be used as an indicator of possible receipt of RSV monoclonal antibody or maternal antibodies.

The categories will be further detailed in the SAP.

The methodology to determine baseline RSV serostatus is described in Section 8.2.2.3.

8.2.2.2 RSV A and RSV B Serum Antibody Titers

8.2.2.3 Anti-RSV F IgA, anti-RSV F IgG, and anti-RSV G IgG Serum Antibody levels

[redacted]

8.2.3 Vaccine Virus Shedding

Shedding of the attenuated RSV vaccine strain will be evaluated in nasal samples collected from planned visits (D08 and D64). [redacted]

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.4.

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

8.3.1 Physical Examinations

At Visit 1 and Visit 3 (main set)/[redacted] the investigator will perform a clinical or medically-driven physical examination, including but not limited to a cardiopulmonary exam [redacted]. Information will be recorded in the source document.

8.3.2 Vital Signs

Axillary pre-vaccination body temperature will be collected by the investigator on the source document during vaccination visits (ie, V01 and V03 [main set]/[redacted]
Tympanic, skin, and temporal artery thermometers must not be used. [redacted]
[redacted], vital signs will be collected in the CRF.

8.3.3 Clinical Safety Laboratory Tests

There are no laboratory tests planned in this study as part of clinical safety.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded in the CRF for safety purposes but will not be part of the clinical database.

8.3.4 Viremia/Vaccinemia

Vaccine viral shedding will be assessed as described in Section 8.2.3.

8.4 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' parent(s) / LAR(s) to the investigator, then by the investigator to the Sponsor.

The investigator is 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 or study (see Section 7). This includes events reported by the participants' parent(s) / LAR(s).

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.

8.4.1 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 administration site reactions include:



Solicited systemic 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 include:



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

Unsolicited Non-serious Adverse Events

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

The intensity grading scale for unsolicited non-serious adverse events is presented in Appendix 10.2.5.3.

Medically Attended Adverse Events (MAAEs)

MAAEs will be collected from D01 to the end of the study.

Adverse Events of Special Interest (AESIs)

AESIs will be collected from D01 to the end of the study.

See Section 8.4.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from inclusion until the end of the study. However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the CRF (eg, SAEs related to blood sampling).

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 the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

Individual participant diaries, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants' parent(s) / LAR(s) for the recording of daily safety information. These participant diaries 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' parent(s) / LAR(s) will also be provided standard digital thermometers for measuring daily body temperatures. To ensure consistency of reporting, the study sites will instruct participants' parent(s) / LAR(s) on how to correctly use these tools.

At specified intervals, the investigator will interview the participants' parent(s) / LAR(s) to collect the information recorded in the participant diary, 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 using a web-based CRF. Any information that was not documented in the participant diary will first be captured in the source document and then reported electronically.

The 6-month safety 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' parent(s) / LAR(s) either during a visit or over the telephone using a questionnaire to capture SAEs, AESIs, and MAAEs, 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.

8.4.3 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 participants' parent(s) / LAR(s) refuse/s 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 AESIs (as defined in Section 8.4.6), 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 and related AESIs 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.

8.4.4 Regulatory Reporting Requirements for SAEs and Other Safety Reporting

- 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/or other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with international/regional and country-specific regulatory

requirements relating to safety reporting to the regulatory authority, Independent Ethics Committees (IEC)/Institutional Review Boards (IRB), and investigators.

- An investigator who receives an investigator safety report describing an 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 IEC/IRB, 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.

For the European Union, safety reporting to the agency is described in Section 10.5.1.1.

8.4.5 Pregnancy

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

8.4.6 Adverse Events of Special Interest

The following AESIs will be collected:

[redacted]

A diagnosis of an AESI will be reported to the Sponsor in an expedited manner similar to that for an SAE. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the participant's CRF.

The definitions and intensity grading scales for the AESIs are presented in Appendix 10.2.5.3.

8.4.7 Medically Attended Adverse Events

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

8.4.8 Medication Errors, Misuses or Abuses of Medicinal Product

Definitions of medication error, misuse or abuse can be found in Appendix 10.3.

Since the study intervention*s* are administered by a health care professional, misuse and abuse are not applicable in this study. Medication errors will be recorded in the PV database.

8.4.9 Medical Device Deficiencies

Medical devices are being provided for use in this study as study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 10.4.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Appendix 10.4 of the protocol.

8.4.9.1 Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 10.4.

8.4.9.2 Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.9.3 Prompt Reporting of Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the Sponsor by the Product Technical Complaint (PTC) form completed in the Pharmacy Manual.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.4.9.4 Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal

responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

The investigator will retain medical devices subject to a complaint/deficiency for return to Sponsor for investigation.

8.4.10 Safety Surveillance by the Sponsor

8.4.10.1 Early Safety Data Review

The safety of the RSVt vaccine will be continuously monitored by the Sponsor. All safety data collected will be summarized and reviewed by the Sponsor's internal SMT.

To allow for a cautious, stepwise approach to vaccine administration in preterm participants (Cohort 1), an unblinded early safety data review (ESDR) will be performed for participants of Groups 1 and 2 (ie, Step 1, ESDR1). This safety review is planned when [redacted] participants of Groups 1 and 2 have been vaccinated and have provided safety data for [redacted] vaccination. Enrollment for Groups 3 and 4 in Cohort 1 will not begin until a positive outcome of the ESDR1 by the Sponsor's SMT, see below for Go/No Go criteria.

Prematurely born children will be allowed in Cohort 2 following an unblinded SMT review - ESDR2 - of the HD safety data (Groups 3 and 4), [redacted]vaccination in Cohort 1 participants and[redacted] SD vaccination of Groups 1 and 2, Cohort 1 participants. For the purposes of ESDR2 and the review of HD data versus Placebo, safety data[redacted] [redacted]accination for Group 4 will be pooled with [redacted]

Enrollment of Cohort 1 participants will be paused during ESDR1 and ESDR2, yet dosing of the subsequent dose for already enrolled participants will continue.

For Cohort 2, periodic and pre-planned blinded safety review meetings, will be performed by the Sponsor's SMT, see Section 10.1.5.

8.4.10.1.1 Go / No Go Criteria for Dose Escalation in Cohort 1 and Transition of Cohort 1 to Cohort 2

[redacted]

The outcome of each ESDR will be determined by the SMT and, if needed, decision-making will be escalated to the appropriate Sponsor Safety Oversight Committee.

8.4.10.2 Alert Thresholds

Ongoing and Periodic Safety Data Review

Alert Thresholds applicable to Cohort 1 and Cohort 2

Data will be reviewed on an ongoing and periodic basis by the Sponsor for the identification of the following events:

[redacted]

Alert thresholds linked to individual events will trigger ad-hoc reviews of the safety data.

If any of the above criteria are met, a decision based on the SMT recommendation will be made as to whether enrollment in Cohort 1 and Cohort 2 needs to be paused, or whether any modification of the study is needed.

8.4.10.3 Pausing Rules

At any time during the recruitment period, enrollment will be paused, and data reviewed, if the following events are observed:

- Any deaths within 3 days of vaccine administration, regardless of causal relationship
- Any deaths related to the investigational product
- Any AE which, in the opinion of the investigator and Sponsor, indicates that human participants would be exposed to an unreasonable and significant risk of illness or injury.

If any of the above criteria is met, a decision based on benefit/risk-based decision will be made by the Sponsor as to whether enrollment in the study will be allowed to resume or any study modifications will be needed.

Case unblinding may be performed for the above safety reviews, if necessary.

8.5 PHARMACOKINETICS

Pharmacokinetics parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamics parameters are not evaluated in this study.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

No other biomarkers than those described in the immunogenicity assessments section (Section 8.2.2) are evaluated in this study.

8.9 IMMUNOGENICITY ASSESSMENTS

See Section 8.2.2.

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

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

8.11 LEFTOVER BIOLOGICAL SAMPLES

Any unused part of the biological samples collected for this study (blood, nasal, [redacted] samples) are being retained in long-term storage (for up to 25 years after the end of the study or as required by local regulations) 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. Relating data will be stored for up to 25 years or as required by local regulations.

Any other biological samples collected to monitor the participants' 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.

8.12 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) collected as part of the study 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 codeveloping 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 study data may be shared.

Coded study data and biological samples will be stored and used for future research only when consented to by participants / participants' parent(s) / LAR(s) (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participants' parent(s) / LAR(s), unless prohibited by local laws or IECs/IRBs (in such case, consent for future use of data/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' parent(s) / LAR(s) will be provided with all mandatory details of the data processing in the ICF. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Study participant data for future research will be stored for up to 25 years after the end of the study.

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.

The study participants' parent(s) / LAR(s) will be provided with all mandatory details of the use of the human biological samples (leftover) in the ICF.

Biological samples for future research will be stored for up to 25 years after the end of the study unless local regulations require a different retention period.

Any samples remaining at the end of the retention period will be destroyed. If participants or participants' parent(s) / LAR(s) request destruction of the 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 at the latest prior to the first statistical analysis 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 secondary endpoints.

9.1 STATISTICAL HYPOTHESES

Primary Immunogenicity Objective

Twenty-eight days after the second administration of the RSVt vaccine to participants in Cohort 2, the geometric mean titers (GMTs) of neutralizing RSV (A and B) antibodies of the LD RSVt group will be compared to SD RSVt group. The following hypotheses will be tested for each RSV antibody:

$$H_0 : \text{GMT(rsv, LD)/GMT(rsv, SD)} \leq 2/3$$
$$H_1 : \text{GMT(rsv, LD)/GMT(rsv, SD)} > 2/3$$

where GMT(rsv, LD) and GMT(rsv, SD) are GMTs of RSV antibodies (A and B) in LD RSVt and SD RSVt from Cohort 2, respectively.

If the lower limit of the 2-sided 95% CI of the ratio of the GMTs between LD RSVt and SD RSVt groups is > 2/3 for both neutralizing RSV antibodies (A and B), the inferiority null-hypothesis will be rejected and non-inferiority (NI) of LD RSVt compared to SD RSVt will be demonstrated.

9.1.1 Multiplicity Adjustment

Each of the anti-RSV antibodies (A and B) will be tested separately for primary immunogenicity objective. No multiplicity adjustment will be performed.

9.2 ANALYSIS SETS

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

Analysis Set	Description
Randomized	Participants for whom a study intervention group has been allocated.
Safety Analysis Set (SafAS)	Participants who have received at least one administration of the study intervention. All participants will have their safety analyzed after each administration according to the study intervention they actually received, and after any vaccination according to the study intervention received at the 1st administration of the study intervention. 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 participants who received at least 1 administration of the study intervention. Participants will be analyzed according to the intervention to which they were randomized.

Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: [redacted]

9.3 STATISTICAL ANALYSES

9.3.1 General Considerations

All endpoints will be summarized at each timepoint by study intervention group (and overall for baseline and demographics characteristics). For the analysis of cohort 1, group 2 and group 4 (ie, placebo groups) may be pooled. Results will be presented separately for each cohort.

The statistical methodology will be based on the use of 2-sided 95% CIs.

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 (35).

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 calculation for normal distribution. Then, antilog transformations will be applied to the results of calculations, to compute GMTs and GMTRs and their 95% CIs.

The immunogenicity analyses on primary endpoints will be performed on the PPAS and will be confirmed on the FAS.

For other immunogenicity endpoints, analyses will be performed on the PPAS and may be confirmed on the FAS if the difference between the number of participants in the PPAS and the number of participants in the FAS is not less than 10%.

Vaccine virus shedding and safety analyses will be performed on the Safety Analysis Set (SafAS).

9.3.2 Primary Objectives Analysis

Immunogenicity

The 2-sided 95% CIs of the ratio of GMTs between LD RSVt group and SD RSVt group from Cohort 2 will be calculated assuming that log10 transformation of the titers follows a normal distribution. If the lower limits of the 2-sided 95% CIs are greater than 2/3 for both RSV A and RSV B antibodies, the inferiority null hypothesis will be rejected.

The primary estimand (Estimand 1) defined for the primary immunogenicity objective is presented in Section 3, Table 6.

The primary objective will be evaluated on the FAS as supplementary supportive analysis, with any relevant intercurrent events handled according to Treatment Policy Strategy; the missing data handling rule is the same as for the primary estimand.

Safety

Solicited adverse reactions (ARs), unsolicited AEs, SAEs, MAAEs and AESIs will be summarized. The main parameters will be described by study intervention group after each and any study intervention administration with the 95% CIs of point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions. At least the following parameters will be summarized:

- Unsolicited systemic AEs occurring within 30 minutes of administration (immediate unsolicited AEs)
- Solicited administration site reactions and solicited systemic reactions within 21 days after each / any administration according to occurrence, time to onset, intensity, number of days of occurrence, action taken, and whether the reaction led to early termination from the study
- Unsolicited AEs occurring within 28 days after each / any administration by system organ class (SOC) and preferred term (PT), relationship, intensity, time to onset, duration and whether the AE led to early termination from the study
- All SAEs that occur within 28 days and throughout the study after each / any administration by SOC and PT, seriousness criteria, time to onset, outcome, relationship, and whether the SAE led to early termination
- All MAAEs and AESIs that occur within 28 days and throughout the study after each / any administration by SOC and PT and relationship

9.3.3 Secondary Objectives Analysis

Immunogenicity

Distribution of baseline serostatus (D01) will be described with 95% CIs.

Immunogenicity endpoints will be summarized at each timepoint by study intervention group with 95% CIs, overall and by baseline serostatus.

The 95% CIs for the Geometric Mean Titers (GMTs) and GMT ratios (GMTRs) will be calculated using a normal approximation of log10-transformed titers.

Percentage of participants with a ≥ 4-fold rise in RSV serum neutralizing antibody titers post vaccination 2 (D85) relative to baseline (D01) will be described with 95% CIs.

The 95% CIs for the proportions will be based on the Clopper-Pearson method.

Vaccine Virus Shedding

Presence of vaccine virus detected in D08 and D64 nasal samples and titer distribution of vaccine virus shedding, will be summarized for all participants by study intervention group with 95% CIs.

9.3.4 Exploratory Objective Analysis

[redacted]

9.3.5 Other Analysis

Immunogenicity and safety main endpoints will be described by subgroups such as countries, age groups, baseline serostatus, and other demographic subgroups.

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

9.4 SEQUENCE OF ANALYSES

An unblinded primary completion analysis will be performed on data collected up to 28 days post-dose 2 for immunogenicity and safety in all participants for each cohort. Randomization code will be broken for the sponsor, but blinding will be maintained at sites and at participants/parents level.

9.5 SAMPLE SIZE DETERMINATION

[redacted]

Table 13: [redacted]

[redacted]

[redacted]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Note: The term "participant" is used throughout this protocol and in the participant diary. 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. In addition, the term "investigator" is used throughout this protocol, however some tasks can be delegated to a designee according to local regulations.

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 the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines

  Applicable ICH Good Clinical Practice (GCP) guidelines

  The General Data Protection Regulation (GDPR) and any other applicable data protection laws

  Any other laws and regulations as applicable, eg:

  The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use 21 CFR

- The protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IEC/IRB by the investigator or the Sponsor (according to local regulations) and reviewed and approved by the IEC/IRB before the study is initiated
- Any amendments to the protocol will require IEC/IRB 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, as applicable:

  Providing written summaries of the status of the study to the IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB in addition to summaries required from the Sponsor.

  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 participants (and/or their 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 IEC/IRB of SAEs or other significant safety findings as required by IEC/IRB procedures

- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IEC/IRB, and if applicable, 21 CFR, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical study Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical study regulation that is likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

The Sponsor shall ensure that all parties involved in the conduct of the clinical study promptly report any events that might meet the definition of a serious breach.

Therefore, investigators shall, within 48 hours after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal investigator must have a process in place to ensure that the site staff or service providers engaged by the principal investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious

breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The ICF will be provided to the study participant in paper version. When feasible, an eConsent process may be used at global level and/or locally if permitted by country regulations.
- The investigator or the investigator's representative will explain the nature of the study, including the potential risks and benefits, to the participants' parents / LARs and answer all questions regarding the study, including what happens to the participants when their participation ends (post-study access strategy for the study).
- Potential participants' parents / LARs must be informed that their child participation is voluntary. Participants' parents / LARs 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.
- 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 participants' parents / LARs willingness to let their child continue participation in the study, this will be communicated to them in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- Participants 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' parents / LARs 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 participants' parents / LARs.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 5 days from the previous ICF signature date.

The core ICF contains 2 separate sections that address the use for research of participants' data and/or samples (remaining mandatory ones) Future research is to be defined in the core ICF Part 2. Each option is subject to an independent consent and must be confirmed by ticking checkboxes in the core 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 will explain to each participant why data and samples are important for future research. Participants 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.

Rationale for Including Participants Unable to Give Consent

See Section 2.1 for the rationale for conducting this study in the pediatric population.

Study VAD00015 will be conducted in children 6 months to < 22 months of age. Since these participants are unable to give their consent, written informed consent must be obtained from the parent or LAR in accordance with local practices before participation in the study and before any study-related procedure is done. The parent or LAR should be able to consent for their child. The child of minor parents must not be included in the study.

Recruitment Procedures

Participants may be recruited from the general population. 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.

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 US Food Drug Administration or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- 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, when applicable, 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.
- Participants' parents / LARs must be informed that their children 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 participants' parents / LARs as described in the informed consent.

- Participants' parents / LARs must be informed that their children medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.
- The contract between Sponsor, investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of participants concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants' parents / LARs must be informed that their children 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 personal 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 25 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 at once 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 request the 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 - 46 Avenue de la Grande Armée - 75017 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

An IDMC will be appointed for this study. The IDMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for harms or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. The membership composition, specific responsibilities of members, timing of reviews, objectives for review, and decision criteria will be documented in the IDMC Charter.

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, 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 and Results

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 studies and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical study disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult studies, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical study worldwide (ie, the last active, participating country).

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

Individual anonymized 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 studies. 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 product 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 either recorded on CRFs (reported by the investigator or integrated [eg, from electronic participant diary]), or 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, IEC/IRB 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 the safety of participants 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 different 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, participant diary, 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.

- The Sponsor or designee will perform monitoring 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 IEC/IRB 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, or more severe than expected for the participant's condition) eg, leading to IMP discontinuation or modification of dosing, and/or fulfilling a seriousness criterion • 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. • Signs, symptoms, or the clinical sequelae of any medication errors with the IMP

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/administration 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 or vomiting 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 site reactions or solicited systemic reactions

Injection / 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 telephone 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

The following SAE definition is in compliance with the full definition of an SAE and includes all the key criteria as defined in ICH E2A and ICH E2D. Some criteria may not apply to all study populations.

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 authorized medicinal product.

The program-specific AESIs of [redacted] will be reported in a manner similar to that for an SAE. AESIs can also be reported as SAEs if they meet any of the seriousness criteria.

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 IMP 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 (IMP) will usually be assessed by the investigator only.

  For SAEs and non-serious AESIs, relationship to study intervention (IMP) will be assessed by both the investigator and the Sponsor (except for injection site reactions at the site of IMP injection which will be related to IMP by default). Sponsor assessment is entered in the PV 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 PV database only.

- The investigator is obliged to 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) and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

  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.
- For causal relationship assessment, the investigator will also consult the IB and/or Product Information, for marketed products.
- The investigator must review and provide an assessment of causal relationship for each unsolicited AE/SAE and document this in the medical notes. 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 investigators may change their 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: [redacted]

- Mailbox:

In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted]

Using a Verbal Autopsy Questionnaire to Aid in Determining the Cause of Death

- In case of the absence or inadequacy of health information that would allow a thorough evaluation of the causes of the death of a study participant, the verbal autopsy procedure may be triggered by either the investigator or the Sponsor. Detailed instructions on the use of the verbal autopsy questionnaire, as well as the questionnaire itself, will be provided separately.

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 PV Department.

In case of emergency code-breaking, the investigator is required to follow the code-breaking procedures described in Section 6.4.

10.2.5 Assessment of Intensity

The investigator will assess 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 Intensity Grading Scales for Clinical Abnormalities

10.2.5.1.1 Solicited AR Intensity Grading Scale

Table 14: Solicited administration site reactions: terminology, definitions, and intensity scales – Infants and toddlers aged < 24 months

CRF term (MedDRA lowest level term [LLT])	[redacted]
Participant diary term	
Definition	
CRF and Participant diary intensity scale*	

* For measurable reactions of [redacted], the scale will be provided in the CRF and the intensity will be transcribed from the participant diary.

Table 15: Solicited systemic reactions: terminology, definitions, and intensity scales – Infants and toddlers aged < 24 months

CRF term (MedDRA lowest level term [LLT])	[redacted]
Participant diary term	
Definition	
CRF and Participant diary intensity scale*	

* For all reactions ([redacted]), the scale will be provided in the participant diary and the intensity will be transcribed in the CRF. [redacted]

Important notes for the accurate assessment of body temperature:

Participants' parents / LARs 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 preferred unit for this study is Celsius. The optimal time for measurement is the evening, when body temperature is the highest. Body temperature is also to be measured at the time of any apparent fever. The observed daily body temperature and the route of measurement are to be recorded in the participant diary / memory aid, and the highest body temperature will be recorded by the site in the CRF. The preferred route for this study is axillary.

10.2.5.2 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:

- Grade 1: No interference with activity.
- Grade 2: Some interference with activity and not requiring therapeutic medical intervention
- Grade 3: Prevents daily activity and requires therapeutic medical intervention

10.2.5.3 AESIs Definitions and Grading Scale

[redacted]

[redacted]

10.3 APPENDIX: MEDICATION ERRORS, MISUSES OR ABUSES OF MEDICINAL PRODUCT

All reports of medication error, misuse or abuse in relation to the IMP with or without an AE must be collected and transmitted to the PV database following standard processes. The Investigator will assess whether or not the medication error, misuse or abuse event has to be reported together with an AE or SAE.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant. This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, “getting high” (euphoria).

10.4 APPENDIX: MEDICAL DEVICE ADVERSE EVENTS (AES), ADVERSE DEVICE EFFECTS (ADES), SERIOUS ADVERSE EVENTS (SAES) AND DEVICE DEFICIENCIES: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research.
- Both the investigator and the Sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of Sponsor medical devices.

10.4.1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. 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 an

investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.4.2 Definition of Medical Device SAE, SADE and USADE

The definitions of Medical Device SAE are the same as those provided in Section 10.2.2 for the study intervention.

SADE definition

- A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.
- Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

10.4.3 Definition of Device Deficiency

- A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.4.4 Recording and Follow-Up of Medical Device AE and/or SAE and Device Deficiencies

Medical Device AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency 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/device deficiency information in the participant's medical records, along with any corrective actions that were necessary, in accordance with the investigator's normal clinical practice and on the appropriate form.

- 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 AE/SAE/device deficiency form.
- 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.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
    - The Sponsor will evaluate all device deficiencies along with the device manufacturer as appropriate to determine and implement corrective or preventative actions required to prevent recurrence of the reported device deficiencies.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE reported during the study and assign it to one of the categories described in Section 10.2.5.2.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- 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, as part of the assessment.
- For each AE/SAE/device deficiency, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- 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 assesses causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
    - The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Medical Device AE/SAE and device deficiency

- 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 causality of the AE/SAE/device deficiency 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, 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 completed form.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.4.5 Reporting of Medical Device SAEs

Medical Device 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 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 offline 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 offline, then the site can report this information on a paper SAE form or to the Sponsor/medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the investigator site file.

10.4.6 Reporting of SADEs

SADE Reporting to the Sponsor

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE or a SADE not associated with a device deficiency must be reported to the Sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The Sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IECs/IRBs as required by national regulations.
- Contacts for SAE reporting can be found in the investigator site file.

10.5 APPENDIX: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.5.1 European Union

10.5.1.1 Safety Reporting to the Agency

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs (suspected serious adverse reactions which are unexpected as per reference safety information section of the IB) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines (electronic submission).

10.6 APPENDIX: COLLECTION, STORAGE, AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.6.1 Compliance with Member State Applicable Rules for the Collection, Storage and Future Use of Human Biological Samples (Article 7.1h) of EU Regulation 536/2014

This appendix is provided separately.

10.6.2 Compliance with Member State Applicable Rules for the Collection, Storage and Future Use of (Personal) Data (Article 7.1d) of EU Regulation 536/2014

This appendix is provided separately.

10.7 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.

10.8 APPENDIX: PROTOCOL AMENDMENT HISTORY

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

The main reason for updating protocol version 2.0 to protocol version 3.0 was to increase the number of participants to be enrolled to the high-dose RSVt group in Cohort 2 to provide a better understanding of the reactogenicity and safety profile for this dose.

The main reason for updating protocol version 3.0 to protocol version 4.0 was to incorporate comments received from the European Medicines Agency. However, the EU CTA was withdrawn, and this protocol version was never submitted.

The main reasons for updating protocol version 3.0 to protocol version 5.0 (Amendment 1) were to clarify an exclusion criterion and include additional instructions for medical history, physical examinations, and vital signs.

The main reason for updating protocol version 5.0 (Amendment 1) to protocol version 6.0 (Amendment 2) was to add an additional potential risk including risk mitigation and management.

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12 SPONSOR SIGNATURE PAGE

Signature Page for VV-CLIN-0656773 v7.0
vad00015-protocol

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