# Safety, Immunogenicity, Infectivity, and Dose-Finding Study of an Investigational Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccine in Infants and Toddlers

Phase I/II, randomized, observer-blind, placebo-controlled, multi-center, dose-finding study to evaluate the safety, immunogenicity, infectivity, and vaccine virus shedding after 1 and 2 administrations of the live-attenuated Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L vaccine in infants and toddlers 6 to 18 months of age in the United States, Canada, Latin America, and South Africa

# Clinical Study Protocol, Amendment 5

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| **Health Authority File Number(s):** | BB-IND #: IND #22050 |
| **WHO Universal Trial Number (UTN):** | U1111-1238-1869 |
| Study Code: | VAD00001 |
| **Development Phase:** | Phase I/II |
| **Sponsor:** | Sanofi Pasteur Inc.<br>Discovery Drive, Swiftwater, PA 18370-0187, USA |
| **Investigational Product(s):** | Live-Attenuated Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L vaccine |
| **Form / Route:** | Suspension of virus / Intranasal |
| **Indication For This Study:** | Active immunization of infants and toddlers 6 to 18 months of age for the prevention of medically attended lower respiratory tract illness |
| **Manufacturer:** | Same as Sponsor |
| **Coordinating Investigators** | Not Applicable<br>This is a multi-center study with multiple investigators. Investigators and study sites are listed in the "List of Investigators and Centers Involved in the Trial" document. |
| **Sponsor's Responsible Medical Officer:** | [redacted] |
| **Local Medical Officer / Clinical Team Leader / Medical Team Leader** | |

**Global Safety Officer:** [redacted]

**Clinical Study Manager:**

**Version and Date of the Protocol:** Version 9.0 dated 19 January 2023

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# History of Protocol Versions

| Version | Date | Comments |
|---|---|---|
| 1.0 | 24 February 2020 | Version not approved by the IEC/IRB |
| 2.0 | 04 May 2020 | IEC/IRB-approved version not used in the study |
| **3.0** | 27 July 2020 | Original study protocol (first version used in the study) |
| 4.0 | 29 September 2020 | Amendment 1 |
| **5.0** | 06 November 2020 | Amendment 2 |
| **6.0** | 24 September 2021 | Amendment 3 |
| **7.0** | 08 December 2021 | Amendment 4 |
| 8.0 | 09 January 2023 | Version not used in the study |

* Versions in bold font have been approved by the Independent Ethics Committee(s) (IEC[s]) / Institutional Review Board(s) (IRB[s]) and used in the study.

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# Synopsis

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| **Company:** | Sanofi Pasteur |
| **Investigational Product:** | Live-Attenuated Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L vaccine |
| **Active Substance(s):** | Live-attenuated RSV with (i) a 523 nucleotide (nt) deletion of the NS2 gene (ΔNS2), (ii) an amino acid deletion in the L protein (Δ1313; deletion of S1313), and (iii) genetically stabilizing mutation in the L gene (I1314L) (RSVΔ NS2/Δ1313/I1314L) |
| **Title of the Study:** | Safety, Immunogenicity, Infectivity, and Dose-Finding Study of an Investigational Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccine in Infants and Toddlers |
| **Development Phase:** | Phase I/II |
| **Coordinating Investigator:** | Not Applicable |
| **Study Sites:** | This will be a multi-center, multinational study including approximately 30 sites in the United States (US), approximately 2 sites in Canada, approximately 6 sites in Latin America (Argentina, Chile, and Honduras), and approximately 2 sites in South Africa. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document. |
| **Planned Study Period:** | Q3 2020 to Q2 2023 |
| **Study Design, Schedule of Study Procedures, and Methodology:** | Phase I/II, randomized, observer-blind, placebo-controlled, multi-center, dose-finding study to evaluate the safety, immunogenicity, infectivity, and vaccine virus shedding after 1 or 2 administrations of a live-attenuated RSV ΔNS2/Δ1313/I1314L vaccine in infants and toddlers 6 months to 18 months (Cohorts 1 to 4) of age in the United States, Canada, Latin America (Argentina, Chile, and Honduras), and South Africa.<br>**Vaccination:**<br>A total of 300 infants and toddlers 6 to18 months of age will be enrolled into 1 of 4 cohorts, sequentially, and within each cohort will be randomized to receive intranasal administration of their assigned study product as follows.<br>• Cohort 1 – 40 infants and toddlers to receive 1 administration, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose) or placebo (same formulation buffer as the RSV ΔNS2/Δ1313/I1314L vaccine)<br>• Cohort 2 – 40 infants and toddlers to receive 2 administrations, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose) or placebo<br>• Cohort 3 – 40 infants and toddlers to receive 1 administration, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (high-dose) or placebo<br>• Cohort 4 – 180 infants and toddlers to receive 2 administrations, 1:1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose), RSV ΔNS2/Δ1313/I1314L [redacted] (high-dose) or placebo.<br>**Cohort 1 (Northern Hemisphere):**<br>1:1 randomized, placebo-controlled, 1 dose of RSV ΔNS2/Δ1313/I1314L ([redacted]), 1 administration ([redacted] in total per administration) at Day (D) 0, n=20 per vaccine group. Participant enrollment will be initiated at |

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| | approximately 15 sites in the US in August/September 2020. Vaccine administration will be completed at least 5 days before the beginning of RSV season (the average 5-month RSV season in the northern hemisphere is 01 November to 31 March). If recruitment in Cohort 1 does not reach the goal of n=40, no attempt will be made to include more participants in subsequent cohorts.<br>**Cohort 2 (Southern Hemisphere):**<br>1:1 randomized, placebo-controlled, 1 dose of RSV ΔNS2/Δ1313/I1314L ([redacted]), 2 administrations ([redacted] in total per administration) at D0 and D56, n=20 per vaccine group. Participant enrollment will be initiated at approximately 4 sites in Latin America (Argentina and Chile) at the earliest in November/December 2020. The first and the second vaccine administrations (D0 and D56, respectively) will be completed at least 5 days before the beginning of the RSV season (the average 5-month RSV season in the southern hemisphere is 01 May to 30 September). If recruitment in Cohort 1 does not reach the goal of n=40, no attempt will be made to include more participants in subsequent cohorts.<br>**Cohort 3 (Northern Hemisphere):**<br>1:1 randomized, placebo-controlled, 1 dose of RSV ΔNS2/Δ1313/I1314L ([redacted]), 1 administration ([redacted] per administration in total) at D0, n=20 per vaccine group. Participant enrollment will be initiated at approximately 30 sites in the US in April 2021. Vaccine administrations will be completed before 31 May 2021 If recruitment in Cohort 1 does not reach the goal of n=40, no attempt will be made to include more participants in subsequent cohorts.<br>**Cohort 4 (Northern and Southern Hemisphere)**<br>1:1:1 randomized, placebo-controlled, 2 doses of RSV ΔNS2/Δ1313/I1314L ([redacted]), 2 administrations ([redacted] per administration in total) at D0 and D56, n=60 per vaccine group.<br>Participant enrollment will be initiated at approximately 30 sites in the US at the earliest in June 2021, approximately 2 sites in Canada at the earliest in May 2022, approximately 2 sites in Chile at the earliest in November 2021, approximately 2 sites in Honduras, at the earliest in April 2022, and approximately 2 sites in South Africa, at the earliest in June 2022. The first and the second vaccine administrations (D0 and D56, respectively) will be completed at any time of the year, including during the winter RSV season, regardless if normal RSV seasonality is restored after the disruption due to COVID-19 nonpharmaceutical interventions.<br><br>**<u>Blood Sampling:</u>**<br>All participants screened for inclusion in Cohorts 1, 2, 3 and 4 will provide a blood sample at enrollment (Visit 01) for baseline RSV serum antibody testing.<br>All participants in each vaccine group in Cohorts 1, 2, 3 and 4 will provide a blood sample at the D56 Visit (before the second vaccine administration for Cohorts 2 and 4), for the measurement of post-vaccination 1 serum antibody titers to RSV.<br>All participants in each vaccine group in Cohorts 2 and 4 will provide a blood sample at the D84 visit (28 days post-vaccination 2) for the measurement of post-vaccination 2 serum antibody titers to RSV. |

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| | All participants in Cohorts 1, 2, 3 and 4 will provide a blood sample during the month following the end of RSV season or at least 5 months after the last vaccine administration for the measurement of post-season RSV antibody titers, to determine if a 4-fold or greater rise in RSV antibody titers has occurred during the RSV season, indicating infection with wild-type (wt) RSV that was not detected by surveillance.<br>**Nasal swab samples:**<br>Nasal swab samples will be collected in all participants at D7 for Cohorts 1, 2, 3 and 4; and on D63 for Cohorts 2 and 4 for the following:<br>• Quantification of vaccine virus shedding on D7 for Cohorts 1, 2, 3 and 4 and D63 for Cohorts 2 and 4.<br>• The same nasal swab specimens will be tested for respiratory pathogens if the child is ill at the same time points (D7 for Cohorts 1, 2, 3 and 4 and D63 for Cohorts 2 and 4).<br>• A nasal swab specimen for the detection of RSV and respiratory pathogens will be collected from participants during illness visits and 48 h later at any other protocol specified time point in the study including the medically attended surveillance during the RSV season.<br>**Collection of Safety Data:**<br>The Acute Phase for the first vaccine administration begins on D0 post-vaccination and ends at midnight on D28. The Acute Phase for the second vaccine administration begins on D56 post-vaccination and ends at midnight on D84. Any adverse reactions, AEs, AESIs, MAAEs, or SAEs that begin within the Acute Phase (i.e. within 28 days after a vaccination) but are diagnosed by a medical professional after 28 days will still be considered as occurring within the Acute Phase.<br>The Post-Acute Phase for participants receiving 1 administration begins at 12:01am on D29 and ends at midnight on D56. The first Post-Acute Phase for participants receiving 2 administrations begins at 12:01am on D29 and ends at midnight on D56, except if second administration is exactly on D56 when it ends immediately before receipt of the second administration. The second Post-Acute Phase for participants receiving 2 administrations begins at 12:01am on D85 and ends at midnight on D112.<br>All participants will be observed for 30 minutes after each vaccine administration and any unsolicited systemic adverse events (AEs) occurring at that time will be recorded as immediate unsolicited systemic AEs in the case report book (CRB).<br>All participants will be followed for solicited administration site reactions and systemic reactions, unsolicited adverse events, adverse events of special interest (AESIs) and medically attended adverse events (MAAEs) within 28 days after each and any vaccination, and from vaccination to the end of study participation for serious adverse events (SAEs).<br>The participant's parent / guardian / legally authorized representative will record information in a Diary Card (DC) / Electronic Diary Card (eDC) to capture solicited reactions, unsolicited AEs, AESIs and MAAEs from D0 to D28 for Cohorts 1, 2, 3 and 4 and D56 to D84 for Cohorts 2 and 4. Parents / guardians / legally authorized representatives should alert the study site regarding reactions, AEs and any symptoms suggestive of respiratory tract illness. The study sites will follow up via phone calls. The eDC allows daily safety monitoring of the study participant also. In certain cases, when an |

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| | eDC cannot be used, a paper diary card will be used for daily safety monitoring. All solicited reactions will be graded by the Sanofi Pasteur Intensity scale, except for runny nose/rhinorrhea and stuffy or blocked nose/nasal congestion which will be graded by the Division of AIDS (DAIDS) scale. Adverse events of special interest will be graded by the DAIDS scale, except for wheeze, which will be graded according to Brighton Collaboration specifications.<br><br>Based on previous National Institutes of Health (NIH) clinical experience with live-attenuated RSV vaccine candidates and Sanofi Pasteur Safety Guideline Standard Practice for the Collection, Analysis, and Reporting of Safety Data, the following predefined solicited reactions will be assessed during the Acute Phase for each vaccine administration:<br><br>• Administration site reactions<br>  - Runny nose<br>  - Stuffy or blocked nose / nasal congestion<br>• Systemic reactions<br>  - Fever<br>  - Vomiting<br>  - Crying abnormally<br>  - Drowsiness<br>  - Appetite loss<br>  - Irritability<br><br>The following AESIs will be assessed during the Acute Phases of the study:<br><br>• Acute otitis media<br>• Upper respiratory tract illness (URI)<br>  - Pharyngitis<br>  - Cough without LRI<br>• Lower respiratory tract illness (LRI)<br>  - Stridor<br>  - Rales<br>  - Tachypnea<br>  - Acute wheeze<br>  - Pneumonia<br>  - Laryngotracheobronchitis<br>• Immediate hypersensitivity reactions including urticaria, anaphylaxis, or other immunoglobulin (Ig) E-mediated responses are possible as with any vaccine.<br>• MAAEs will be collected during the Acute Phase for either vaccination using the same process as other AEs.<br>• SAEs will be recorded throughout the participant's participation in the study. The participant's parent / guardian / legally authorized |

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| | representative will be asked to notify the site immediately about any potential SAE at any time during the study. In addition, the participant's parent / guardian / legally authorized representative will record information in a DC / eDC about SAEs from the D0 to D56 visits (Cohorts 1 and 3), and from D0 to D84 visits (Cohorts 2 and 4). Participant's parent / guardian / legally authorized representative will receive a memory aid (MA) to record the SAEs from the D56 visit until the end of the study (Cohorts 1 and 3) and from the D84 visit until the end of the study (Cohorts 2 and 4).<br>• The completed DC / eDC or MA will be reviewed with the participant's parent / guardian / legally authorized representative at each visit. |
| **Early Safety Data Review (ESDR):** | The safety of the investigational product will be continuously monitored by the Sponsor. To allow for a cautious, stepwise approach to vaccine administration, early safety data review (ESDR) will be performed during scheduled Safety Management Team (SMT) meetings:<br>• Cohort 1<br>o D7 post-vaccination ESDR/SMT<br>o D28 post-vaccination ESDR/SMT<br>o D56 post-vaccination ESDR/SMT<br>• Cohort 2<br>o D7 post-vaccination ESDR/SMT<br>o D28 post-vaccination ESDR/SMT<br>o D84 post-vaccination ESDR/SMT<br>• Cohort 3<br>o D7 post-vaccination ESDR/SMT<br>o D28 post-vaccination ESDR/SMT<br>o D56 post-vaccination ESDR/SMT<br>• Cohort 4<br>o D7 post-vaccination ESDR/SMT<br>o D28 post-vaccination ESDR/SMT<br>o D84 post-vaccination ESDR/SMT<br>The safety data collected will be entered into the CRBs and summarized by the Sponsor in a blinded manner for each ESDR. The ESDR will be performed by the Sponsor during the SMT meetings. Enrollment will not be paused during SMT reviews.<br>It is understood that all reviews are based on preliminary data that have not been subjected to validation and database lock. The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined early interim safety analysis will continue unchanged.<br>If at any other time point in the study the predetermined alert threshold for a safety event as outlined in the SMT charter is reached, regardless of the study time point, the trial will be paused for enrollment in order for an ad-hoc SMT to be convened.<br>In cases where the review of data by the SMT does not result in the identification of a potential safety signal, SMT oversight proceeds as assigned in the SMT charter. When a safety signal(s) is identified, the SMT |

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| | investigates the event(s), completes the Safety Analysis and/or Evaluation Report and decides about the safety signal and further actions and/or recommendations including:<br>• Extending or pausing the trial and escalate to the Vaccine Adjudication Committee (VAC)<br>• Investigate and develops a report<br>• Recommends continuing the trial<br><br>Within the investigation, the team may consult with non-clinical safety experts and research team members on whether there is a possible underlying mechanism for the event and review of toxicology data or other internal experts depending on the need.<br><br>In case of disagreement in the team, the core team seeks respective functional management advice from the VAC shortly after the SMT meeting. The Vaccine Pharmacovigilance Global Business Unit (PV GBU) Head or Vaccines GBU Clinical & Sciences Head may be also consulted, especially in instance where escalation of the signal for PSB review is in question.<br><br>Once the SMT core team agrees that there is a safety signal that can potentially impact the participant's safety, study conduct (pause, extended pause, or termination) or design (modifications needed), the SMT PM informs the Vaccine PV GBU Head who validates the signal and urgently contacts the Vaccines GBU Clinical & Sciences Head and the Chair of the PSB. The decision is made on whether to convene a PSB or not.<br><br>Based on the outcomes and recommendations from the PSB, the SMT may carry out any of the following operational actions related to the conduct and oversight of the study including:<br>• Continue the trial<br>• Extend the pause to conduct a further evaluation e.g., an ad hoc independent data monitoring committee (IDMC)<br>• Modify the trial design, or<br>• Stop the trial.<br><br>An ad-hoc IDMC, which ideally will include at least 2 pediatric respiratory virus vaccine experts, will review upon request of the SMT unblinded study data. The ad-hoc IDMC will upon request review the relevant safety information and available data, including magnitude of vaccine virus shedding. If an ad hoc IDMC meeting is required, the ad hoc IDMC will review the data on safety available at that time point to determine if attributable to an etiology, a cause, or a diagnosis unrelated to the study vaccine, and if the adverse event(s) are associated with shedding of vaccine virus at the time of the event (even if another is identified). If the ad-hoc IDMC decides there is no proven causal relationship between the adverse events and study vaccine, the study can continue unchanged. Based on evaluation of the ad-hoc IDMC, the Sanofi Pasteur SMT will decide if there is a causal relationship between the adverse event and the study vaccine, then SMT will decide whether to:<br>• Conduct internal signal detection processes (SOP # RDWIN-000390)<br>• Escalate validated signals to PSB as needed<br>• Continue the trial |

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| | • Modify the trial design (with PSB and ad-hoc IDMC input) or,<br>• Stop the trial (with PSB and ad-hoc IDMC input). |
| | The following safety parameters will be assessed as part of the early safety review:<br>• Immediate reactions<br>• Solicited respiratory and systemic reactions<br>• Unsolicited adverse reactions<br>• SAEs, MAAEs and AESIs<br>The data will be examined for the following thresholds:<br>1. Any deaths, regardless of causality.<br>2. Any vaccine related SAEs.<br>3. Grade 3 fever reported in > 2 participants.<br>4. Any Grade 3 or above solicited adverse reaction other than fever<br>5. >1 participant experiencing lower respiratory tract illness of >Grade 2 DAIDS scale (except for wheeze by Brighton Collaboration Severity Scale) during the acute phase (i.e., within 28 days post-vaccination).<br>6. Any participant experiencing an AESI of Grade 3 or above by the DAIDS scale (except for wheeze by Brighton Collaboration Severity Scale), including lower respiratory tract illness during the acute phase (i.e., within 28 days post-vaccination).<br>7. >1 participant with a Grade 3 unsolicited AE during the acute phase (i.e., within 28 days post-vaccination).<br>8. Any other pattern of research laboratory values or clinical symptoms other than fever that is considered a significant safety issue by Investigator.<br>If any of the above thresholds are met, the study will be paused for enrollment and an ad-hoc SMT convened to review the available safety data. |
| **Interruption of the Study** | The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), or the governing regulatory authorities in the countries where the study is taking place.<br>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 study participants' parents / guardians / legally authorized representatives and should assure appropriate participant therapy and / or follow-up. |
| **Primary Objectives:** | **<u>Primary Safety Objective:</u>**<br>• To assess the safety profile of each dose of RSV ΔNS2/Δ1313/I1314L after each and any administration in all infants and toddlers regardless of baseline serostatus.<br>**<u>Primary Immunogenicity Objective:</u>**<br>• To characterize the RSV A serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for |

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| | Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 in RSV-naïve participants. |
| **Primary Endpoints:** | **Primary Safety Endpoints:**<br>In all infants and toddlers regardless of baseline serostatus:<br>• Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each and any vaccination.<br>• Occurrence of solicited (i.e., pre-listed in the participant's DC / eDC and in the CRB) administration site and systemic reactions within 28 days after each and any vaccination (i.e, Acute Phase).<br>• Occurrence of any unsolicited (spontaneously reported) AEs within 28 days after each and any vaccination.<br>• Occurrence of any AESIs within 28 days after each and any vaccination.<br>• Occurrence of any MAAEs within 28 days after each and any vaccination.<br>• Occurrence of any SAEs throughout the study.<br>• Other safety endpoints will be recorded or derived as described in the statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activity [MedDRA] preferred term), time of onset, duration, number of days of occurrence, intensity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.<br>**Primary Immunogenicity Endpoint:**<br>RSV A serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4 and by D84 for Cohorts 2 and 4 in RSV-naïve participants.<br>For this Sanofi Phase I/II trial, data will be analyzed according to baseline serostatus. Baseline serostatus will be retrospectively determined from serum samples collected at baseline (V01). Participants will be categorized into RSV-experienced or RSV-naïve based on the presence or absence of detectable RSV serum anti-F IgA antibodies. This biomarker has been chosen since it is produced only in response to RSV infection and not transferred trans placentally from mother to child |
| **Secondary Objectives:** | **Secondary Safety Objectives:**<br>• To quantify the amount of vaccine virus shed by each participant on D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4, measured by [redacted] by baseline-serostatus.<br>**Secondary Infectivity Objective:**<br>• To determine the proportion of vaccinated infants and toddlers in each vaccine group infected[a] with the vaccine virus at D56 (56 days after vaccination 1) for Cohorts 1, 2, 3 and 4, and at D84 (28 days after vaccination 2) for Cohorts 2 and 4, by baseline serostatus. |

[a] Infection defined as detection of vaccine in nasal swab sample by [redacted] and / or a ≥ 4-fold rise in RSV A serum neutralizing antibody titers, or RSV serum anti-F IgG antibody titers.

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| | *Infection defined as detection of vaccine in nasal swab sample by [redacted] and / or a ≥ 4-fold rise in RSV A serum neutralizing antibody titers, or in RSV serum anti-F IgG antibody titers.<br><br>**Secondary Immunogenicity Objectives:**<br>• To characterize the RSV A serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) in Cohorts 2 and 4 in RSV-experienced participants.<br>• To characterize RSV serum anti-F IgG antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4, by baseline serostatus.<br>• To characterize RSV serum antibody responses (RSV A-neutralizing and anti-RSV F IgG) to the study product in each vaccine group after the RSV surveillance season or at least 5 months after the last vaccine administration by baseline serostatus. |
| **Secondary Endpoints:** | **Secondary Safety Endpoints:**<br>• Titer of vaccine virus shedding by D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4 measured by [redacted] assay.<br>**Secondary Infectivity Endpoint:**<br>• Vaccinees infected with the vaccine virus. Infection defined as detection of vaccine in nasal swab by [redacted] and / or a ≥ 4-fold rise in serum RSV A neutralizing antibodies, or in RSV serum anti-F IgG antibody titers.<br>**Secondary Immunogenicity Endpoints:**<br>• RSV A serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4 in RSV-experienced participants.<br>• RSV serum anti-F IgG antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.<br>• RSV A serum neutralizing and RSV serum anti-F IgG antibody titers after the RSV surveillance season or at least 5 months after the last vaccine administration. |
| **Exploratory Objectives:** | **Exploratory Safety Objective**<br>• To assess the safety profile of each dose of RSV after each and any administration by baseline serostatus.<br>**Exploratory Immunogenicity Objectives:**<br>• To characterize the RSV A serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.<br>• To characterize the RSV A serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.<br>• To characterize the RSV B serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for |

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| | Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.<br>• To characterize the RSV B serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.<br>• To characterize the RSV B serum neutralizing antibody responses to the study product in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.<br>• To characterize the RSV B serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.<br>• To characterize RSV A and RSV B serum anti-RSV protein G central conserved (anti-Gcc) IgG antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.<br>• To characterize RSV A and RSV B serum anti-Gcc IgG antibody responses to the study product in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.<br>• To characterize the RSV serum anti-F IgA antibody responses after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4 and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.<br>• To characterize the RSV serum anti-F IgA antibody responses after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.<br>**<u>Exploratory Efficacy Objective</u>**<br>• To describe the frequency and severity of RSV-associated, medically attended acute respiratory illness (RSV MAARI) and RSV-associated, medically attended acute lower respiratory illness (RSV MAALRI) in all infants and toddlers in each vaccine group during the RSV season or at least 5 months after the last vaccine administration. |

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| **Exploratory Endpoints:** | **<u>Exploratory Safety Endpoints</u>**<br>• Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each and any vaccination.<br>• Occurrence of any unsolicited (spontaneously reported) AEs within 28 days after each and any vaccination.<br>• Occurrence of solicited (i.e., pre-listed in the participant's DC / eDC and in the CRB) administration site and systemic reactions within 28 days after each and any vaccination (i.e, Acute Phase).<br>• Occurrence of any AESIs within 28 days after each and any vaccination.<br>• Occurrence of any MAAEs within 28 days after each and any vaccination.<br>• Occurrence of any SAEs throughout the study.<br>**<u>Exploratory Immunogenicity Endpoints:</u>**<br>• RSV A serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4 converted into international units* (IU)/mL.<br>• RSV A serum neutralizing antibody titers converted into IU/mL, after the RSV season or at least 5 months after the last vaccine administration.<br>*The RSV A serum neutralizing antibody titer values obtained are further calibrated and converted into IU/mL against the World Health Organization (WHO) 1st international reference standard NIBSC 16/284 (with an assigned value of 2000 IU/mL) or converted with a qualified internal reference with an assigned IU/mL value. The calibrator (reference standard) is included in the same assay run.<br>• RSV◦B serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.<br>• RSV B serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4, converted into international units* (IU)/mL.<br>• RSV◦B serum neutralizing antibody titers after the RSV season or at least 5 months after the last vaccine administration.<br>• RSV B serum neutralizing antibody titers converted into IU/mL, after the RSV season or at least 5 months after the last vaccine administration.<br>*The RSV B serum neutralizing antibody titer values obtained are further calibrated and converted into IU/mL against the World Health Organization (WHO) 1st international reference standard NIBSC 16/284 (with an assigned value of 2000 IU/mL) or converted with a qualified internal reference with an assigned IU/mL value. The calibrator (reference standard) is included in the same assay run.,<br>• RSV A and RSV B serum anti-Gcc IgG antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.<br>• RSV A and RSV B serum anti-Gcc IgG antibody titers after the RSV season or at least 5 months after the last vaccine administration. |

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| | • RSV serum anti-F IgA antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.<br>• RSV serum anti-F IgA antibody titers after the RSV season or at least 5 months after the last vaccine administration.<br><br>**<u>Exploratory Efficacy Endpoints</u>**<br><br>The following exploratory efficacy endpoints will be assessed through the RSV season surveillance phase or for at least five months after the last vaccine administration:<br>• RSV medically attended acute respiratory illness (RSV MAARI)<br>• RSV medically attended acute lower respiratory illness (RSV MAALRI)<br>• A diagnosis of RSV MAARI requires a respiratory sample positive for RSV by [redacted] AND documented physical exam findings of respiratory tract illness including any of the following:<br>o Fever<br>o Acute otitis media<br>o URI:<br>▪ Runny nose/rhinorrhea<br>▪ Stuffy or blocked nose/nasal congestion<br>▪ Pharyngitis<br>▪ Cough without LRI<br>o LRI (see MAALRI below)<br>• A diagnosis of RSV MAALRI (a subset of MAARI) requires a respiratory sample positive for RSV by [redacted] AND documented physical exam findings of lower respiratory tract illness including any of the following:<br>o Stridor<br>o Rales<br>o Tachypnea<br>o Acute wheeze<br>o Pneumonia<br>o Laryngotracheobronchitis |

<table>
<tr><td>Planned Sample Size:</td><td>A total of 300 participants are planned to be enrolled.
<table>
<tr><td></td><td></td><td colspan="4">Cohort</td></tr>
<tr><td>Vaccine Groups</td><td>Total (n)</td><td>1 (n)</td><td>2 (n)</td><td>3 (n)</td><td>4 (n)</td></tr>
<tr><td>Administration(s)</td><td></td><td>x1</td><td>x2</td><td>x1</td><td>x2</td></tr>
<tr><td>RSV ΔNS2/Δ1313/I1314L [redacted] per administration (low-dose)</td><td>100</td><td>20</td><td>20</td><td></td><td>60</td></tr>
<tr><td>RSV ΔNS2/Δ1313/I1314L [redacted] per administration (high-dose)</td><td>80</td><td></td><td></td><td>20</td><td>60</td></tr>
<tr><td>Placebo</td><td>120</td><td>20</td><td>20</td><td>20</td><td>60</td></tr>
<tr><td>TOTAL</td><td>300</td><td>40</td><td>40</td><td>40</td><td>180</td></tr>
</table></td></tr>
<tr><td>Duration of Participation in the Study:</td><td>The duration of active participation of each participant in each cohort is up to a maximum of 12 months.</td></tr>
<tr><td>Investigational Product:</td><td>Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L Vaccine [redacted]</td></tr>
<tr><td>Form:</td><td>Suspension of virus</td></tr>
<tr><td>Composition:</td><td>Each [redacted] dose of RSV ΔNS2/Δ1313/I1314L will contain the live-attenuated RSV with (i) a 523-nucleotide deletion of the NS2 gene, (ii) an amino acid deletion in the L protein (Δ1313; deletion of S1313), and (iii) genetically stabilizing mutation in the L gene (I1314L), [redacted], approximately [redacted] to be delivered [redacted] per nostril, using an intranasal [redacted] device.</td></tr>
<tr><td>Route:</td><td>Intranasal</td></tr>
<tr><td>Batch Number:</td><td>To be determined</td></tr>
<tr><td>Investigational Product:</td><td>Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L Vaccine [redacted]</td></tr>
<tr><td>Form:</td><td>Suspension of virus</td></tr>
<tr><td>Composition:</td><td>Each [redacted] dose of RSV ΔNS2/Δ1313/I1314L will contain the live-attenuated RSV with (i) a 523-nucleotide deletion of the NS2 gene, (ii) an amino acid deletion in the L protein (Δ1313; deletion of S1313), and (iii) genetically stabilizing mutation in the L gene (I1314L), [redacted], approximately [redacted] to be delivered [redacted] per nostril, using an intranasal [redacted] device.</td></tr>
<tr><td>Route:</td><td>Intranasal</td></tr>
<tr><td>Batch Number:</td><td>To be determined</td></tr>
<tr><td>Non-Investigational Product:</td><td>Placebo</td></tr>
<tr><td>Form:</td><td>Solution</td></tr>
<tr><td>Composition:</td><td>Same formulation buffer as the RSV ΔNS2/Δ1313/I1314L vaccine, to be delivered as approximately [redacted] per nostril</td></tr>
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| ***Route:*** | Intranasal |
| ***Batch Number:*** | To be determined |
| ***Device:*** | [redacted] |

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| | [redacted] |
| **Screening Criteria:** | There are no screening criteria other than the inclusion and exclusion criteria. The Investigator must review the inclusion and exclusion criteria at enrollment (Visit 01). |
| **Inclusion Criteria:** | An individual must fulfill all of the following criteria to be eligible for study enrollment at Visit 01:<br>1. Aged 6 through 18 months at D0.<br>2. Informed consent form has been signed and dated by the parent(s) / guardian / or other legally authorized representative (and by independent witness if required by local regulations).<br>3. Participant and parent / guardian / legally authorized representative are able to attend all scheduled visits and to comply with all trial procedures. |
| **Exclusion Criteria:** | An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment:<br>1. Participation at the time of study enrollment (or in the 6 weeks preceding the first trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure.<br>2. Receipt of any of the following vaccines prior to enrollment:<br>• any influenza vaccine within 7 days prior, or<br>• any inactivated vaccine within the 14 days prior, or<br>• live-attenuated rotavirus vaccine within the 14 days prior, or<br>• any live vaccine, other than rotavirus vaccine, within the 28 days prior, or<br>• another investigational vaccine or investigational drug within 28 days prior.<br>3. Previous receipt of a licensed or investigational RSV vaccine or previous receipt or planned administration of any anti-RSV product (such as ribavirin or RSV immune globulin [IG] or RSV monoclonal antibody).<br>4. Receipt of immune globulins, blood or blood-derived products in the past 6 months prior to enrollment. |

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| | 5. 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).<br>6. Probable or confirmed case of Coronavirus Disease 2019 (COVID-19).<br>7. Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances.<br>8. Any chronic illness.<br>• Chronic illness may include, but is not limited to, cardiac disorders, lung disease (including any history of reactive airway disease, receipt of bronchodilator therapy, or medically diagnosed wheezing), renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases<br>9. Any history of medically diagnosed wheezing.<br>10. Any acute febrile, respiratory or gastrointestinal illness in the past 24 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.<br>11. Receipt of any of the following medications within 3 days prior to study enrollment:<br>• systemic antibacterial, antiviral, antifungal, anti-parasitic, or anti-tuberculous agents, whether for treatment or prophylaxis, or<br>• intranasal medications, or<br>• other prescription medication except as permitted concomitant medications (prescription or non-prescription) including nutritional supplements, medications for gastroesophageal reflux, eye drops, and topical medications, including (but not limited to) cutaneous (topical) steroids, topical antibiotics, and topical antifungal agents.<br>12. Receipt of salicylate (aspirin) or salicylate-containing products within the 28 days prior to enrollment.<br>13. Deprived of freedom in an emergency setting or hospitalized involuntarily.<br>14. Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.<br>15. Any previous anaphylactic reaction.<br>16. Any previous vaccine-associated adverse reaction that was Grade 3 or above. Note: if grading is not possible, determine if the reaction was considered severe or life-threatening; if so, it is exclusionary.<br>17. Member of a household that contains, or will contain, an infant who is less than 6 months of age at the enrollment date (or in the 6 weeks preceding the first trial vaccination) through Day 28.<br>18. Member of a household that contains another child/other children who is/are, or is/are scheduled to be, enrolled in this study in the same year AND the date of enrollment will not be concurrent with the other |

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| | participant(s) living in the household (i.e., all eligible children from the same household must be enrolled on the same date).<br>19. Member of a household that contains an immunocompromised individual, including, but not limited to:<br>• a person who is HIV infected<br>• a person who has received chemotherapy within the 12 months prior to enrollment<br>• a person receiving immunosuppressant agents<br>• a person living with a solid organ or bone marrow transplant.<br>20. Attends a daycare facility and shares a daycare room with infants less than 6 months of age, and parent/ guardian / legally authorized representative is unable or unwilling to suspend daycare for 28 days following inoculation.<br>21. Scheduled administration of the following after planned inoculation:<br>• any influenza vaccine within 7 days after, or<br>• inactivated vaccine or live-attenuated rotavirus vaccine within the 14 days after, or<br>• any live vaccine other than rotavirus in the 28 days after, or<br>• another investigational vaccine or investigational drug in the 56 days after.<br>22. Born at less than 34 weeks gestation.<br>23. Born at less than 37 weeks gestation and less than 1 year of age at the time of enrollment.<br>24. Current suspected or documented developmental disorder, delay, or other developmental problem.<br>25. Any previous receipt of supplemental oxygen therapy in a home or hospital setting, except the temporary receipt of supplemental oxygen for transient tachypnea in newborn. |
| **Statistical Methods:** | The analysis will be performed with a stepwise approach as follows:<br>• Several blinded early safety data reviews will be performed on safety data collected in participants from each cohort at specific timepoints, as specified in ESDR section<br>• An unblinded interim analysis for dose confirmation of RSV ΔNS2/Δ1313/I1314L vaccine is planned on participants from Cohorts 1, 2 and 3 and at least 90 participants enrolled in Cohort 4. The interim analysis will take place when participants have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. Based on the results of this analysis, the dose for future clinical studies (frozen product) will be confirmed. The acceptability of safety, infectivity, and immunogenicity results of the two doses tested to justify clinically the future dose range boundaries of the non-frozen liquid formulation for final commercialization will also be descriptively assessed.<br>• An early unblinded analysis is planned on all participants when they have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. Based on the results of this analysis, a dose will be confirmed for future studies. |

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| | • The final unblinded analysis will address the objectives on all participants (Cohorts 1, 2, 3 and 4) including the post season follow up.<br><br>All analyses will be descriptive; no hypotheses will be tested.<br><br>During a cohort's safety review and/or at the end of the study, a Bayesian approach based on posterior distribution of the difference in incidence between groups may be applied.<br><br>The Safety Analysis Set will be used for safety analyses. Immunogenicity analyses will be performed on the Full Analysis Set and, on the Per-Protocol Analysis Set for main immunogenicity parameters.<br><br>All endpoints will be summarized by vaccine group. For the main parameters, 95% confidence intervals (CIs) of point estimates will be calculated using the normal approximation for quantitative data, and the exact binomial distribution (Clopper-Pearson method) for proportions.<br><br><u>Calculation of Sample Size:</u><br><br>No sample size calculation was done as there are no statistical hypotheses in this study.<br><br>A total of 300 participants are planned to be enrolled into 1 of the 4 cohorts sequentially:<br>• Cohort 1 (1 administration): 40 participants, i.e., 20 per vaccine group (RSV low-dose or placebo)<br>• Cohort 2 (2 administrations): 40 participants, i.e., 20 per vaccine group (RSV low-dose or placebo)<br>• Cohort 3 (1 administration): 40 participants, i.e., 20 per vaccine group (RSV high-dose or placebo)<br>• Cohort 4 (2 administrations): 180 participants, i.e., 60 per vaccine group (RSV high-dose or RSV low-dose or placebo). |

# Table of Study Procedures for Cohorts 1 and 3

Phase I/II Study, 4 Planned Visits, 30 (32) non-visit telephone contacts, 1 Vaccination, 3 Planned Blood Samples, 1 Planned Nasal Swab, up to a Maximum of 12 Months of Participation per Participant

| **Visit (V) / Contact** | **Visit 01** | **Phone contacts 1 - 6** | **Visit 02** | **Phone contacts 7 - 16** | **Phone Contact 17** | **Phone contact 18** | **Visit 03** | **Phone contacts 19 -30 (32)** ‡‡ | **Visit 04**§§ | **Illness Visit(s) Visit 99***** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study timelines - Days(D)** | **D0** | **Daily (x6)** | **D7** | **Three times weekly (x10)** | **D29 (+1)** | **D42** (+1) | **D56 (+7)** | **Every 2 weeks** | **1 – 30 Apr (NH)** | |
| In-person visit | X | | X | | | | X | | X | X |
| Non-visit contact* | | X | | X | X | X | | X | | |
| Informed consent | X | | | | | | | | | |
| Demography data | X | | | | | | | | | |
| Inclusion / Exclusion criteria | X | | | | | | | | | |
| Medical history and physical examination | X | | | | | | | | | |
| Vital signs† | X | | X | | | | X | | | X |
| COVID-19 test | X | | | | | | | | | X |
| Interim history | | | X | | | | X | | | X |
| Focused clinical examination | | | X | | | | X | | | X |
| Collection of reportable concomitant medications/vaccinations | | | | | | | X | | | X |
| Allocation participant number | X | | | | | | | | | |
| Randomization / Dose number | X | | | | | | | | | |
| Blood samples | BL0001 | | | | | | BL0002 | | BL00P2 | |
| Nasal swab‡ | | | NS0001 | | | | | | | NS0001 or UN0001 to UN000X |
| Vaccination | X | | | | | | | | | |
| Immediate surveillance (30 min) § | X | | | | | | | | | |

| **Visit (V) / Contact** | **Visit 01** | **Phone contacts 1 - 6** | **Visit 02** | **Phone contacts 7 - 16** | **Phone Contact 17** | **Phone contact 18** | **Visit 03** | **Phone contacts 19 -30 (32)** ‡‡ | **Visit 04**§§ | **Illness Visit(s) Visit 99***** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study timelines - Days(D)** | **D0** | **Daily (x6)** | **D7** | **Three times weekly (x10)** | **D29 (+1)** | **D42** (+1) | **D56 (+7)** | **Every 2 weeks** | **1 – 30 Apr (NH)** | |
| Diary Card (DC) electronic DC (eDC) provided | DC1/eDC | | DC2 | | | | | | | |
| DC / eDC reviewed | | DC1/eDC ** | DC1/eDC | DC1 /eDC ** | DC2/eDC ** | DC2/eDC** | DC2 | | X | X |
| DC collected | | | | | | | DC1/DC2 | | | |
| Memory aid (MA) provided | | | | | | | X | | | |
| MA reviewed | | | | | | | | | X | X |
| Collection of solicited local respiratory and systemic reactions†† | X | X | X | X | X | | | | | |
| Collection of unsolicited adverse events†† | X | X | X | X | X | | | | | |
| Collection of adverse events of special interest†† | X | X | X | X | X | | | | | |
| Collection of medical attended adverse events†† | X | X | X | X | X | | | | | |
| Collection of serious adverse events | X | | | | | | | | | |

*Non-site visit contacts are to be made by phone at scheduled timepoints in the study.
† Vital signs will be collected in the eCRF.
‡All participants will provide a nasal swab sample for quantification of vaccine virus shedding at D7, i.e., 7 days after vaccination. The same nasal swab specimens may also be tested for respiratory pathogens (including COVID-19), if the participant is ill at the time of D7 visit.
§Any unsolicited systemic adverse events occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic adverse events in the case report book.
**Diary Card (DC) / Electronic Diary Card (eDC) will be reviewed by telephone contact.
††The participant's parent / guardian / legally authorized representative will record information in a DC / eDC about solicited reactions, unsolicited AEs, AESIs and MAAEs from D0 to D28 after vaccine administration.
‡‡Phone contact during the RSV season every 2 weeks.
§§Visit 04: Post-RSV season visit in the month after the cessation of the RSV season.
***Illness Visits: Additional nasal swab specimens for the detection of RSV and respiratory pathogens" (including COVID-19) will also be collected from participants during illness visits and 48 hours later at any other protocol specified time point in the study (Table 5-4) including medically attended visits during RSV season. If a participant visits any other non-study doctor / hospital for a serious adverse event (SAE) at any time in the study, a nasal swab sample will be obtained at the study site once the participant is discharged, if deemed appropriate by the study investigator. All the nasal swab specimens will be collected in the recommended viral transport media tube and will be stored between -60°C and -80°C until ready to ship. The requirement for an onsite or at home illness visit will be evaluated first by video call to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.

# Table of Study Procedures for Cohorts 2 and 4 – Vaccination 1 (D0 to D55)

Phase I/II Study, 6 Planned Visits, 40 (42) Non-visit Telephone Contacts, 2 Vaccinations, 4 Planned Blood Samples, 2 Planned Nasal Swabs, up to a Maximum of 12 Months of Participation per Participant

| **Visit (V) / Contact** | **Visit 01** | **Phone contacts 1-6** | **Visit 02** | **Phone contacts 7-16** | **Phone contact 17** | **Phone contact 18** | **Illness Visit(s) ‡ Visit 99** |
|---|---|---|---|---|---|---|---|
| **Study timelines – Days (D)** | **D0** | **Daily (x6)** | **D7** | **Three times weekly (x10) between D8 and D28** | **D29** (+1) | **D42** (+1) | **Any time between Visit 01 and Visit 06** |
| In-person visit | X | | X | | | | X |
| Non-visit contact* | | X | | X | X | X | |
| Informed consent | X | | | | | | |
| Demography data | X | | | | | | |
| Inclusion / Exclusion criteria | X | | | | | | |
| Medical history and physical examination | X | | | | | | |
| Vital signs† | X | | X | | | | X |
| COVID-19 test | X | | | | | | X |
| Interim history | | | X | | | | X |
| Focused clinical examination | | | X | | | | X |
| Collection of reportable concomitant medications/ vaccinations | | | | | | | X |
| Allocation of participant number | X | | | | | | |
| Randomization / Dose number | X | | | | | | |
| Blood samples | BL0001 | | | | | | |
| Nasal swabs‡ | | | NS0001 | | | | NS0001 or UN0001 to UN0000X |
| Vaccination (1st administration) | X | | | | | | |
| Immediate surveillance (30 min) § | X | | | | | | |

| **Visit (V) / Contact** | **Visit 01** | **Phone contacts 1-6** | **Visit 02** | **Phone contacts 7-16** | **Phone contact 17** | **Phone contact 18** | **Illness Visit(s) ‡ Visit 99** |
|---|---|---|---|---|---|---|---|
| **Study timelines – Days (D)** | **D0** | **Daily (x6)** | **D7** | **Three times weekly (x10) between D8 and D28** | **D29** (+1) | **D42** (+1) | **Any time between Visit 01 and Visit 06** |
| Diary Card (DC) / electronic DC (eDC) provided | DC1/eDC | | DC2 | | | | |
| DC / eDC reviewed | | DC1/eDC** | DC1/eDC | DC1/eDC ** | DC2/eDC ** | DC2/eDC ** | X |
| Collection of solicited local respiratory and systemic reactions** | X | X | X | X | X | | |
| Collection of unsolicited adverse events** | X | X | X | X | X | | |
| Collection of adverse events of special interest** | X | X | X | X | X | | |
| Collection of medical attended adverse events** | X | X | X | X | X | | |
| Collection of serious adverse events | X | | | | | | |

*Non-site visit contacts are to be made by phone at scheduled timepoints in the study.

† Vital signs will be collected in the eCRF.

‡All participants will provide a nasal swab sample for quantification of vaccine virus shedding at D7, i.e., 7 days after vaccination 1. The same nasal swab specimen may also be tested for respiratory pathogens (including COVID-19), if the participant is ill at the time of D7 visit.

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

**Diary Card / Electronic Diary Card (DC / eDC) will be reviewed by telephone contact.

††The participant's parent / guardian / legally authorized representative will record information in a DC / eDC about solicited reactions, unsolicited AEs, AESIs and MAAEs from D0 to D28 after vaccine administration 1 (Acute phase 1).

‡‡Illness Visits (between V01 and V06): Additional nasal swab specimens for the detection of RSV and respiratory pathogens" (including COVID-19) will also be collected from participants during illness visits and 48 hours later at any other protocol specified time point in the study (Table 5-4) including medically attended visits during RSV season. If a participant visits any other non-study doctor / hospital for a serious adverse event (SAE) at any time in the study, a nasal swab sample will be obtained at the study site once the participant is discharged, if deemed appropriate by the study investigator. All the nasal swab specimens will be collected in the recommended viral transport media tube and will be stored between -60°C and -80°C until ready to ship. The requirement for an at home or onsite illness visit will be evaluated first by video call to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.

# Table of Study Procedures for Cohorts 2 and 4 – Vaccination 2 (D56 to End of Study)

Phase I/II Study, 6 Planned Visits, 40 (42) Non-visit Telephone Contacts, 2 Vaccinations, 4 Planned Blood Samples, 2 Planned Nasal Swabs, up to a Maximum of 12 Months of Participation per Participant

| **Visit (V) / Contact** | **Visit 03** | **Phone contacts 19-24** | **Visit 04** | **Phone contacts 25-30** | **Visit 05†††** | **Phone contact 31 – 40 (42)‡‡** | **Visit 06‡‡** | **Illness Visit(s) *** Visit 99** |
|---|---|---|---|---|---|---|---|---|
| **Study timelines – Days (D)** | **D56+7** | **Daily (x6)** | **D63 (+7)** | **Twice weekly (x6) between D64 and D83** | **D84 (+8)** | **Every 2 weeks between Visit 05 and Visit 06** | **1 – 31 Oct (SH) 1 – 30 Apr (NH) or > 5 months after last vaccine admin.** | **Any time between Visit 01 and Visit 06** |
| In-person visit | X | | X | | X | | X | X |
| Non-visit contact* | | X | | X | | X | | |
| Vital signs† | X | | X | | X | | | X |
| Interim history | X | | X | | X | | | X |
| Focused clinical examination | X | | X | | X | | | X |
| COVID-19 test | X | | | | | | | X |
| Collection of reportable concomitant medications/ vaccinations | X | | | | | | | X |
| Dose Number | X | | | | | | | |
| Blood samples | BL0002 | | | | BL0003 | | BL00P2 | |
| Nasal swabs ‡ | | | NS0002 | | | | | NS0002 or UN0001 to UN000X |
| Vaccination (2nd administration) | X | | | | | | | |
| Immediate surveillance (30 min) § | X | | | | | | | |
| Diary Card (DC1) | DC3 | | | | | | | |
| DC / eDC reviewed** | DC2/eDC | DC3/eDC ** | DC3/eDC | DC3/eDC ** | DC3/eDC | | X | X |
| DC collected | DC1/DC2 | | | | DC3 | | | |

| **Visit (V) / Contact** | **Visit 03** | **Phone contacts 19-24** | **Visit 04** | **Phone contacts 25-30** | **Visit 05†††** | **Phone contact 31 – 40 (42)‡‡** | **Visit 06‡‡** | **Illness Visit(s) *** Visit 99** |
|---|---|---|---|---|---|---|---|---|
| **Study timelines – Days (D)** | **D56+7** | **Daily (x6)** | **D63 (+7)** | **Twice weekly (x6) between D64 and D83** | **D84 (+8)** | **Every 2 weeks between Visit 05 and Visit 06** | **1 – 31 Oct (SH) 1 – 30 Apr (NH) or > 5 months after last vaccine admin.** | **Any time between Visit 01 and Visit 06** |
| Memory aid (MA) provided | | | | | X | | | |
| MA reviewed | | | | | | | X | X |
| Collection of solicited local respiratory and systemic reactions†† | X | X | X | X | X | | | |
| Collection of unsolicited adverse events†† | X | X | X | X | X | | | |
| Collection of adverse events of special interest†† | X | X | X | X | X | | | |
| Collection of medical attended adverse events†† | X | X | X | X | X | | | |
| Collection of serious adverse events | X | | | | | | | |

*Non-site visit contacts are to be made by phone at scheduled timepoints in the study.
† Vital signs will be collected in the eCRF.
‡All participants will provide a nasal swab sample for quantification of vaccine virus shedding at D63, i.e., 7 days after vaccination 2. The same nasal swab specimen will also be tested for respiratory pathogens (including COVID-19), if the participant is ill at the time of D63 visit.
§Any unsolicited systemic adverse events occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic adverse events in the case report book.
**Diary Card (DC) / Electronic Diary Card (eDC) will be reviewed by telephone contact.
††The participant's parent / guardian / legally authorized representative will record information in a DC / eDC about solicited reactions, unsolicited AEs, AESIs and MAAEs from D56 to D84 (Acute phase 2).
‡‡Phone contact during the RSV season, every 2 weeks.
§§Visit 06: Post-RSV season visit – In the month after the cessation of the RSV season in sites with differing seasons or at least 5 months after last vaccine administration. Study participants enrolled during the routine RSV season (ie November to March for NH and May to September for SH) will be followed up for at least 5 months after the last vaccine administration.
***Illness Visits (between V01 and V06): Additional nasal swab specimen for the detection of RSV and respiratory pathogens (including COVID-19) will also be collected from participants during illness visits and 48 hours later at any other protocol specified time point in the study (Table 5-4) including medically attended visits during the RSV season. If a participant visits any other non-study doctor / hospital for a serious adverse event (SAE) at any time in the study, a nasal swab sample will be obtained at the study site once the participant is discharged, if deemed appropriate by the study investigator. All the nasal swab specimens will be collected in the recommended viral transport media tube and will be stored between -60°C and -80°C until ready to ship. The requirement for an at home or onsite illness visit will be evaluated first by video call to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.
††† Visit 05 is to occur 84 days after the first vaccination at Visit 01 and 28 days after the second vaccination visit at Visit 03.

# List of Abbreviations

| | |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| AR | adverse reaction |
| CDC | Centers for Disease Control |
| CDM | Clinical Data Management |
| CI | confidence interval |
| COVID-19 | Coronavirus Disease 2019 |
| CQA | Clinical Quality Assessment |
| CRA | Clinical Research Associate |
| CRB | (electronic) case report book [all the case report forms for a participant] |
| CRF | (electronic) case report form |
| D | Day |
| DAIDS | Division of AIDS |
| DC | diary card |
| eDC | Electronic Diary Card |
| EDC | electronic data capture |
| EENT | eye, ear, nose, throat |
| [redacted] | [redacted] |
| ESDR | early safety data review |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FVFP | first visit, first participant |
| FVLP | first visit, last participant |
| Gcc | G (glycoprotein) central conserved region |
| GCI | Global Clinical Immunology |
| GCP | Good Clinical Practice |
| GMTs | geometric mean titers |
| GMTRs | geometric mean titers ratios |
| GPV | Global Pharmacovigilance |
| HIV | human immunodeficiency virus |
| IATA | International Air Transport Association |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IDMC | Independent Data Monitoring Committee |

| | |
|---|---|
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin |
| IME | important medical event |
| IND | investigational new drug (application) |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| LCLS | last contact, last participant |
| LID | Laboratory of Infectious Diseases |
| LLOQ | lower limit of quantification |
| LLT | lowest level term |
| LRI | lower respiratory illness |
| MA | memory aid |
| MAAE | medically attended adverse event |
| MAARI | medically attended acute respiratory illness |
| [redacted] | [redacted] |
| MAALRI | medically attended acute lower respiratory illness |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | milliliter |
| MN | microneutralization |
| nAb | neutralizing antibody |
| NC | Negative Control |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| NS | nasal swab |
| NSAID | non-steroidal anti-inflammatory drug |
| PFU | plaque forming units |
| PC | Positive Control |
| [redacted] | [redacted] |
| PSB | Product Safety Board |
| POC | Point of care |
| PPAS | per-protocol analysis set |
| PT | preferred term |
| RCDCs | Reverse cumulative distribution curves |
| RSV | Respiratory Syncytial Virus |
| RSV ΔNS2/Δ1313/I1314L | Live-Attenuated Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L Vaccine |
| RSV-LRI | RSV-associated lower respiratory illness |
| RSV MAARI | RSV-associated, medically attended acute respiratory illness |

| | |
|---|---|
| RSV MAALRI | RSV-associated, medically attended acute lower respiratory illness |
| RMO | Responsible Medical Officer |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| SAE | serious adverse event |
| SafAS | safety analysis set |
| SMT | Safety Management Team |
| SOC | system organ class |
| TBD | to be determined |
| TMF | trial master file |
| ULOQ | upper limit of quantification |
| URI | upper respiratory tract illness |
| US | United States |
| VAC | Vaccine Adjudication Committee |
| VTM | viral transport medium |
| WHO | World Health Organization |
| wt | wild-type |

# 1 Introduction

## 1.1 Background

This is a study using the investigational RSV ΔNS2/Δ1313/I1314L vaccine against respiratory syncytial virus (RSV) disease in infants and toddlers.

RSV is the most important cause of severe acute lower respiratory illness (LRI) in infants and children (1) (2) and the most common cause of severe pneumonia requiring hospital admission in children worldwide (3). According to global estimates, RSV caused approximately 33 million cases of LRI and approximately 118 000 deaths in children <5 years of age in 2015 (2). Greater than 80% of all RSV-associated LRIs (RSV-LRIs) and more than 50% of the RSV-associated deaths in low- and middle-income countries were estimated to occur in infants ≥6 months old (4).

Live-attenuated intranasal RSV vaccines are an attractive option for pediatric immunization because they mimic mild natural infections and induce durable cellular, humoral, local, and systemic immunity. Several trials of live-attenuated RSV vaccine candidates (5) (6) (7) (8) (9) (10) (11) (12) have indicated that these vaccines do not cause the vaccine-associated enhanced RSV disease observed in children who received formalin-inactivated RSV (13).

Progress has been made in the understanding of the RSV gene function (14), and the use of reverse genetic systems to engineer rationally designed attenuated RSV strains (15), including strains attenuated through deletion of the NS2 gene, like the current RSV ΔNS2/Δ1313/I1314L vaccine candidate. RSV NS2 is a virally encoded type I and III interferon antagonist that interferes with interferon induction and signaling (16) (17) (18). In chimpanzees, intranasal and intratracheal inoculation with a NS2 gene-deleted derivative of wild-type (wt) strain RSV-A2 resulted in reduced replication in the upper and lower respiratory tract compared to wt-RSV, and significant resistance to consequent challenge with wt RSV (19). Deletion of the NS2 or NS1 gene in bovine RSV (BRSV) led to increased interferon response to BRSV infection in calves (20). NS2 also functions as a pathogenicity factor, promoting epithelial cell shedding in vitro and in the hamster model (21) and its deletion may potentially reduce small airways obstruction improving the safety profile of such vaccine candidates. Deletion of the NS2 gene may be beneficial for vaccine safety, and the additional deletion of codon 1313 in the polymerase (L) gene, which also confers mild temperature sensitivity (shutoff temperature of 38°C–39°C [100.4°F-102.2°F]) for added safety (21). Substitution of leucine (L) for isoleucine (I) at codon 1314 further stabilizes the deletion of codon 1313 genetically and phenotypically. The level of attenuation, genetic stability and immunogenicity exhibited by the resultant RSV ΔNS2 Δ1313/I1314L in nonhuman primates indicated that it was a promising candidate for evaluation in pediatric Phase I studies (22). Recently, safety and immunogenicity of RSV ΔNS2 Δ1313/I1314L was evaluated in RSV seronegative children, 6-24 months of age. In this study, [redacted]. At the [redacted] dose, the vaccine candidate was highly attenuated and infectious for 80% of vaccine recipients. However, only 8 of 15 (53%) of vaccine recipients developed four-fold or greater increases in RSV-neutralizing serum antibodies. At the [redacted] dose, this candidate vaccine was shown to be well tolerated, infectious (resulted in successful infection in 100% of vaccinees) and immunogenic, inducing four-fold or greater

increases in RSV-neutralizing serum antibodies in 16 of 20 (80%) vaccine recipients (23), warranting further evaluation of this candidate as a vaccine for RSV.

## 1.2 Background of the Investigational Product

The RSV genome can be manipulated genetically to introduce predetermined mutations into infectious RSV via a cDNA intermediate (15).

The investigational RSV ΔNS2/Δ1313/I1314L vaccine is based on an attenuation approach involving the deletion of the gene encoding the RSV interferon / apoptosis antagonist NS2 protein (ΔNS2) in the RSV A2 wt strain (23). Deletion of NS2 gene attenuates the virus and may enhance immunogenicity. RSV ΔNS2/Δ1313/I1314L vaccine additionally contains a genetically stabilized attenuating and temperature sensitivity mutation in the L protein (codon deletion Δ1313, as well as a missense mutation I1314L that prevents a de-attenuating mutation that otherwise can occur at position 1314), and as a result RSV ΔNS2/Δ1313/I1314L is temperature sensitive, with a shut-off temperature for virus replication of 38ºC-39°C (100.4ºF-102.2ºF).

## 1.3 Potential Benefits and Risks

### 1.3.1 Potential Benefits to Participants

Participants may not receive direct study product-related benefit from enrollment in this study. Placebo recipients will not receive any direct benefit from enrollment in this study. It is hoped that information gained in this study will contribute to the development of a safe and effective vaccine for the prevention of illness associated with RSV infection.

### 1.3.2 Potential Risks to Participants

***Venipuncture***

Risks occasionally associated with venipuncture include pain and bruising at the site of venipuncture, lightheadedness, infection, and syncope (rarely).

***Nasal Swab***

Risks occasionally associated with nasal swab include pain or discomfort and occasionally epistaxis. Nasal swabs are not standard care in well children, but pediatric mid-turbinate swabs are sometimes performed on children with respiratory tract illness.

***Topical Anesthetic Cream***

Risks occasionally associated with the use of topical anesthetic cream include temporary skin discoloration, skin irritation, rash, hives, and rarely, dizziness or drowsiness.

***Receipt of Study Product***

If a live-attenuated RSV vaccine is insufficiently attenuated, participants could experience upper or lower respiratory tract illness. Immediate hypersensitivity reactions, which could be life-threatening, including urticaria, anaphylaxis, or other Immunoglobulin (Ig) E-mediated responses are possible, as with any vaccine. There is a theoretical possibility, as with any

investigational vaccine, of risks about which there is no present knowledge. Parents / guardians / legally authorized representatives will be informed of any such risks should further data become available.

## 1.4 Rationale for the Study

Prior to RSV ΔNS2/Δ1313/I1314L vaccine, 3 RSV vaccine viruses with the NS2 gene deletion (rA2cpΔNS2, rA2cp248/404ΔNS2, and rA2cp530/1009ΔNS2) had been evaluated in clinical studies (7). The rA2cpΔNS2 candidate was over-attenuated for adults but under-attenuated for use in young children, whereas both rA2cp248/404ΔNS2 and rA2cp530/1009ΔNS2 were over-attenuated and insufficiently immunogenic in seronegative children. Based on these results RSV ΔNS2/Δ1313/I1314L was developed. In a recent Phase Ia study sponsored by the National Institutes of Health (NIH) in RSV seronegative children aged 6 to 24 months, (n=20) (23), at the [redacted] dose, RSV ΔNS2/Δ1313/I1314L was safe, had good infectivity (100% of vaccinated participants infected) and immunogenicity (80% of participants with a ≥4-fold rise in neutralizing antibody titers) and primed for a strong anamnestic response to wt RSV infection in the post-RSV season surveillance.

The NIH proceeded to age de-escalate in order to evaluate RSV ΔNS2/Δ1313/I1314L in younger infants, aged 4 to 6 months, who are the likely primary target population for a live-attenuated RSV vaccine since they are at highest risk for severe RSV-associated LRI. This study is currently ongoing, with 2:1 randomization to receive either [redacted] of RSV ΔNS2/ Δ1313 /I1314L or placebo, and a sample size of up to 30 infants (ClinicalTrials.gov Identifier: NCT01893554) (23). To date, data is available on 15 infants aged 4 to 6 months who have been enrolled up to date and have completed the post-vaccination Acute and Post-Acute Phase of follow-up. Based on this data, the vaccine was well tolerated at the [redacted] dose, infectivity was 100% and vaccine virus replication was limited. Immunogenicity data from this study is pending.

RSV ΔNS2/Δ1313/I1314L vaccine appears to be safe and immunogenic in RSV seronegative infants and toddlers aged 6 to 24 months; and appears to be safe with restricted shedding in infants aged 4 to 6 months. Based on NIH Phase I trial data, RSV ΔNS2/Δ1313/I1314L will be evaluated by Sanofi Pasteur for further clinical development.

# 2 Study Objectives

## 2.1 Primary Objectives

***Primary Safety Objective:***

- To assess the safety profile of each dose of RSV ΔNS2/Δ1313/I1314L after each and any administration in all infants and toddlers regardless of baseline serostatus.

***Primary Immunogenicity Objective:***

- To characterize the RSV A serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 in RSV-naive participants.

The endpoints for the primary objectives are presented in Section 9.1.

## 2.2 Secondary Objectives

***Secondary Safety Objectives:***

- To quantify the amount of vaccine virus shed by each participant on D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4, measured by [redacted] by baseline serostatus.

***Secondary Infectivity Objective:***

- To determine the proportion of vaccinated infants and toddlers in each vaccine group infected[a] with the vaccine virus at D56 (56 days after vaccination 1) for Cohorts 1, 2, 3 and 4, and at D84 (28 days after vaccination 2) for Cohorts 2 and 4 by baseline serostatus.

***Secondary Immunogenicity Objectives:***

- To characterize the RSV A serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) in Cohorts 2 and 4 in RSV-experienced participants.
- To characterize RSV serum anti-F IgG antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize RSV serum antibody responses (RSV A-neutralizing and anti-RSV F IgG) to the study product in each vaccine group after the RSV surveillance season or at least 5 months after the last vaccine administration by baseline serostatus.

The endpoints for the secondary objectives are presented in Section 9.2.

[a] Infection defined as detection of vaccine in nasal swab sample by [redacted] and / or a ≥ 4-fold rise in RSV A serum neutralizing antibody titers, or RSV serum anti-F IgG antibody titers.

## 2.3 Exploratory Objectives

***Exploratory Safety Objective***

- To assess the safety profile of each dose of RSV after each and any administration by baseline serostatus.

***Exploratory Immunogenicity Objectives:***

- To characterize the RSV A serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize the RSV A serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.
- To characterize the RSV B serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize the RSV B serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize the RSV B serum neutralizing antibody responses to the study product in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.
- To characterize the RSV B serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.
- To characterize RSV A and RSV B serum anti-RSV protein G central conserved (anti-Gcc) IgG antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize RSV A and RSV B serum anti-Gcc IgG antibody responses to the study product in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.
- To characterize the RSV serum anti-F IgA antibody responses after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4 and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize the RSV serum anti-F IgA antibody responses after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.

***Exploratory Efficacy Objective***

- To describe the frequency and severity of RSV-associated, medically attended acute respiratory illness (RSV MAARI) and RSV-associated, medically attended, acute lower respiratory illness (RSV MAALRI) in all infants and toddlers in each vaccine group during the RSV season or at least 5 months after last vaccine administration.

The endpoints for the exploratory objectives are presented in Section 9.3.

# 3 Investigators and Study Organization

This study will be conducted in approximately 30 centers in the United States and approximately 10 centers in Canada, Latin America, and South Africa. Details of the study centers and Investigators at each center, are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal safety management team (SMT) will perform an analysis of safety data during the conduct of the study.

If the predetermined alert threshold for a safety event as outlined in Section 5.1.6 and the SMT charter is reached, regardless of the study time point, the trial will be paused for enrollment in order for an ad hoc SMT to be convened to investigate and complete a study report, and the situation will be escalated to the Vaccine Adjudication Committee (VAC). The VAC decides whether to escalate the findings further up to the level of a Product Safety Board (PSB). Based on the recommendations of the PSB, an ad hoc Independent Data Monitoring Committee (IDMC) may be utilized to review upon request of the SMT unblinded study data and recommend to Sanofi Pasteur whether to continue, modify, or stop the study. The IDMC will make recommendations to the Sponsor on a medical and ethical basis.

The Sponsor's Responsible Medical Officer (the RMO, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted].

# 4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first participant, this protocol, the informed consent form (ICF), participant recruitment procedures, and any other written information to be provided to participants must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committee(s) (IEC[s]) or Institutional Review Board(s) (IRB[s]).

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and / or the Sponsor are responsible for obtaining this approval and / or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator to the Sponsor together with the composition of the IEC / IRB (the names and qualifications of the members attending and voting at the meetings).

The Investigator or Sponsor will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All serious adverse events (SAEs) occurring during the study that are related to the product administered will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy.

# 5 Investigational Plan

## 5.1 Description of the Overall Study Design and Plan

### 5.1.1 Study Design

This is a Phase I/II, randomized, observer-blind, placebo-controlled, multi-center, dose-finding study to evaluate the safety, immunogenicity, infectivity, and vaccine virus shedding after 1 or 2 administrations of a live-attenuated RSV ΔNS2/Δ1313/I1314L vaccine in infants and toddlers 6 months to 18 months (Cohorts 1 to 4) of age in the United States, Canada, Latin America (Argentina, Chile, and Honduras), and South Africa).

***Vaccination:***

A total of 300 infants and toddlers 6 to18 months of age will be enrolled into 1 of 4 cohorts, sequentially, and within each cohort will be randomized to receive intranasal administration of their assigned study product as follows:

- Cohort 1 – 40 infants and toddlers to receive 1 administration, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose) or placebo (same formulation buffer as the RSV ΔNS2/Δ1313/I1314L vaccine)
- Cohort 2 – 40 infants and toddlers to receive 2 administrations, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose) or placebo
- Cohort 3 – 40 infants and toddlers to receive 1 administration, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (high-dose) or placebo
- Cohort 4 – 180 infants and toddlers to receive 2 administrations, 1:1:1 of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose), RSV ΔNS2/Δ1313/I1314L [redacted] (high-dose) or placebo.

***Cohort 1 (Northern Hemisphere):***

1:1 randomized, placebo-controlled, 1 dose of RSV ΔNS2/Δ1313/I1314L [redacted]), 1 administration ([redacted] in total per administration) at Day (D) 0, n=20 per vaccine group. Participant enrollment will be initiated at approximately 15 sites in the US in August/September 2020. Vaccine administration will be completed at least 5 days before the beginning of RSV season (the average 5-month RSV season in the northern hemisphere is 01 November to 31 March). If recruitment in Cohort 1 does not reach the goal of n=40, no attempt will be made to include more participants receiving 1 administration in Cohort 2.

***Cohort 2 (Southern Hemisphere):***

1:1 randomized, placebo-controlled, 1 dose of RSV ΔNS2/Δ1313/I1314L [redacted] 2 administrations ([redacted] in total per administration) at D0 and D56, n=20 per vaccine group. Participant enrollment will be initiated at approximately 4 sites in Latin America ((Argentina and Chile) at the earliest in November/December 2020. The first and the second vaccine administrations (D0 and D56, respectively) will be completed at least 5 days before the beginning

of the RSV season (the average 5-month RSV season in the southern hemisphere is 01 May to 30 September).

***Cohort 3 (Northern Hemisphere):***

1:1 randomized, placebo-controlled, 1 dose of RSV ΔNS2/Δ1313/I1314L [redacted]
1 administration ([redacted] per administration in total) at D0, n=20 per vaccine group. Participant enrollment will be initiated at approximately 30 sites in the US in April 2021. Vaccine administrations will be completed before 31 May 2021. If recruitment in Cohort 3 does not reach the goal of n=40, no attempt will be made to include more participants receiving 1 administration in Cohort 4.

***Cohort 4 (Northern and Southern Hemisphere):***

1:1:1 randomized, placebo-controlled, 2 doses of RSV ΔNS2/Δ1313/I1314L ([redacted]), 2 administrations ([redacted] per administration in total) at D0 and D56, n=60 per vaccine group. Participant enrollment will be initiated at approximately 30 sites in the US at the earliest in June 2021, approximately 2 sites in Canada at the earliest in May 2022, approximately 2 sites in Chile at the earliest in November 2021, approximately 2 sites in Honduras at the earliest in April 2022, and approximately 2 sites in South Africa at the earliest in June 2022.

The first and the second vaccine administrations will be completed at any time of the year, including the winter RSV season, regardless if normal RSV seasonality is restored after the disruption due to COVID-19 non-pharmaceutical interventions.

***Blood Sampling:***

All participants screened for inclusion in Cohorts 1, 2, 3 and 4 will provide a blood sample at enrollment (Visit 01), for baseline RSV serum antibody testing.

All participants in each vaccine group in Cohorts 1, 2, 3 and 4 will provide a blood sample at the D56 Visit (before vaccination 2 for Cohorts 2 and 4), for the measurement of post-vaccination serum antibody titers to RSV.

All participants in each vaccine group in Cohorts 2 and 4 will provide a blood sample at the D84 visit (28 days post-vaccination 2) for the measurement of post-vaccination 2 serum antibodies to RSV.

All participants in Cohorts 1, 2, 3 and 4 will provide a blood sample during the month following the RSV season or at least 5 months after the last vaccine administration for the measurement of post-season RSV antibody titers, to determine if a 4-fold or greater rise in RSV antibody titers has occurred during the RSV season, indicating infection with wt RSV that was not detected by surveillance.

***Nasal swab samples:***

Nasal swab samples will be collected in all participants at D7 for Cohorts 1, 2, 3 and 4; and on D63 for Cohorts 2 and 4 for the following:

- Quantification of vaccine virus shedding on D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4.
- The same nasal swab specimens will be tested for respiratory pathogens if the child is ill at the same time points (D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4).

- A nasal swab specimen for the detection of RSV and respiratory pathogens will be collected from participants during illness visits and 48 hours later at any other protocol-specified time point in the study (see Table 5-4) including the medically attended surveillance during the RSV season.

***Collection of Safety Data:***

The Acute Phase for the first vaccine administration begins on D0 post-vaccination and ends at midnight on D28. The Acute Phase for the second vaccine administration begins on D56 post-vaccination and ends at midnight on D84. Any adverse reactions, AEs, AESIs, MAAEs, or SAEs that begin within the Acute Phase (i.e., within 28 days after a vaccination) but are diagnosed by a medical professional after 28 days will still be considered as occurring within the Acute Phase.

The Post-Acute Phase for participants receiving 1 administration begins at 12:01 am on D29 and ends at midnight on D56. The first Post-Acute Phase for participants receiving 2 administrations begins at 12:01am on D29 and ends at midnight on D56, except if second administration is exactly on D56 when it ends immediately before receipt of the second administration. The second Post-Acute Phase for participants receiving 2 administrations begins at 12:01 am on D85 and ends at midnight on D112.

- All participants will be observed for 30 minutes after each vaccine administration and any unsolicited systemic adverse events (AEs) occurring at that time will be recorded as immediate unsolicited systemic AEs in the case report book (CRB).
- All participants will be followed for solicited administration site reactions and systemic reactions, unsolicited adverse events, adverse events of special interest (AESIs), medically attended adverse events (MAAEs) within 28 days after each and any vaccination, and from vaccination to the end of study participation for serious adverse events (SAEs).
- The participant's parent / guardian / legally authorized representative will record information in a Diary Card (DC) / Electronic Diary Card (eDC) to capture solicited reactions, unsolicited AEs, AESIs and MAAEs from D0 to D28 for Cohorts 1, 2, 3 and 4, and D56 to D84 for Cohorts 2 and 4. Parents / guardians / legally authorized representatives should alert the study site regarding reactions, AEs and any symptoms suggestive of respiratory tract illness. The study sites will follow up via phone calls. The eDC allows daily safety monitoring of the study participant also. In certain cases, when an eDC cannot be used, a paper diary card will be used for daily safety monitoring. All solicited reactions will be graded by the Sanofi Pasteur Intensity scale, except for runny nose/rhinorrhea and stuffy of blocked nose/nasal congestion which will be graded by the Division of AIDS (DAIDS) scale. Adverse events of special interest will be graded by the DAIDS scale, except for wheeze which will be graded according to Brighton Collaboration specifications.
- Based on previous NIH clinical experience with live-attenuated RSV vaccine candidates and Sanofi Pasteur Safety Guideline Standard Practice for the Collection, Analysis, and Reporting of Safety Data, the following predefined solicited reactions will be assessed during the Acute Phase for each vaccine administration:
    - Administration site reactions
        - Runny nose

    - Stuffy or blocked nose /nasal congestion
  - Systemic reactions
    - Fever
    - Vomiting
    - Crying abnormally
    - Drowsiness
    - Appetite loss
    - Irritability

The following AESIs will be assessed during the Acute Phase of the study:

- Acute otitis media
- Upper respiratory tract illness (URI)
  - Pharyngitis
  - Cough without LRI
- Lower respiratory tract illness (LRI)
  - Stridor
  - Rales
  - Tachypnea
  - Acute wheeze
  - Pneumonia
  - Laryngotracheobronchitis

- Immediate hypersensitivity reactions including urticaria, anaphylaxis, or other IgE-mediated responses are possible as with any vaccine.
- MAAEs will be collected during the Acute Phase for either vaccination using the same process as other AEs.
- SAEs will be recorded throughout the participant's participation in the study. The participant's parent / guardian / legally authorized representative will be asked to notify the site immediately about any potential SAE at any time during the study. In addition, the participant's parent / guardian / legally authorized representative will record information in a DC / eDC about SAEs from the D0 to D56 visits (Cohorts 1 and 3), and from D0 to D84 visits (Cohorts 2 and 4). Participant's parent / guardian / legally authorized representative receives a memory aid (MA) to record the SAEs from the D56 visit until the end of the study (Cohorts 1 and 3) and from the D84 visit until the end of the study (Cohorts 2 and 4).
- The completed DC / eDC or MA will be reviewed with the participant's parent / guardian/ legally authorized representative at each visit.

### 5.1.2 Justification of the Study Design

For this Sanofi Phase I/II trial, data will be analyzed according to serostatus. Baseline serostatus will be retrospectively determined from serum samples collected at baseline. Participants will be categorized into RSV-experienced or RSV-naïve based on the presence or absence of detectable serum RSV anti-F IgA antibodies. This biomarker has been chosen since it is produced only in response to RSV infection and not transferred trans-placentally from mother to child.

***Evaluation of post-vaccination immunogenicity on Day 56 for Cohorts 1, 2, 3 and 4 and Day 84 for Cohorts 2 and 4:***

To date, all studies with live-attenuated RSV candidate vaccines have used Day 56 as the time point to assess serum antibody response post-vaccination with a single dose administration. This time point is used for two reasons: 1) since this is a primary response (rather than an anamnestic [memory] response), serum antibody response may not have reached maximal levels by Day 28 and 2) maximal replication of these highly attenuated vaccine viruses does not typically occur until Day 7, which may also delay induction of the immune response. In participants receiving 2 administrations of vaccine, this is no longer likely to be a primary response and rather an anamnestic (memory) response and serum antibody response is likely to be maximal by Day 28 after the second vaccination.

***RSV season or post-vaccination RSV surveillance for Cohort 4:***

Based on previous data regarding the seasonality of RSV in the US, Canada, Chile, Honduras, and South Africa, surveillance for RSV-associated disease will be largely conducted during the NH (1st November to 31st March) and SH (1st May to 30 September) RSV seasons respectively, adjusted for local site RSV seasonality. Due to the disruption of the seasonal pattern of RSV globally (24) (25), it is unclear when the normal seasonal transmission will resume though there is some suggestion of a rebound in the winter of 2021–2022 in the NH (26). Because of the unpredictability of the RSV season due to the impact of COVID-19 nonpharmaceutical interventions, study participant enrollment and vaccination will continue regardless of RSV activity. Study participants enrolled before the routine winter RSV season for that locality will be followed up until the consequent month after the end of the routine season (i.e. April for NH and October for SH). Study participants enrolled during the routine RSV season (i.e. November to March for NH and May to September for SH) will be followed up for at least 5 months after the last vaccine administration. During the RSV season or post-vaccination RSV surveillance, study participants will be monitored for symptomatic medically attended respiratory illness. Note, this surveillance may overlap with the Acute and Post-Acute phases. In this case, evaluations required for each of the relevant phases of the study will be conducted.

***Evaluation of two vaccine doses [redacted]:***

Previous Phase Ia studies done by the NIH have demonstrated that the [redacted] dose of RSV ΔNS2/Δ1313/I1314L vaccine resulted in better infectivity and neutralizing antibody seroresponse than the [redacted] dose, with no evidence of an excess of respiratory tract illness associated with receipt of the higher dose ([redacted]). However, in these studies, the vaccine was administered intranasally using a sterile, needle-less 1 mL oral syringe, at a volume of 0.5 mL as nasal drops (approximately 0.25 mL per nostril). In VAD00001 study, the vaccine would be administered at a total volume of [redacted]

[redacted] Use of an intranasal [redacted] may improve the overall delivery of the vaccine and may increase replication in both doses. Use of the [redacted] may also improve the infectivity of the low dose [redacted] doses will be the minimal doses explored using the [redacted].

***Evaluation of two administrations of vaccine doses:***

There are several published studies evaluating 2 or 3 administrations of attenuated RSV or parainfluenza virus type 3 (PIV3) candidate vaccines (5) (6) (9) (27) (28) (29) (30) (31) (32). Generally, there was a high level of restriction of the second administration, and limited serum immune responses. The main effect was vaccine infectivity in the individuals who did not respond to the first administration. Two administrations of RSV ΔNS2/Δ1313/I1314L may improve the infectivity of either dose.

***Selection of vaccine dose using safety, infectivity, viral shedding and immunogenicity in infants and toddlers regardless of baseline RSV serostatus:***

Given the plan for a future liquid formulation in which the targeted dose will decay over the shelf life of the product, the dose selection based on this study relates to the future clinical development with frozen product. The data will be analyzed for comparable safety, infectivity, and immunogenicity profile between the two doses utilized in this study to justify clinically the future dose range boundaries of the non-frozen liquid formulation for final commercialization. The vaccine dose for the frozen liquid product to be utilized in future late-stage studies is expected to be around mid-range of the planned operative range for the future liquid formulation of [redacted].

Therefore, an unblinded interim analysis for dose confirmation of RSV ΔNS2/Δ1313/I1314L vaccine is planned on participants from Cohorts 1, 2 and 3 and at least 90 participants enrolled in Cohort 4. The interim analysis will take place when participants have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. Based on the results of this analysis, the dose for future clinical studies (frozen product) will be confirmed. The acceptability of safety, infectivity, and immunogenicity results of the two doses tested to justify clinically the future dose range boundaries of the non-frozen liquid formulation for final commercialization will also be descriptively assessed. The selected dose will then be confirmed during an early analysis.

An unblinded early analysis is planned on all participants when they have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. Based on the results of this analysis, the dose for future studies will be confirmed.

***Placebo group:***

Placebo recipients will be included in each cohort to establish the background rates of respiratory and febrile illnesses that occur in infants and toddlers.

***Clinical hypothesis:***

Both doses of the live-attenuated RSV ΔNS2/Δ1313/I1314L vaccine are anticipated to be safe and immunogenic in infants and toddlers. However, administration of either dose may be associated

with adverse events that become apparent only when analyzed in a larger number of participants than the numbers enrolled in Laboratory of Infectious Disease (LID)/ National Institute of Allergy and Infectious Diseases (NIAID)/NIH Phase Ia studies, where each study assessed 10 to 40 vaccinees. Additionally, the rate, magnitude and durability of antibody responses may differ according to dose, as well as the magnitude of the memory (anamnestic) seroresponse observed following naturally occurring RSV infection. The intranasal [redacted] device used in this study may also impact the safety and immunogenicity of the vaccine. Dose selection will be based on a descriptive comparison of the safety, infectivity and immunogenicity of 1 or 2 administrations of either dose category.

### 5.1.3 Study Plan

See Table of Study Procedures and Section 5.1.4 Visit Procedures for the plan of activities for the study period. Figure 5.1 shows an overview of the study design. Figure 5.2 and Figure 5.3 provide overviews of the study plan and the timeframes for Cohorts 1 and 3, and Cohorts 2 and 4, respectively.

**Figure 5.1: Study Design**

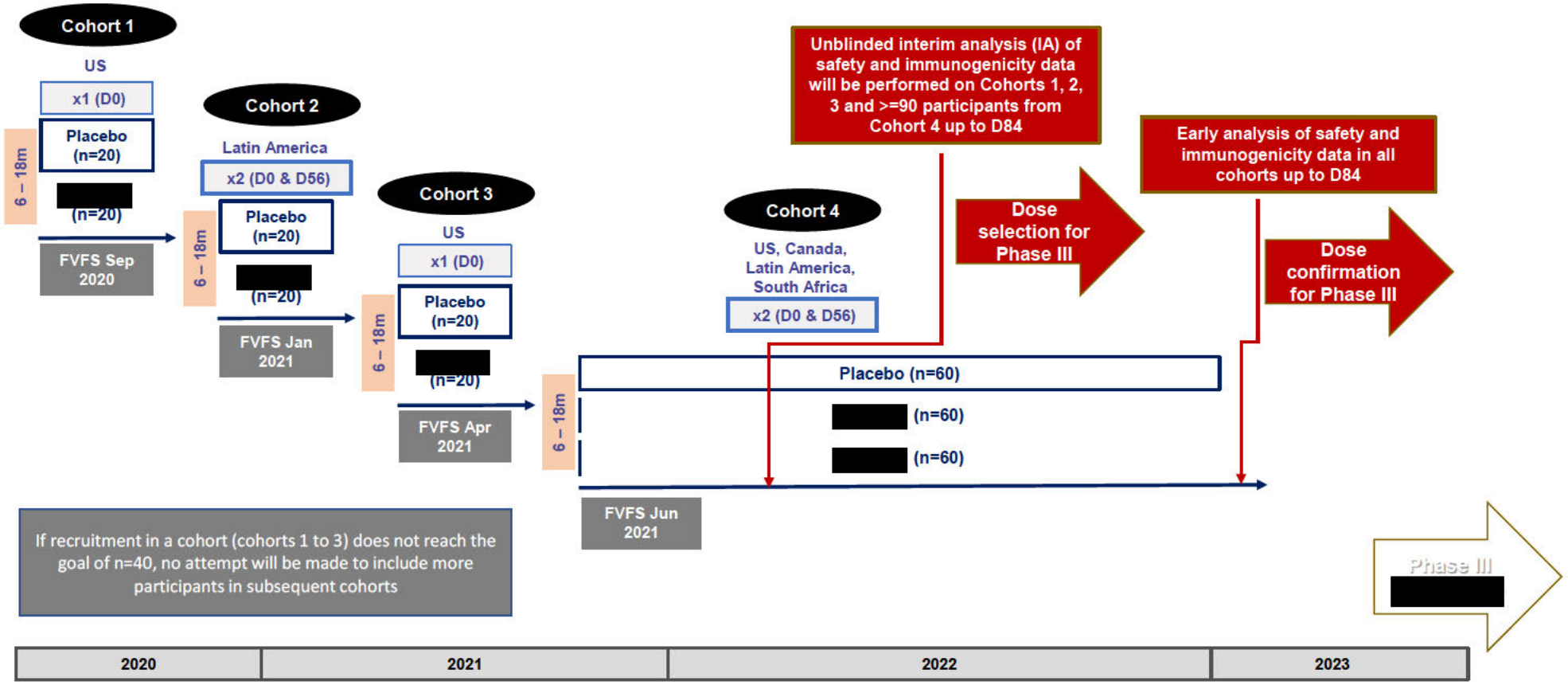

**Figure 5.2: Study Plan and Timeframe for Cohorts 1 and 3**

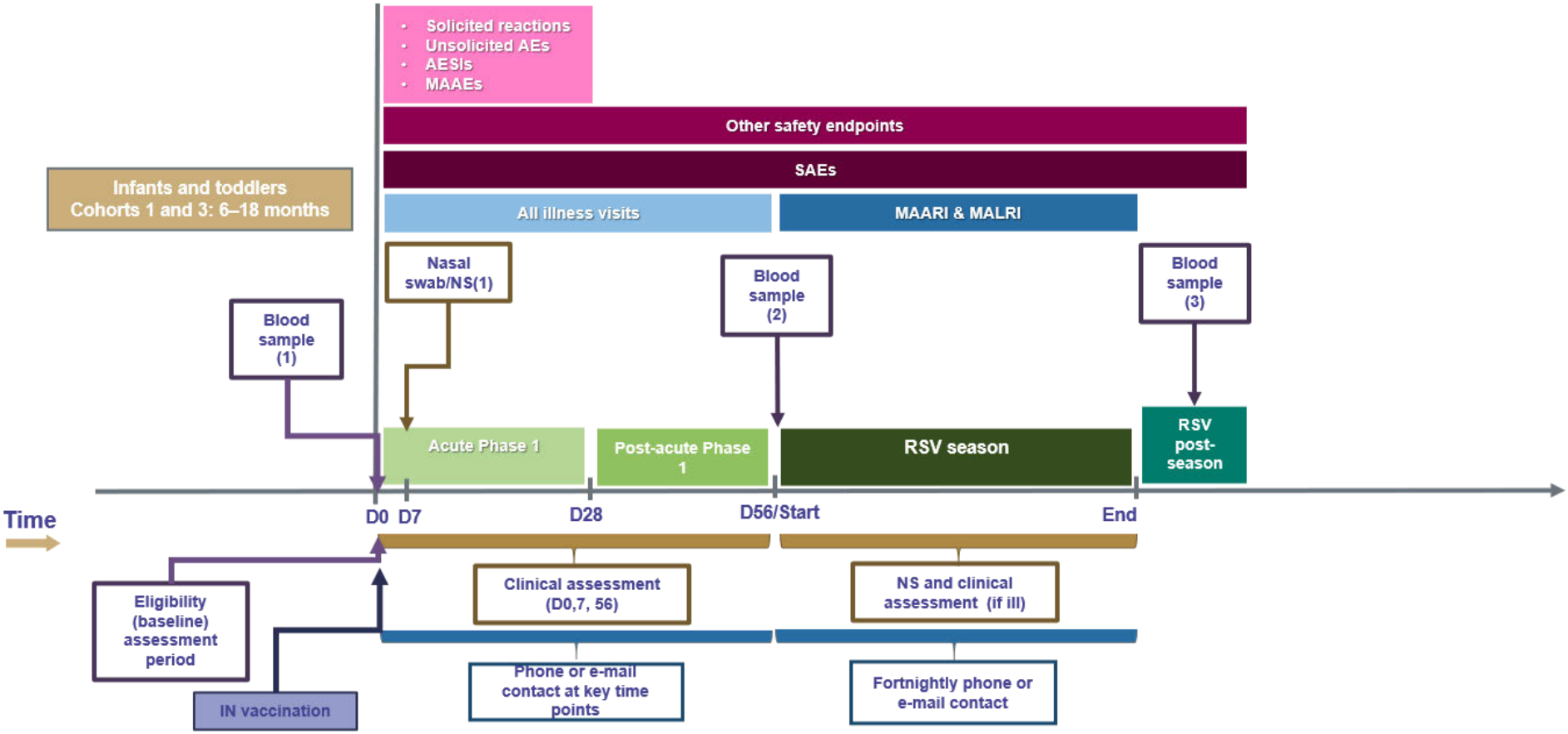

**Figure 5.3: Study Plan and Timeframe for Cohorts 2 and 4**

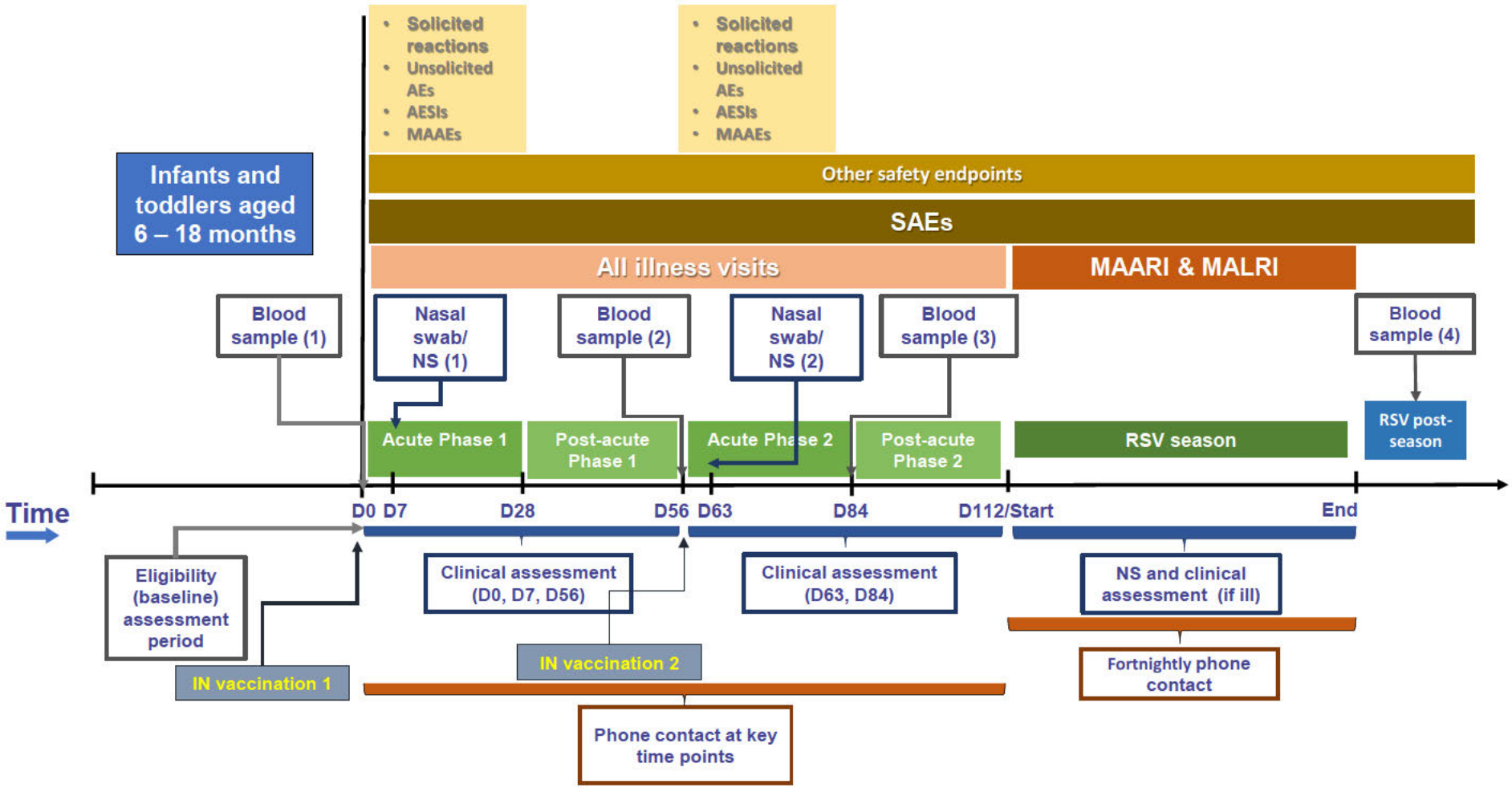

**Table 5-1: Schedule of blood sample collection (volume in mL) – Cohorts 1 and 3**

| **Visit Number** | **Visit 01** | **Visit 02** | **Visit 03** | **Visit 04** |
|---|---|---|---|---|
| **Study Timelines** | **D0** | **D7** | **D56+7** | **Post-RSV season*** |
| **Time Windows (Days)** | | | | |
| Vaccination | X | | | |
| Blood Samples (mL) | 5† | - | 5 | 5* |
| Total volume of blood collected (mL) | **5** | **-** | **5** | **5** |

† All participants screened will provide a blood sample up to 5 mL at enrollment (Visit 01) prior to receipt of the first administration of assigned study product, for baseline RSV serum antibody testing.
*All participants will provide a blood sample up to 5 mL during the month following the RSV season or at least five months after the last vaccine administration for the measurement of post-season RSV antibody titers, respectively, to determine if a 4-fold or greater rise in RSV antibody titers has occurred during the RSV season.

**Table 5-2: Schedule of blood sample collection (volume in mL) – Cohorts 2 and 4**

| **Visit Number** | **Visit 01** | **Visit 02** | **Visit 03** | **Visit 04** | **Visit 05** | **Visit 06** |
|---|---|---|---|---|---|---|
| **Study Timelines** | **D0** | **D7** | **D56+7** | **D63+7** | **D84+8** | **Post-RSV season‡** |
| **Time Windows (Days)** | | | | | | |
| Vaccination | X | | X | | | |
| Blood samples (mL) | 5† | - | 5* | - | 5* | 5‡ |
| Total volume of blood collected (mL) | **5** | **-** | **5** | **-** | **5** | **5** |

† All participants screened will provide a blood sample up to 5 mL at enrollment (Visit 01) prior to receipt of the first administration of assigned study product, for baseline RSV serum antibody testing.
*All the participants will provide a blood sample up to 5 mL at the D56 Visit (before vaccination 2), and then at D84 Visit for the measurement of post-vaccination serum antibodies to RSV.
‡All participants will provide a blood sample up to 5 mL during the month following the RSV season or at least five months after the last vaccine administration for the measurement of post-season RSV antibody titers, to determine if a 4-fold or greater rise in RSV antibody titers has occurred during the RSV season.

### 5.1.4 Visit Procedures

See Table of Study Procedures for Cohorts 1, 2, 3 and 4.

#### 5.1.4.1 In-Person Visits

***Visit 01 (Day 0) for Cohorts 1, 2, 3 and 4***

Timelines for the end of enrollment (Visit 01), vaccination and RSV surveillance per hemisphere are shown in Table 5-3.

**Table 5-3: Timelines for end of enrollment and vaccination per hemisphere**

| | Infants and Toddlers 6 to 18 Months of Age | | | |
|---|---|---|---|---|
| | **Northern Hemisphere (USA)**<br>**Cohort 1 (1 administration)** | **Southern Hemisphere (Latin America)**<br>**Cohort 2 (2 administrations)** | **Northern Hemisphere (USA)**<br>**Cohort 3 (1 administration)** | **Northern and Southern Hemispheres (USA and Latin America)**<br>**Cohort 4 (2 administrations)** |
| **Earliest day for enrollment (Visit 01)** | 01 August 2020 | 01 November 2020 | 01 April 2021 | USA - 01 June 2021<br>Canada – May 2022<br>Chile - November 2021<br>Honduras - April 2022<br>South Africa - June 2022 |
| **Last day for enrollment (Visit 01)** | 5 days before the start of the RSV season | 61 days before the start of the RSV season | 31 May 2021 | Not applicable |
| **Last day for Visit 03 (D56) Vaccination 2** | - | 5 days before the start of the RSV season | - | Not applicable |

***Visit 01 (Day 0): Enrollment, Randomization, and Vaccination Procedures for Cohorts 1, 2, 3 and 4 (All Participants)***

1) Give the participant's parent / guardian / legally authorized representative information about the study, obtain written informed consent, and give him / her a signed copy.
2) Collect demographic data (including date of birth, sex, race, and ethnicity).
3) Check inclusion and exclusion criteria for eligibility.
4) Obtain verbal medical history about the participant, including past and ongoing medication, any signs and symptoms, and developmental delays.
5) Review any past medical records including the immunization record to ensure participant will not meet exclusion criteria 2, 3 and 21.
6) Prior to randomization conduct a full physical examination including body temperature, heart rate, respiratory rate, weight, length and assessment of HEENT [head, ears, eyes, nose, and throat], lungs, heart, and abdomen, musculoskeletal, age-appropriate neurological and skin exam.
7) Perform Coronavirus Disease 2019 (COVID-19) point of care diagnostic test (POC).
8) Contact the IRT for participant number, randomization and dose number based on age sub-group. Additional information regarding randomization is in the Operating Guidelines.
9) Obtain the first blood sample, to test the baseline RSV antibody serostatus, i.e., serum RSV-nAb titer (Section 7.1 for detailed instructions regarding the handling of blood samples and Operating Guidelines for further details).
10) Administer the appropriate study product, follow the instructions provided for the intranasal administration of study vaccine using the [redacted] in the Study Operating Guideline.
11) Keep the participant under observation for 30 minutes and record any adverse reaction in the source document.
12) Give or download the parent / guardian / legally authorized representative a diary card (DC1) / eDC and a thermometer and go over the instructions for their use, as detailed in the Study Operating Guideline, and remind to complete the Day 0–7 pages of DC1 / eDC. The parent / guardian / legally acceptable representative will record the child's temperature and signs of illness (solicited reactions and unsolicited AEs, including AESIs, MAAEs and SAEs) on the DC1 / eDC.
13) Remind the parent / guardian / legally authorized representative to expect a telephone call from the study site nurse daily after this immunization Visit 01 to review what they have entered daily in the DC1 / eDC; and to complete the remaining entries of DC1 / eDC and bring to Visit 02 at the specified date.
14) Remind the parent / guardian / legally authorized representative to notify the site in case of an SAE or any illness. The site staff, upon evaluation, will schedule an Illness Visit within the stipulated time frame of site notification, if required.
15) Complete the relevant case report forms (CRFs) for this visit.

***Visit 02: Day 07 Post-Vaccination 1 Visit Procedures for Cohorts 1, 2, 3 and 4 (All Participants)***

1) Review medical history, including past and ongoing medication since the last visit.
2) Perform a focused clinical examination including temperature, pulse, and respirations, ears, eyes, nose, throat (EENT), respiratory, cardiac and lymphatic system.
3) Obtain a nasal swab sample for viral quantification of vaccine virus shedding. If the participant meets criteria for an Illness Visit at Day 7, the same nasal swab specimens may also be tested for respiratory pathogens.
4) Review the solicited reactions and unsolicited AEs, AESIs, MAAEs and SAEs in the completed DC1 / eDC with the participant's parent / guardian / legally authorized representative. Provide instruction to complete DC2.
5) If an SAE occurred, follow the instructions in Section 10 for reporting it. Remind to notify the site in case of an SAE.
6) Complete the relevant CRFs for this visit.
7) Remind the parent / guardian / legally acceptable representative of the following visit.

***Visit 03: Day 56+7 Post-Vaccination 1 Visit Procedures for Cohort 1 and 3***

1) Review medical history, including past and ongoing medication since the last visit. Check for contraindications.
2) Perform a focused clinical examination including temperature, pulse, and respirations, EENT, respiratory, cardiac and lymphatic system.
3) Obtain a blood sample for serum antibodies to RSV (see Section 7.1 for detailed instructions regarding the handling of blood samples).
4) Collect and review SAEs in the completed DC1 and DC2 / eDC with the participant's parent / guardian / legally authorized representative. Provide MA.
5) If an SAE had occurred, follow the instructions in Section 10 for reporting it. Remind to notify the site in case of an SAE.
6) Complete the relevant CRFs for this visit.
7) Remind the parent / guardian / legally authorized representative of the following visit.

***Visit 03: Day 56+7 Post-Vaccination 1 Visit Procedures for Cohorts 2 and 4***

1) Obtain verbal medical history about the participant, including past and ongoing medication and immunizations.
2) Check for contraindications for receipt of second vaccination.
3) Prior to vaccination, conduct a focused clinical examination including temperature, pulse, and respirations, EENT, respiratory, cardiac and lymphatic system.
4) Perform COVID-19 POC diagnostic test.
5) Collect reportable concomitant medications / vaccinations.

6) Contact the IRT for dose number.
7) Obtain a blood sample for serum antibodies to RSV (see Section 7.1 for detailed instructions regarding the handling of blood samples).
8) Administer the appropriate study product, follow the instructions provided for the intranasal administration of study vaccine using the [redacted] in the Study Operating Guideline.
9) Keep the participant under observation for 30 minutes and record any adverse reaction in the source document.
10) Collect and review solicited reactions and unsolicited AEs, including AESIs, MAAEs and SAEs in the completed DC1 and DC2 / eDC with the participant's parent / guardian / legally authorized representative.
11) Give or download the parent / guardian / legally authorized representative a diary card (DC3) /eDC and a thermometer and go over the instructions for their use, as detailed in the Study Operating Guideline, and remind to complete the Day 0–7 pages of DC3 / eDC. The parent / guardian / legally authorized representative will record the child's temperature and signs of illness (solicited reactions and unsolicited AEs, including AESIs, MAAEs and SAEs) on the DC3 / eDC.
12) Remind the parent / guardian / legally authorized representative to expect a telephone call from the study site nurse daily after this Visit 04 to review what they have entered daily in the DC3 / eDC, and to complete the entries of DC3 and bring to Visit 05 at the specified date and time.
13) Remind the parent / guardian / legally authorized representative to notify the site in case of an SAE or any illness. The site staff, upon evaluation, will schedule an Illness Visit within the stipulated time frame of site notification, if required.
14) Complete the relevant CRFs for this visit.

***Post-RSV Season or ≥ 5 Months After Last Vaccine Administration Visit for All Cohorts (Visit 04 for Cohorts 1 and 3 or Visit 06 for Cohorts 2 and 4)***

1) Obtain a blood sample for serum antibodies to RSV.
2) Review the MA for SAEs with the participant's parent / guardian / legally authorized representative.
3) If an SAE had occurred, follow the instructions in Section 10 for reporting it. Remind to notify the site in case of an SAE.
4) Complete the relevant CRFs for this visit and the End of Study CRF.

***Visit 04: D63+7 Post-Vaccination 1 (Day 07 Post-Vaccination 2) Visit Procedures for Cohorts 2 and 4***

1) Review medical history, including past and ongoing medication since the last visit.
2) Perform a focused clinical examination including temperature, pulse, and respirations, EENT, respiratory, cardiac and lymphatic system.

3) Obtain a nasal swab sample for quantification of vaccine virus shedding. If the participant meets criteria for an Illness Visit, the same nasal swab specimens may also be tested for respiratory pathogens.
4) Review the solicited reactions and unsolicited AEs, AESIs, MAAEs and SAEs in the completed DC3 / eDC with the participant's parent / guardian / legally authorized representative.
5) If an SAE occurred, follow the instructions in Section 10 for reporting it. Remind to notify the site in case of an SAE.
6) Complete the relevant CRFs for this visit.

***Visit 05: D84+8 Post-Vaccination 1 (Day 28+8 Post-Vaccination 2) Visit Procedures for Cohorts 2 and 4***

1) Review medical history, including past and ongoing medication and immunizations since the last visit.
2) Perform a focused clinical examination including temperature, pulse, and respirations, EENT, respiratory, cardiac and lymphatic system.
3) Obtain a blood sample for serum antibodies to RSV.
4) Collect and review the solicited reactions and unsolicited AEs, AESIs, MAAEs and SAEs in the completed DC3 / eDC with the participant's parent / guardian / legally authorized representative. Provide MA.
5) If an SAE had occurred, follow the instructions in Section 10 for reporting it. Remind to notify the site in case of an SAE.
6) Complete the relevant CRFs for this visit.

***Visit 99: Illness Visits***

Illness visits can be conducted remotely, as a home visit or an onsite visit depending on the judgment of the investigator. The requirement for an Illness Visit and which type of illness visit will be evaluated first by video call. The video call will be used to initially remotely evaluate the study participant's clinical status and whether the illness can be managed remotely especially for mild (Grade 1) illness. This staged management of illness visits is required during the current COVID-19 pandemic situation to limit the number of contacts between the study participant and study site staff to only those that are absolutely required. Guidelines for remote evaluation are described in the Operating Guidelines.

The timeframe after site notification in which the Illness Visit must occur, if deemed necessary by the Investigator, depends on grading of the fever and respiratory symptoms and the phase of the study. If the Illness Visit occurs on a day concurrent with a routine Study Visit when a nasal swab specimen is to be collected, the same nasal swab specimen would be used to test for respiratory pathogens. A second nasal swab should be collected 48 hours later. If the Illness Visits occurs on a day concurrent with a routine Study Visit when a nasal swab specimen is not collected, a nasal

swab specimen is required to test for respiratory pathogens. A second nasal swab should be collected 48 hours.

If illnesses/safety events occur, the study participant should be managed according to the site/local standard of care, including the conduct of lab investigations required for diagnosis and/or management of the study participant. Following an Illness Visit, medical personnel should continue to follow participants until resolution.

Illness visits may occur at any time during the study. The Illness visit timeframes are summarized in Table 5-4.

**Table 5-4: Illness visit timeframe**

| Phase | Symptom | Grade | Visit timeframe |
|---|---|---|---|
| Acute (post-vaccination to midnight 28 days after each vaccination)* | Fever, acute otitis media or URI | 1 | Within 3 days |
| | | > 1 | Within 2 days |
| | LRI | Any | Within 2 days |
| | SAEs | Any | Within 2 days |
| Post-acute (12:01am on 29th day after post-vaccination to midnight 56 days after each vaccination)* | SAEs | Any | Within 2 days |
| RSV surveillance season (on average, 01 November to 31 March for NH and 01 May to 30 September for SH)* | Medically attended fever, acute otitis media, URI or LRI | >2 | Within 3 days |
| | SAEs | Any | Within 2 days |
| Post-RSV season (on average, 01 to 31 April for NH and 01 to 31 October for SH) or at least 5 months after last vaccine administration | SAEs | Any | Within 2 days |

LRI, lower respiratory tract illness; NH, Northern hemisphere; RSV, Respiratory Syncytial Virus; SAE, serious adverse event; SH, Southern hemisphere; URI, upper respiratory tract illness

*In some circumstances, acute phase or post-acute phase may overlap with the RSV surveillance season, in which case the more conservative visit timeframe should be considered.

Illness Visit procedures are as follows:

1) Obtain verbal medical history about the participant, including past and ongoing medication and immunizations.
2) Determine whether the participant can be managed remotely or if an at home visit or an onsite illness visit is required.
3) If an at home or onsite visit, perform a focused clinical examination including temperature, pulse, and respirations, EENT, respiratory, cardiac and lymphatic system. Instructions for

conducting a focused clinical examination remotely are described in the Operating Guidelines.

4) Collect and review the solicited and unsolicited AEs, AESIs, MAAEs and SAEs in the completed DC / eDC or memory aid with the participant's parent / guardian / legally authorized representative.
5) If an SAE had occurred, follow the instructions in Section 10 for reporting it. Remember to notify the site in case of an SAE, if illness starts within the 28 days of vaccination.
6) Obtain a nasal swab sample for RSV viral detection and [redacted] for respiratory pathogens.
7) COVID-19 testing if required according to the opinion of the investigator and CDC COVID testing algorithm.[a]
8) Complete the relevant CRFs for this visit.
9) Schedule follow-up as appropriate, including a visit for the collection of a confirmation nasal swab 48 hour later.
10) If illnesses/safety events occur, the participant should be managed according to the site/local standard of care, including the conduct of lab investigations required for diagnosis and/or management of the study participant.

Specific guidance for illness visits, including use of personal protective equipment (PPE) for full contact and droplet precaution, are described in the Operating Guidelines.

Follow-up of participants with solicited reactions or with AEs That Led to Study/Vaccination Discontinuation:

Unless a participant or participant's parent / guardian / legally authorized representative refuses further contact, each participant who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the participant's participation in the study) if either of the following is true:

1. The AE is considered by the Investigator to be related to the product administered.
2. The AE caused the discontinuation of the participant from the study or from vaccination.

#### 5.1.4.2 Non-Visit Telephone Contacts

***Acute Phase Telephone Contacts to Review the DCs up to D29+1 (Cohorts 1, 2, 3 and 4) and D84+8 (Cohorts 2 and 4)***

**Note**: If any of the Acute Phase non-visit contacts fall on a weekend or a holiday, the telephone call may be made on the following business day. All telephone contacts with the participant's parent / guardian / legally authorized representative must be made by a qualified person, such as a physician or qualified study nurse.

[a] For CDC COVID testing algorithm, see: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/Antigen_Testing_Algorithm_2020-12-14_v03_NO_DRAFT_SPW_508.pdf

1) Review the information entered in the DC for solicited reactions and unsolicited AEs, AESIs, MAAEs and SAEs. The site staff upon evaluation, if required, will schedule an Illness Visit within the appropriate time window of site notification (Table 5-4).

2) Record relevant information concerning the participant's health status including any changes in medications and immunizations on the telephone contact form, and in the CRF, if required. The site staff, upon evaluation, will schedule an Illness Visit within the stipulated time frame of site notification, if required.

3) If an SAE had occurred, follow the instructions in Section 10 for reporting it. Also remind to notify the site in case of an SAE.

4) Remind the parent / guardian / legally authorized representative to do the following:
   - Complete the remaining pages of the diary card / electronic diary card and bring them to next visit.
   - Notify the site in case of an SAE.

***Day 42+1 Telephone Contact (Cohorts 1, 2, 3 and 4)***

1) Record relevant information concerning the participant's health status including any changes in medications and immunizations on the telephone contact form, and in the CRF, if required. The site staff, upon evaluation, will schedule an Illness Visit within the stipulated time frame of site notification, if required.

2) If an SAE had occurred, follow the instructions in Section 10 for reporting it. Also remind to notify the site in case of an SAE.

3) Remind the parent / guardian / legally authorized representative to do the following:
   - Complete the remaining pages of the diary card / electronic diary card and bring them to next visit.
   - Notify the site in case of an SAE.

***Telephone Contacts During the RSV Season or Post-vaccination RSV Surveillance***

During the RSV season (01 November to 31 March in the northern hemisphere and 01 May to 30 September in the southern hemisphere) or post-vaccination RSV surveillance (at least 5 months after last vaccine administration), make phone contacts every 2 weeks with the parent / guardian / legally authorized representative.

1) Record relevant information concerning the participant's health status including any changes in medications and immunizations on the telephone contact form.

2) Schedule an Illness Visit within the guidelines and stipulated time frame from the phone contact for a medically attended illness of the following types: fever, URI, LRI or otitis media. If this illness overlaps with the Acute or Post-Acute Phases, the time frames specified for the relevant Acute or Post-Acute phase should be used (see Table 5-4).

3) If a participant had visited any other non-study doctor / hospital for a serious adverse event (SAE) (at any time in the study), schedule a site visit once the participant is discharged to obtain a nasal swab sample for RSV viral detection and [redacted] for respiratory pathogens.

4) If an SAE had occurred, follow the instructions in Section 10 for reporting it. Remind to notify the site in case of an SAE.

### 5.1.5 Planned Study Calendar

The following dates are approximate. The actual dates may differ as, for example, the study will not start until all the appropriate regulatory and ethical approvals have been obtained.

Estimated planned study period:
Cohort 1 – 03 September 2020 (FVFP) to 30 April 2021 (LCLS)
Cohort 2 – 11 December 2020 (FVFP) to 31 October 2021 (LCLS)
Cohort 3 – 01 April 2021 (FVFP) to 30 April 2022 (LCLS)
Cohort 4 – 01 June 2021 (FVFP) to 30 April 2023 (LCLS)

Estimated enrollment / 1st vaccination period:
Cohort 1 –03 September 2020 to 27 October 2020
Cohort 2 –11 December 2020 to 01 March 2021
Cohort 3 – 01 April 2021 to 31 May 2021
Cohort 4 – From 01 June 2021

Estimated 2nd vaccination period:
Cohort 2 –05 February 2021 to 26 April 2021
Cohort 4 – From 27 July 2021

Planned date of final clinical study report:
First Interim CSR (6- to 18-month-old participants, Cohorts 1, 2, 3 and at least 90 participants from Cohort 4) – Planned January 2023.
Based on timelines for Cohort 4, assuming 4 months from Day 84 timepoint for the 90th participant (July 2022) to the generation of final key tables for interim data.
Early analysis CSR (all participants) – June 2023
Final CSR – December 2023.
Assuming 4 months from LCLS (April 2023) and 3 months for final statistical analysis and completion of CSR.

### 5.1.6 Early Safety Data Review

The safety of the investigational product will be continuously monitored by the Sponsor. To allow for a cautious, stepwise approach to vaccine administration, early safety data review (ESDR) will be performed during scheduled SMT meetings:

- Cohort 1
  - D7 post-vaccination ESDR/SMT
  - D28 post-vaccination ESDR/SMT
  - D56 post-vaccination ESDR/SMT

- Cohort 2
  - D7 post-vaccination ESDR/SMT
  - D28 post-vaccination ESDR/SMT
  - D84 post-vaccination ESDR/SMT
- Cohort 3
  - D7 post-vaccination ESDR/SMT
  - D28 post-vaccination ESDR/SMT
  - D56 post-vaccination ESDR/SMT
- Cohort 4
  - D7 post-vaccination ESDR/SMT
  - D28 post-vaccination ESDR/SMT
  - D84 post-vaccination ESDR/SMT

The safety data collected will be entered into the CRBs and summarized by the Sponsor in a blinded manner for each ESDR. The ESDR will be performed by the Sponsor during the SMT meetings. Enrollment will not be paused during SMT reviews.

It is understood that all reviews are based on preliminary data that have not been subjected to validation and database lock. The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined early interim safety analysis will continue unchanged.

If at any other time point in the study the predetermined alert threshold for a safety event is reached, regardless of the study time point, the trial will be paused for enrollment in order for an ad-hoc SMT to be convened.

During the safety evaluation, a Bayesian approach based on Posterior Distribution may be used to assess the difference between each RSV formulation and placebo on the following safety endpoints:

- Any Grade 3 lower respiratory tract illness e.g., wheezing, pneumonia, sustained tachypnea, laryngotracheobronchitis (see Section 9.1.1.3.5)
- Grade 3 fever

The probability that the difference of percentages of events between one RSV formulation and Placebo is greater than a pre-specified margin (δ) can be calculated based on posterior distribution, using non-informative prior Beta (1,1) (33) and observed binomial data:

Proba (%RSV - %Placebo > δ)

If this probability is high (e.g., >=80%) then it may be recommended to drop the formulation. Thus, it can help decision making for safety evaluation by SMT and/or IDMC (if applicable) and can also be applied at the end of the study.

In cases where the review of data by the SMT does not result in the identification of a potential safety signal, SMT oversight proceeds as assigned in the SMT charter. When a safety signal is identified, the SMT investigates the event(s), completes the Safety Analysis and/or Evaluation Report and decides about the safety signal and further actions and/or recommendations including:

- Extending or pausing the trial and escalate to the Vaccine Adjudication Committee (VAC)
- Investigate and develops a report
- Recommends continuing the trial

Within the investigation, the team may consult with non-clinical safety experts and research team members on whether there is a possible underlying mechanism for the event and review of toxicology data or other internal experts depending on the need.

In case of disagreement in the team, the core team seeks respective functional management advice from the VAC shortly after the SMT meeting. The Vaccine Pharmacovigilance Global Business Unit (PV GBU) Head or Vaccines GBU Clinical & Sciences Head may be also consulted, especially in instance where escalation of the signal for PSB review is in question.

Once the SMT core team agrees that there is a safety signal that can potentially impact the participant's safety, study conduct (pause, extended pause, or termination) or design (modifications needed), the SMT PM informs the Vaccine PV GBU Head who validates the signal and urgently contacts the Vaccines GBU Clinical & Sciences Head and the Chair of the PSB. The decision is made on whether to convene a PSB or not.

Based on the outcomes and recommendations from the PSB, the SMT may carry out any of the following operational actions related to the conduct and oversight of the study including:

- Continue the trial
- Extend the pause to conduct a further evaluation e.g., an ad hoc IDMC
- Modify the trial design, or
- Stop the trial.

An ad-hoc IDMC, which ideally will include at least 2 pediatric respiratory virus vaccine experts, will review upon request of the SMT unblinded study data. The ad-hoc IDMC will upon request review the relevant safety information and available data, including magnitude of vaccine virus shedding. If an ad hoc IDMC meeting is required, the ad hoc IDMC will review the data on safety available at that time point to determine if attributable to an etiology, a cause, or a diagnosis unrelated to the study vaccine, and if the adverse event(s) is associated with shedding of vaccine virus at the time of the event (even if another is identified). If the ad-hoc IDMC decides there is no proven causal relationship between the adverse events and study vaccine, the study can continue unchanged. Based on evaluation of the IDMC, the Sanofi Pasteur SMT will decide if there is a causal relationship between the adverse event and the study vaccine, then SMT will decide whether to:

- Conduct internal signal detection processes (SOP # RDWIN-000390)
- Escalate validated signals to PSB as needed
- Continue the trial
- Modify the trial design (with PSB and ad-hoc IDMC input) or,
- Stop the trial (with PSB and ad-hoc IDMC input).

The following safety parameters will be assessed as part of the early safety review:

- Immediate reactions
- Solicited respiratory and systemic reactions
- Unsolicited reactions i.e., AEs reported as related by the Investigator
- SAEs, MAAEs and AESIs

Enrollment will not be paused during the review. The data will be examined for the following:

1) Any deaths, regardless of causality.
2) Any vaccine related SAEs.
3) Grade 3 fever reported in > 2 participants.
4) Any Grade 3 or above solicited adverse events other than fever.
5) >1 participant experiencing lower respiratory tract illness of >Grade 2 DAIDS scale (except for wheeze by Brighton Collaboration Severity Scale) during the acute phase (i.e., within 28 days post-vaccination).
6) Any participant experiencing an AESI of Grade 3 or above by DAIDS scale (except for wheeze by Brighton Collaboration Severity Scale), including lower respiratory tract illness during the acute phase (i.e., within 28 days post-vaccination).
7) >1 participant with a Grade 3 unsolicited AE during the acute phase (i.e., within 28 days post-vaccination).
8) Any other pattern of research laboratory values or clinical symptoms other than fever that is considered a significant safety issue by the Investigator.

If any of the above criteria are met, a decision will be made as to whether enrollment in the study will be allowed to resume.

Case unblinding may be performed, if necessary, as determined by the SMT.

## 5.2 Enrollment and Retention of Study Population

### 5.2.1 Recruitment Procedures

Before the start of the study the Investigator and/or study staff will determine the recruitment strategy to be used at their site for this study (e.g., advertising, database, direct mailing, word of mouth referrals). Using the relevant methods, they will contact an appropriate pool of potential parents / guardians/ legally authorized representatives and invite them to participate in the study. The sites will ensure that any materials used to recruit participants (e.g., information brochures, letters, pamphlets, posters, other advertisements, etc.) are submitted to Sanofi Pasteur prior to submission to the IRB for approval.

In addition, a parent / guardian / legally authorized representative who brings a child to the study site for routine visit will be invited to enroll the participant in the study, if eligible. Participants may also be recruited from the general population.

### 5.2.2 Informed Consent Procedures

Informed consent is the process by which a participant's guardian or appropriate legally acceptable representative voluntarily confirms his or her willingness to participate in a particular study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF.

In accordance with GCP, prior to signing and dating the consent form, the participant's guardian/ representative must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate and must have sufficient time and opportunity to ask any questions.

If the participant's guardian /legally authorized representative is not able to read and sign the ICF, then it must be signed and dated by an impartial witness who is independent of the Investigator. A witness who signs and dates the consent form is certifying that the information in this form and any other written information had been accurately explained to and understood by the participant or his / her guardian / representative.

The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.

If new information becomes available that may be relevant to the participant's guardian / legally authorized representative willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

Informed consent forms will be provided in duplicate, or a photocopy of the signed consent will be made. The original will be kept by the Investigator, and the copy will be kept by the participant's guardian / legally acceptable representative.

Documentation of the consent process should be recorded in the source documents.

***Rationale for Including Participants Unable to Give Consent:***

See Section 1.4 for the rationale for conducting this study in pediatric population.

### 5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria. The Investigator must review the inclusion and exclusion criteria at enrollment (Visit 01).

### 5.2.4 Inclusion Criteria

An individual must fulfill *all* of the following criteria to be eligible for study enrollment (Visit 01):

1) Aged 6 through 18 months at D0.[a]
2) Informed consent form has been signed and dated by the parent(s) / guardian / or other legally authorized representative (and by independent witness if required by local regulations).
3) Participant and parent / guardian / legally authorized representative are able to attend all scheduled visits and to comply with all trial procedures.

### 5.2.5 Exclusion Criteria

An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment:

1) Participation at the time of study enrollment (or in the 6 weeks preceding the first trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure.
2) Receipt of any of the following vaccines prior to enrollment:
    - any influenza vaccine within 7 days prior, or
    - any inactivated vaccine within the 14 days prior, or
    - live-attenuated rotavirus vaccine within the 14 days prior, or
    - any live vaccine, other than rotavirus vaccine, within the 28 days prior, or
    - another investigational vaccine or investigational drug within 28 days prior.
3) Previous receipt of a licensed or investigational RSV vaccine or previous receipt or planned administration of any anti-RSV product (such as ribavirin or RSV immune globulin [IG] or RSV monoclonal antibody).
4) Receipt of immune globulins, blood or blood-derived products in the past 6 months prior to enrollment.
5) 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).
6) Probable or confirmed case of Coronavirus Disease 2019 (COVID-19).
7) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances.[b]

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[a] 6 through 18 months means from 6th month after birth to the day before the 19th month after birth.

[b] The components of the study vaccine are listed in Section 6.1 and in the Investigator's Brochure.

8) Any chronic illness.
   - Chronic illness may include, but is not limited to, cardiac disorders, lung disease (including any history of reactive airway disease, receipt of bronchodilator therapy, or medically diagnosed wheezing), renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases
9) Any history of medically diagnosed wheezing.
10) Any acute febrile, respiratory or gastrointestinal illness in the past 24 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.
11) Receipt of any of the following medications within 3 days prior to study enrollment:
    - systemic antibacterial, antiviral, antifungal, anti-parasitic, or antituberculous agents, whether for treatment or prophylaxis, or
    - intranasal medications, or
    - other prescription medication except as permitted concomitant medications (prescription or non-prescription) including nutritional supplements, medications for gastroesophageal reflux, eye drops, and topical medications, including (but not limited to) cutaneous (topical) steroids, topical antibiotics, and topical antifungal agents.
12) Receipt of salicylate (aspirin) or salicylate-containing products within the 28 days prior to enrollment.
13) Deprived of freedom in an emergency setting or hospitalized involuntarily.
14) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.
15) Any previous anaphylactic reaction.
16) Any previous vaccine-associated adverse reaction that was Grade 3 or above. Note: if grading is not possible, determine if the reaction was considered severe or life-threatening; if so, it is exclusionary.
17) Member of a household that contains, or will contain, an infant who is less than 6 months of age at the enrollment date (or in the 6 weeks preceding the first trial vaccination) through Day 28.
18) Member of a household that contains another child/other children who is/are, or is/are scheduled to be, enrolled in this study in the same year AND the date of enrollment will not be concurrent with the other participant(s) living in the household (i.e., all eligible children from the same household must be enrolled on the same date).
19) 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 enrollment
    - a person receiving immunosuppressant agents
    - a person living with a solid organ or bone marrow transplant.

20) Attends a daycare facility and shares a daycare room with infants less than 6 months of age, and parent/ guardian / legally authorized representative is unable or unwilling to suspend daycare for 28 days following inoculation.
21) Scheduled administration of the following after planned inoculation:
    - any influenza vaccine within 7 days after, or
    - inactivated vaccine or live-attenuated rotavirus vaccine within the 14 days after, or
    - any live vaccine other than rotavirus in the 28 days after, or
    - another investigational vaccine or investigational drug in the 56 days after.
22) Born at less than 34 weeks gestation.
23) Born at less than 37 weeks gestation and less than 1 year of age at the time of enrollment.
24) Current suspected or documented developmental disorder, delay, or other developmental problem.
25) Any previous receipt of supplemental oxygen therapy in a home or hospital setting, except the temporary receipt of supplemental oxygen for transient tachypnea in newborn.

### 5.2.6 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the participant is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRB. The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

For each condition, the data collected will be limited to:

- Diagnosis (this is preferable to reporting signs and symptoms)
- Presence or absence of the condition at enrollment
- The reporting of signs and symptoms in lieu of a diagnosis is strongly discouraged.

Dates, medications, and body systems are not to be recorded, and the information collected will not be coded. The purpose of limited data is to assist in the later interpretation of safety data collected during the study.

### 5.2.7 Contraindications for Subsequent Vaccinations

#### 5.2.7.1 Temporary Contraindications

Should a participant experience one of the conditions listed below at Day 0 (Cohorts 1, 2, 3 and 4) or Day 56 (Cohorts 2 and 4), the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination i.e., within 5 days of randomization for Day 0 (Cohorts 1, 2, 3 and 4) and within 7 days of Day 56 (Cohorts 2 and 4).

1) Any acute febrile illness (rectal temperature ≥38.0°C [≥100.4°F]), acute otitis media, upper and lower respiratory signs or symptoms (including but not limited to rhinorrhea, cough, and pharyngitis), or nasal congestion in the past 24 hours that according to investigator's judgment is significant enough to interfere with successful absorption of the study product.
2) Receipt of any of the following before any study vaccination or scheduled administration after any study vaccination:
    - any influenza vaccine within 7 days prior, or
    - any inactivated vaccine or live-attenuated rotavirus vaccine within the 14 days prior, or
    - any live vaccine, other than rotavirus vaccine, within the 28 days prior, or
    - another investigational vaccine or investigational drug within 28 days prior.

All eligible participants from the same household who are enrolled on the same date must receive the study product on the same date, and therefore if one child experiences illness as above, product administration should be deferred for both children.

#### 5.2.7.2 Definitive Contraindications

Should a participant experience one of the conditions listed below, the Investigator will discontinue vaccination:

1) An anaphylactic or any other significant allergic reaction to the previous dose of vaccine.
2) Any AE greater than Grade 2, LRI of any grade or SAE assessed by the investigator as related to the previous dose of vaccine.
3) Diagnosis of COVID-19

Participants with a definitive contraindication will continue to be followed up for the study-defined safety and immunogenicity assessments, as applicable.

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

### 5.2.8 Conditions for Withdrawal

Parents / guardians / legally authorized representatives will be informed that they have the right to withdraw their child from the study at any time. Any participant who has received study product will be encouraged to remain in study follow-up for the duration of the study even if sample collection is refused.

A participant may be withdrawn from the study:

- At the request of the parent / guardian / legally authorized representative either verbally or in writing (i.e., withdrawal of consent/dropout).
- At the discretion of the Investigator or Sponsor due to safety concern of significant non-compliance with the protocol (based on the Investigator's judgment), without the parent's / guardian's / legally authorized representative's permission (i.e., non-compliant with the protocol/withdrawal).

The reason for a withdrawal or dropout should be clearly documented in the source documents and in the CRB.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in which case, the reason for discontinuation will be noted as "Adverse Event") or for another reason.

Withdrawn participants will not be replaced.

For any participant who withdraws or is terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort to complete the following final evaluations:

1) Obtain verbal medical history about the participant, including past and ongoing medication and immunizations.
2) Obtain a blood sample for serum antibodies to RSV if possible (see Section 7.1 for detailed instructions regarding the handling of blood samples).
3) Obtain a nasal swab sample for quantification of vaccine virus shedding (if in the Acute Phase), other respiratory pathogens including a COVID-19 POC test on the discretion of the investigator.
4) Complete the relevant section of the CRF.

### 5.2.9 Lost to Follow-up Procedures

In the case of participants who fail to return for a follow-up examination, documented reasonable effort (i.e., documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the source documents.

### 5.2.10 Classification of Participants Who Discontinue the Study

For any participant who discontinues the study prior to completion, the most significant reason for early termination will be checked in the CRB. Reasons are listed below from the most significant to the least significant (refer to the CRF completion instructions for additional details and examples):

| | |
|---|---|
| **Adverse Event** | To be used when the participant is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.1.1.1.<br>This category also applies if the participant experiences a definitive contraindication that is an SAE or AE.<br>IMPORTANT NOTE: in case participants are discontinued from the study due to COVID-19 infection related event, "Adverse Event" should be selected and an Adverse Event Form completed if within the protocol defined period for safety collection. |
| **Lost to Follow-up** | To be used when the participant cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the investigator and returned unsigned, and the participant or parent / guardian/ legally authorized representative did not give any other news and did not come to any following visit. |

| | |
|---|---|
| **Protocol Deviation** | To be used:<br>In case of significant non-compliance with the protocol (e.g., deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration or any issue leading to definitely discontinue the participant from the study due to COVID-19 pandemic like for e.g. quarantine, transportation restriction).<br>If the participant experiences a definitive contraindication that is not an SAE or AE.<br>The participant or the parent / guardian / legally authorized representative signed the certified letter sent by the investigator but did not give any other news and did not come to any following visit. |
| **Withdrawal by Participant or Parent / Guardian / Legally authorized Representative** | To be used:<br>• When the participant or parent / guardian/ legally authorized representative indicated unwillingness to continue in the study<br>• When the participant or parent / guardian/ legally authorized representative made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (e.g., participant is relocating, inform consent withdrawal, including fear of exposure to COVID-19 during pandemic period, etc.) |

### 5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any participant who has prematurely terminated the study because of an AE or a protocol deviation.

For participants where the reason for early termination was lost to follow-up or if the participant withdrew informed consent and specified that they do not want to be contacted again and it is documented in the source document, the site will not attempt to obtain further safety information.

If the participant's status at the end of the study is "Withdrawal by Participant or Parent / Guardian / Legally Authorized Representative", the site will attempt to contact them for the post-RSV season visit except if they specified that they do not want to be contacted again and it is documented in the source document.

### 5.2.12 Follow-up of participants with COVID-19 in the study

If a participant develops COVID-19 during the study, the patient will be followed up according to national/regional/local health authority guidelines for as long as possible. All attempts will be made to monitor the safety of the study participant and collect key samples whilst complying with national/regional/local health authority guidelines.

## 5.3 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 Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

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 Global Pharmacovigilance (GPV) Department (please refer to Section 10).

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

### 5.4 Modification of the Study and Protocol

Any amendments to this study plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments (e.g., those that affect the conduct of the study or the safety of participants) require IEC / IRB approval, and must also be forwarded to regulatory authorities.

An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the participants' safety. The IECs / IRBs should only be notified, no formal approval is required.

The Investigator is responsible for ensuring that changes to an approved study, during the period for which IEC / IRB approval has already been given, are not initiated without IEC / IRB review and approval, except to eliminate apparent immediate hazards to participants.

### 5.5 Interruption of the Study

The study may be discontinued if new data about the investigational product resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in the countries where the study is taking place.

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 applicable regulatory requirements. The Investigator shall promptly inform the participant's parents / guardians / legally authorized representatives and should assure appropriate participant therapy and/or follow-up.

## 6 Products Administered

### 6.1 Identity of the Investigational Product(s)

The identity of the investigational products is described in the sections below for Cohorts 1 through 4.

### 6.1.1 Identity of Study Product 1

Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L Vaccine [redacted], suspension of virus

#### 6.1.1.1 Composition

Each [redacted] dose of RSV ΔNS2/Δ1313/I1314L vaccine contains the following components:

Live-attenuated RSV with (i) a 523-nucleotide deletion of the NS2 gene, (ii) an amino acid deletion in the L protein (Δ1313; deletion of S1313), and (iii) genetically stabilizing mutation in the L gene (I1314L), [redacted] to be delivered [redacted] per nostril, using an intranasal [redacted] device

#### 6.1.1.2 Preparation and Administration

[redacted]

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor.

Participants must be kept under observation for 30 minutes after each vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

#### 6.1.1.3 Dose Selection and Timing

Participants in Cohort 1 will receive 1 administration of RSV ΔNS2/Δ1313/I1314L [redacted] vaccine on Day 0.

Participants in Cohorts 2 and 4 will receive 2 administrations: 1 administration of RSV ΔNS2/Δ1313/I1314L [redacted] vaccine on Day 0 and a subsequent administration on Day 56.

[redacted]

[redacted]

[redacted]

[redacted]

### 6.1.2 Identity of Study Product 2

Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L Vaccine [redacted], suspension of virus

[redacted]

#### 6.1.2.2 Preparation and Administration

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

#### 6.1.2.3 Dose Selection and Timing

Participants in Cohort 3 will receive 1 administration of RSV ΔNS2/Δ1313/I1314L [redacted] vaccine on Day 0.

Participants in Cohort 4 will receive 2 administrations: 1 administration of RSV ΔNS2/Δ1313/I1314L [redacted] vaccine on Day 0 and a subsequent administration on Day 56.

#### 6.1.2.4 Vaccination Device

The vaccination device is described in Section 6.1.1.4.

### 6.1.3 Identity of Control Product(s)

Placebo

#### 6.1.3.1 Composition

Same formulation buffer as the RSV ΔNS2/Δ1313/I1314L vaccine, to be delivered as approximately [redacted]

#### 6.1.3.2 Preparation and Administration

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

#### 6.1.3.3 Dose Selection and Timing

Participants in Cohort 1 and 3 will receive 1 administration of placebo on Day 0.

Participants in Cohorts 2 and 4 will receive 2 administrations: 1 administration of placebo on Day 0 and a subsequent administration on Day 56.

#### 6.1.3.4 Vaccination Device

The vaccination device is described in Section 6.1.1.4 .

## 6.2 Identity of Other Product(s)

Not applicable

## 6.3 Product Logistics

### 6.3.1 Labeling and Packaging

The investigational and placebo products in single-dose vials will be supplied with investigational labeling and packaging according to national regulations. Each single dose of investigational or placebo product will be identified by a unique number on the primary label and on the outer carton label. The carton label will also have a detachable label for the sites to attach to the source documents. See the Operating Guidelines for additional label detail.

The investigational and placebo products are blinded at the level of the carton.

### 6.3.2 Product Shipment, Storage, and Accountability

#### 6.3.2.1 Product Shipment

The Clinical Study Manager or designee will contact the Investigator or a designee to determine the dates and times of delivery of products.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

#### 6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a staff member to assume this responsibility.

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a freezer at <-60°C (<-76ºF) and should be protected from light. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the study site. In case of accidental disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

#### 6.3.2.3 Product Accountability

The person in charge of product management at the site will maintain records of product delivery to the study site, product inventory at the site, the dose(s) given to each participant, and the disposal of or return to the Sponsor of unused doses. Because the vaccine and placebo differ in appearance, an unblinded coordinator(s) will verify the product accountability and also dispense the vaccine.

The necessary information on the product labels is to be entered into the source document and the CRB. If applicable, information may also be entered into the participant's vaccination card.

The Sponsor's monitoring staff will verify the study site's product accountability records against the record of administered doses in the CRBs and the communication from the IRT (if applicable).

In case of any expected or potential shortage of product during the study, the Investigator or an authorized designee should alert the Sanofi Pasteur representative as soon as possible, so that a shipment of extra doses can be arranged.

### 6.3.3 Replacement Doses

If a replacement dose is required (e.g., because the syringe broke or particulate matter was observed in the syringe), the site personnel must either contact the IRT to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

### 6.3.4 Disposal of Unused Products

Unused or wasted products will be returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the study period.

### 6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigator(s) will be informed of what needs to be done.

## 6.4 Blinding and Code-breaking Procedures

The study will be performed in an observer-blind fashion:

- Investigators and study staff who conduct the safety assessment and the participant will not know which vaccine is administered.
- Only the study staff who prepare and administer the vaccine and are not involved with the safety evaluation will know which vaccine is administered.

The parent / guardian / legally authorized representative, the Investigator and study staff members who collect safety data, and laboratory personnel who analyze the blood samples, will not know which product was administered. The vaccinator will be in charge of preparing and administering the products and will not be authorized to collect any safety data. In addition, the vaccinator or authorized designee will have to ensure that the documents on randomization are stored in a secure place where only she / he has access.

The code may be broken in the event of an AE only when the identification of the vaccine 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 or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur 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 CRF is to be completed.

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

- by the GPV Department through an internal system for reporting to Health authorities in the case of an SAE as described in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2A. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (i.e., the participant's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.
- by the ad hoc IDMC if needed to facilitate their assessment of safety.

The IEC / IRB must be notified of the code breaking. All documentation pertaining to the event must be retained in the site's study records and, in the Sanofi Pasteur 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.

An unblinded interim analysis for dose selection of RSV ΔNS2/Δ1313/I1314L vaccine is planned on participants from Cohorts 1, 2 and 3, and at least 90 participants enrolled in Cohort 4. The

interim analysis will take place when participants have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. This unblinded interim analysis requires the unblinding of data; a specific process will be implemented to maintain the blind at the participant and Investigator levels.

An early unblinded analysis is planned on all participants when they have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. Based on the results of this analysis, a dose will be confirmed for future studies.

Testing performed within Global Clinical Immunology (GCI) and GCI outsourced laboratories are blinded with respect to study treatment group assignment. The code(s) linking information on sample vials to study treatment group assignment are retained by the Clinical Department and cannot be accessed by GCI or contract laboratory testing personnel.

## 6.5 Randomization and Allocation Procedures

An IRT will be implemented to assign the participant numbers and allocate vaccine groups with dose numbers to the participants at Visit 01.

At Visit 01 visit, participants who meet the inclusion/exclusion criteria and whose parent / guardian/ legally authorized representative signs the ICF will be randomly assigned to one of the vaccine groups, according to the cohort:

- Cohorts 1 and 2: RSV ΔNS2/Δ1313/I1314L [redacted] (RSV low-dose) or Placebo in a 1:1 ratio
- Cohort 3: RSV ΔNS2/Δ1313/I1314L [redacted] (RSV high-dose) or Placebo in a 1:1 ratio
- Cohort 4: RSV ΔNS2/Δ1313/I1314L [redacted] (RSV high-dose) or RSV ΔNS2/Δ1313/I1314L [redacted] (RSV low-dose) or Placebo in a 1:1:1 ratio

At Visit 01, randomization will be stratified by cohort and by age sub-group (< 12 months / ≥ 12 months).

Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the dose number assignment and have the site staff confirm it. The full detailed procedures are described in the Operating Guidelines. 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). For example, Participant 840000100005 is the fifth participant enrolled in Center Number 1 in the US (840 being the US country code).

## 6.6 Treatment Compliance

The following measures will ensure that the vaccine doses administered comply with those planned, and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified study personnel
- The person in charge of product management at the site will maintain accountability records of product delivery to the study site, product inventory at the site, dose(s) given to each participant, and the disposal of unused or wasted doses

## 6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications and other therapies (e.g., blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during study participation.

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of first vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the day of each vaccination to the end of the solicited and unsolicited follow-up period.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Three standard categories of reportable medications are defined:

- Medications impacting or that may have an impact on the evaluation of the safety (e.g., antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], steroids/corticosteroids).
- Medications impacting or that may have an impact on the immune response (e.g., other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the GCI department, 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 (e.g., steroids/corticosteroids)

The information reported in the CRB for each reported medication will be limited to:

- Trade name
- Origin of prescription: prophylaxis Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the Action Taken of the AE collection tables.
- Start and stop dates
- Reason for treatment

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication(s) received belongs to one of the pre-listed categories.
Medications will be coded.

### 6.7.1 Prohibited Concomitant Medications

The use of the following is prohibited:

- Prophylactic antipyretics, decongestants, or antihistamines during the Acute Phase (28 days following study product administration) – note that use of these medications for treatment of symptoms is allowed.
- An investigational drug or investigational vaccine other than the study product within 56 days after receiving study product.

### 6.7.2 Precautionary Concomitant Medications

Due to their potentially confounding effect on immunogenicity results, the following treatments should be avoided after study product administration unless clinically indicated:

- Systemic corticosteroids for more than 14 days at a dosage equivalent to prednisone at >2 mg/kg or 20 mg daily or other immune-modifying drugs.
- Immunoglobulins and/or any blood products.

The following should be avoided after study product administration unless indicated in an outbreak setting:

- Licensed inactivated vaccine or live-attenuated rotavirus vaccine within 14 days after receiving study product.
- Licensed live virus vaccine, other than rotavirus vaccine, within 28 days after receiving study product

# 7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at Visits 01, 03, and 04 for Cohorts 1 and 3 participants who receive 1 administration and Visits 01, 03, 05 and 06 for Cohorts 2 and 4 participants who receive 2 administrations. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

Nasal swab samples for confirmation of RSV will be collected at Visit 02 (Day 7) for Cohorts 1 and 3 participants who receive 1 administration and at Visit 02 (Day 7) and Visit 04 (Day 63) for Cohorts 2 and 4 participants who receive 2 administrations. A nasal swab specimen for the detection of RSV and respiratory pathogens will be collected from participants during illness visits.

All collection of samples in the US will adhere to the Centers for Disease Control (CDC) recommended Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings (34).

Collection of samples in the sites outside the US will comply to local regulatory guidelines for COVID-19.

See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

## 7.1 Sample Collection

At the above-mentioned visits, up to 5 mL of blood will be collected in tubes provided by or recommended by the Sponsor.

At the above-mentioned visits, nasal swab samples will be collected and transferred into tubes provided by or recommended by the Sponsor. Staff collecting the samples should use adequate infection prevention and control measures, as described in the Operating Guidelines.

Immediately prior to the blood draw or nasal swab, the staff member performing the procedure will verify the participant's identity as well as the assigned participant's number and sampling stage on the pre-printed label and will attach the label to the tube.

## 7.2 Sample Preparation

***Serum Samples***

Detailed instructions on how to prepare blood samples for assessment of immune response are contained in the Operating Guidelines provided to the site. An overview of the procedures is provided here.

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours to allow the blood to clot. Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of +2°C to +8°C (+35.6°F to +46.4°F) after the period of clotting at room temperature and must be centrifuged within a maximum of 24 hours.

The samples are then centrifuged, and the serum is transferred to the appropriate number of aliquoting tubes. These tubes are pre-labeled with adhesive labels that identify the study code, the participant's number and the sampling stage or visit number.

The participant's number and the date of sampling, the number of aliquots obtained, the date and time of preparation, and the participant's consent for future use of his / her samples are to be specified on a sample identification list and recorded in the source document. Space is provided on this list for comments on the quality of samples.

***Nasal Swab Samples***

Detailed instructions on how to collect nasal swab samples in appropriate viral transport media for viral shedding assay(s) are contained in the Operating Guidelines provided to the site.

The participant's identification number and any other required information, the date of sampling, and the date and time of preparation will be clearly documented.

## 7.3 Sample Storage and Shipment

***Serum Samples***

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C (-4°F) or below. The temperature will be monitored and documented on the appropriate form during the entire study. If it rises above -10°C (14°F) for any period of time, the Clinical Logistics Coordinator must be notified. See the Operating Guidelines for further details.

Shipments to the laboratories will be made only after appropriate monitoring and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to Sample, Reagent, & Animal Services within R&D Global Operations at Sanofi Pasteur. The address is provided in the Operating Guidelines.

***Nasal Swab Samples***

Nasal swab samples will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Detailed instructions for the storage of nasal swab samples at study site and shipment of nasal swab samples to testing laboratory are contained in the Operating Guidelines provided to the site.

## 7.4 Future Use of Stored Biological Samples for Research

Any unused part of the serum samples and nasal swab samples will be securely stored at SRAS within Global Research Office (GRO) at Sanofi Pasteur) for at least 25 years after the end of the study. These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results. In addition, these samples will also be used for assay development activities related to RSV or other respiratory pathogens.

The other biological samples collected to qualify the participants for inclusion in the study or to monitor their health are dedicated for immediate use. In case they 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.

In addition, parents / guardians / legally authorized representatives will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

# 8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs, CRBs, SAE reporting forms, diary cards, memory aids and other study documents, as well as with the following study materials: all study vaccines including the device for vaccine administration, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, and digital thermometers.

The means for performing Electronic Data Capture (EDC) will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the study.

The Investigator will supply all vaccination supplies, phlebotomy, and centrifugation equipment, including biohazard and / or safety supplies. The biohazard and safety supplies include needles and syringes, examination gloves, laboratory coats, sharps disposal containers, and absorbent countertop paper. The site will ensure that all biohazard wastes are autoclaved and disposed of in accordance with local practices. The Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products and for the blood samples, and appropriate space in a temperature-monitored freezer for serum aliquots.

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines.

# 9 Endpoints and Assessment Methods

## 9.1 Primary Endpoints and Assessment Methods

### 9.1.1 Safety

#### 9.1.1.1 Safety Definitions

The following definitions are taken from the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

***Adverse Event (AE):***

An AE is any untoward medical occurrence in a patient or in a clinical investigation participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore, an AE may be:

- A new illness
- The worsening of a pre-existing condition
- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

Surgical procedures are not AEs; they are the actions taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the study period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the Investigator there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-vaccination.

***Serious Adverse Event (SAE):***

*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. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability / incapacity[c]
- Is a congenital anomaly / birth defect
- Is an important medical event (IME)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These IMEs should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new-onset diabetes, or auto-immune disease.

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[a] The term "life-threatening" 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.

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or outpatient treatment with no hospitalization.

[c] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

***Adverse Reaction:***

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions (AR).

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility)

The following additional definitions are used by Sanofi Pasteur:

***Immediate Event/Reaction:***

Immediate events are recorded to capture medically relevant unsolicited systemic AEs (including those related to the product administered) that occur within the first 30 minutes after vaccination.

***Solicited Reaction:***

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 CRB (e.g., fever and runny nose occurring between D0 and D28 post-vaccination).

By definition, solicited reactions are to be considered as being related to the product administered.

For vaccines administered nasally, solicited reactions can either be solicited administration site reactions or solicited systemic reactions.

***Unsolicited AE / AR:***

An unsolicited AE is an observed AE that does not fulfill the conditions pre-listed in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if fever between D0 and D28 is a solicited reaction (i.e., pre-listed in the protocol and CRB), then a fever starting on D28 is a solicited reaction, whereas fever starting on D29 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

***Medically Attended AE (MAAE):***

An MAAE is a new onset or a worsening of a condition that prompts the participant or participant's parent / guardian/ legally authorized representative to seek unplanned medical advice at a physician's office or Emergency Department. A physician contact made over the phone or by e-mail will be considered a physician office visit for the purpose of MAAE collection. This definition excludes pre-planned medical office visits for routine medical care, as well as pediatric check-ups or follow-up visits of chronic conditions with an onset prior to entry in the study. An AE discovered during a planned routine visit (e.g., upper respiratory tract infection, otitis) will be collected as an MAAE.

***Administration Site Reaction:***

An administration site reaction is an AR at and around the administration site i.e., the intranasal mucosa. They are considered related to the product administered.

***Systemic AE:***

Systemic AEs are all AEs 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 vaccination or administration site (e.g., conjunctivitis that is localized but that is not occurring at the administration site).

***Adverse Event of Special Interest (AESI):***

An adverse event of special interest is one of scientific and medical concern specific to the Sponsor's product 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 (e.g., regulators) might also be warranted. AESIs include both serious (SAEs) and non-serious unsolicited AEs.

The following definitions are for the different phases of safety follow post-vaccine administration:

***Acute Phase:***

The Acute Phase begins with vaccine administration on D0 and ends at midnight on the 28th day after vaccine administration (D28). The Acute Phase for the second vaccine administration begins on D56 post-vaccination and ends at midnight on D84

During the Acute Phase of the study, a study healthcare professional will be available by telephone 24 hours a day for consultation with parents / guardians / legally authorized representatives regarding any illnesses that may occur during this period. Study personnel will have daily contact with the parents / guardians / legally authorized representatives for the first 7 days after each vaccine administration and then 3 times weekly after Day 07 up to 28 days after each vaccine administration. This 28-day Acute Phase of safety follow-up is consistent with the duration of shedding of live-attenuated RSV viruses in RSV seronegative infants and toddlers (5) (6). If the parent / guardian/ legally authorized representative reports an SAE, a safety event that meets the study pause or stop criteria (Section 5.1.6), or symptoms suggestive of a respiratory tract illness, then an illness visit should be scheduled (Section 5.1.4, Table 5-4). During the Acute Phase, the eDC allows daily safety monitoring of the study participant and will be programmed to send an alert to the parent / guardian / legally authorized representative and study site when there are symptoms suggestive of respiratory tract illness (Table 5-4).

***Post-Acute Phase:***

The Post-Acute Phase for participants receiving 1 administration begins at 12:01am on D29 and ends at midnight on D56. The first Post-Acute Phase for participants receiving 2 administrations begins at 12:01am on D29 and ends at midnight on D56, except if second administration is exactly on D56 when it ends immediately before receipt of the second administration. The second Post-Acute Phase for participants receiving 2 administrations begins at 12:01am on D85 and ends at midnight on D112.

During the Post-Acute Phase of the study, parents / guardians / legally authorized representatives will be instructed to monitor for and contact study staff if their child has had symptoms that are suggestive of a serious adverse event. If the parent /guardian / legally authorized representative reports an SAE or safety event that meets the study pause or stop criteria (Section 5.1.6), then an illness visit should be scheduled (Section 5.1.4, Table 5-4).

#### 9.1.1.2 Safety Endpoints

The primary endpoints for the evaluation of safety are as follows (in all infants and toddlers regardless of baseline serostatus):

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each and any vaccination.
- Occurrence of solicited (i.e., pre-listed in the participant's DC / eDC and in the CRB) administration site and systemic reactions within 28 days after each and any vaccination (i.e, Acute Phase).
- Occurrence of any unsolicited (spontaneously reported) AEs within 28 days after each and any vaccination (i.e, Acute Phase)
- Occurrence of any AESIs within 28 days after each and any vaccination.
- Occurrence of any MAAEs within 28 days after each and any vaccination.
- Occurrence of any SAEs throughout the study period.
- Other safety endpoints will be recorded or derived as described in the statistical analysis plan. Depending on the item, these could include nature (Medical Dictionary for Regulatory Activity [MedDRA] preferred term), time of onset, duration, number of days of occurrence, intensity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.

#### 9.1.1.3 Safety Assessment Methods

At each vaccination in-person or non-visit contact, the Investigator or a delegate will either perform a focused medical examination (in-person visit) or ask the parent / guardian / legally authorized representative about any solicited reactions and unsolicited AEs recorded in the diary card / electronic diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

This study monitors safety, infectivity, replication, and immunogenicity of both doses of RSV ΔNS2/Δ1313/I1314L, with attention to vaccine virus infectivity and replication (i.e., percentage of participants shedding virus, vaccine virus titer in nasal swab) 7 days post-vaccination 1 and 2, which is the most quantifiable metric for the level of attenuation of the vaccine virus.

##### 9.1.1.3.1 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. Any AE that occurs during this period will be noted on the source document and recorded in the CRB, as follows:

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes", and details collected).

- Solicited and unsolicited administration site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination.
- SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in Section 10.

#### 9.1.1.3.2 Reactogenicity (Solicited Reactions from Day 0 to Day 28 After Each Vaccination)

After each vaccination, the participant's parents / guardians / legally authorized representatives will be provided with a DC / eDC, and a digital thermometer, and will be instructed how to use them. The following items will be recorded by the participants in the diary card / electronic diary card on the day of vaccination and for the next 28 days (i.e., Day 0 through Day 28) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement and intensity grade of any solicited administration site reactions (e.g., runny nose) and systemic reactions (e.g., fever)
- Action taken for each event (e.g., medication)

The action(s) taken by the parent /guardian / legally authorized representative to treat and/or manage any solicited reactions will be classified in the CRB using the following list (all applicable items should be checked):

- None
- Medication
- Health care provider contact
- Hospitalized
- Discontinuation of study vaccination

Parents / guardians / legally authorized representatives of study participants will be contacted by telephone each day for the first 7 days after each vaccination and then 3 times weekly after the D07 visit to remind them to record all safety information in the diary card / electronic diary card.

If the timing of the telephone call should fall on a weekend or a holiday, the call should be made on the next business day. If contact is not made on the designated day, study staff will continue calling until contact is made. Every telephone attempt and its outcome will be documented in the source document.

Table 9-1 and Table 9-2 present, respectively, the administration site reaction that is pre-listed in the diary cards and CRB, together with the intensity scales.

**Table 9-1: Solicited administration site reactions: terminology, definitions, and intensity scales**

| CRB term (MedDRA lowest level term [LLT]) | Rhinorrhea | Nasal congestion |
|---|---|---|
| **Diary card term** | Runny nose | Stuffy or blocked nose |
| **Definition** | Two or more consecutive days of clear, mucous or purulent discharge from the nose.<br>Note: Not associated with crying, change of room temperature, or eating and drinking. | Two or more consecutive days of stuffy or blocked nose.<br>Note: Not associated with crying, change of room temperature, or eating or drinking. |
| **Intensity scale*** | Grade 1 (mild): No medical intervention required; may include use of over-the-counter medications managed by the caregiver for treatment of symptoms<br>Grade 2 (moderate): Outpatient medical intervention by a health care provider required; may include use of over-the-counter and/or prescription medications<br>Grade 3 (severe): Prolonged medical intervention and/or hospitalization required<br>Grade 4 (life-threatening): Illness requiring hospitalization with intensive care<br>Grade 5 (death): Event resulting in fatal outcome to the participant | Grade 1 (mild): No medical intervention required; may include use of over-the-counter<br>medications managed by the caregiver for treatment of symptoms<br>Grade 2 (moderate): Outpatient medical intervention by a health care provider required; may include use of over-the-counter and/or prescription medications<br>Grade 3 (severe): Prolonged medical intervention and/or hospitalization required<br>Grade 4 (life-threatening): Illness requiring hospitalization with intensive care<br>Grade 5 (death): Event resulting in fatal outcome to the participant |

* For the measurable reactions of rhinorrhea and nasal congestion, the parent / guardian / legally authorized representative will decide whether or not medical intervention was required and if so the type of intervention, and the classification as Grade 1 - 5 will be assigned at the time of review of the diary card.

**Table 9-2: Solicited systemic reactions: terminology, definitions, and intensity scales**

| CRB term (MedDRA lowest level term [LLT]) | Fever | Vomiting | Crying abnormal | Drowsiness | Appetite lost | Irritability |
|---|---|---|---|---|---|---|
| **Diary card term** | Temperature | Vomiting | Abnormal crying | Drowsiness | Loss of appetite | Irritability |
| **Definition** | Elevation of temperature to ≥ 38.0°C (≥ 100.4°F) | Vomiting does not include spitting up | Inconsolable crying without a determined reason | Reduced interest in surroundings, or increased sleeping | See intensity scale | An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing |
| **Intensity scale*** | Grade 1: ≥ 38.0°C to ≤ 38.5°C **or** ≥ 100.4°F to ≤ 101.3°F | Grade 1: 1 episode per 24 hours | Grade 1: < 1 hour | Grade 1: Sleepier than usual or less interested in surroundings | Grade 1: Eating less than normal | Grade 1: Easily consolable |
| | Grade 2: > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F | Grade 2: 2–5 episodes per 24 hours | Grade 2: 1–3 hours | Grade 2: Not interested in surroundings or did not wake up for a feed / meal | Grade 2: Missed 1 or 2 feeds / meals completely | Grade 2: Requiring increased attention |
| | Grade 3: > 39.5°C **or** > 103.1°F | Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration | Grade 3: > 3 hours | Grade 3: Sleeping most of the time or difficult to wake up | Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals | Grade 3: Inconsolable |

* For all reactions but fever, the parent / guardian / legally authorized representative will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned based on the information in the diary card.

***Important notes for the accurate assessment of temperature:***

Parents / guardians / legally authorized representatives are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is rectal. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic thermometers must not be used.

#### 9.1.1.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, parents / guardians / legally authorized representatives will be instructed to record any other medical events that may occur during the 28-day period after each vaccination. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from the time of enrollment until up the last visit. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports and verbal autopsy questionnaire if used). In case a participant experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the “Guideline for definition and collection of cases of febrile convulsion”, and this event will be considered an SAE. See Section 10 for further details on SAE reporting.

For each unsolicited AE (whether serious or non-serious), the following information is to be recorded:

- Start and stop dates[a]
- Intensity of the event:

  The temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9-2).

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

  - Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

[a] The stop date of all related AEs will be actively solicited. For other events, the investigator will provide the stop date when it becomes available. AEs for which no stop date was obtained during the course of the study will be considered as ongoing at the end of the study.

- Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

- Whether the AE was related to the investigational product (for unsolicited systemic AEs)

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.1.1.3.6.

- Action taken for each AE (e.g., medication)

  The action(s) taken by the parents / guardians / legally authorized representatives to treat and/or manage any unsolicited AEs will be classified in the CRB using the following list (all applicable items should be checked):

  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination

- Whether the AE was an AESI, MAAE and/or SAE.

For each SAE, the investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures)

- Whether the AE caused study discontinuation

#### 9.1.1.3.4 Medically Attended Adverse Events

Any MAAEs occurring within the first 28 days post-vaccination (D0 to D28 for all participants in Cohorts 1, 2, 3 and 4 and D56 to D84 for participants in Cohorts 2 and 4) will be collected using the same process as other AEs. Medically attended acute respiratory illness (MAARI) and medically attended acute lower respiratory illness (MAALRI) events occurring within this time frame and outside the RSV surveillance season will be classified as MAAEs.

#### 9.1.1.3.5 Adverse Events of Special Interest (AESI)

Any AESIs occurring within the first 28 days post-vaccination (D0 to D28 for all participants in Cohorts 1, 2, 3 and 4 and D56 to D84 for participants in Cohorts 2 and 4) will be collected using the same process as other AEs.

All adverse events of special interest in the study would be graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 - July 2017; see Table 9-3) (35) except for acute wheeze, which would be graded by the Brighton Collaboration Wheeze severity grading system (see Table 9-4) (36). The following adverse events of special interest are derived from previous NIH research experience with similar candidates and will be assessed in this study:

- Acute otitis media
- URI
    - Pharyngitis
    - Cough without LRI
- LRI
    - Stridor
    - Rales
    - Tachypnea
    - Acute wheeze
    - Pneumonia
    - Laryngotracheobronchitis

***Acute Otitis media:***

Loss of tympanic membrane landmarks accompanied by erythema and loss of mobility. May or may not be associated with fever or other respiratory symptoms. Confirmed with tympanometry if possible. This diagnosis must be made by a medical professional.

***Pharyngitis:***

Pharyngeal erythema accompanied by exudate or pharyngeal erythema with enlarged tender lymph nodes. Note: May be associated with sore throat, or painful or difficult swallowing. This diagnosis must be made by a medical professional.

***Cough without LRI:***

Two or more consecutive days of 3 or more episodes of cough during a 15-minute timed observation period, or cough awakens child from sleep. There should be no associated lower respiratory tract illness. This diagnosis must be made by a medical professional. Note: Not associated with eating, drinking or choking.

***Stridor:***

Harsh medium-pitched inspiratory sound associated with obstruction of the laryngeal area or the extra-thoracic trachea, often accompanied by croupy cough and hoarse voice. This diagnosis must be made by a medical professional.

***Rales:***

Abnormal lung sound heard through a stethoscope. Rales may be sibilant (whistling), dry (crackling) or wet (more sloshy) depending on the amount and density of fluid refluxing back and forth in the air passages. Must be sustained over 20 minutes and assessed and diagnosed by a medical professional with confirmation by a second medical professional, if possible.

***Tachypnea:***

Increased respiratory rate >40 breaths per minute in infants aged 6-12 months and >30 breaths per minute in toddlers aged 1-3 years. This diagnosis must be made by a medical professional.

***Acute Wheeze (36):***

According to the Brighton Collaboration case definition, for all levels of diagnostic certainty, acute wheeze is a clinical sign defined by:

- Sudden onset, occurred unexpectedly and without warning, leading to a marked change in a participant's previously stable condition, **AND**
- Breath sound audible on auscultation, **AND**
- Audible during expiration, the sound is primarily expiratory though an inspiratory component is possible in severe forms different from stridor, **AND**

Characterized by the following criteria defining the level of diagnostic certainty:

*Level 1*

- Classified as wheeze based on digital stethoscope recording as compared with reference audio file, **OR**
- Classified as wheeze by 2 health care providers with specific training e.g., Pulmonologist or formal auscultation training based on standard wheeze training tool

*Level 2a (one health care provider with specific training)*

- Classified as wheeze by 1 health care provider with specific training e.g., Pulmonologist or formal auscultation training based on standard wheeze training tool, AND
- Immediate response to bronchodilator treatment i.e., absence of wheeze following treatment or improvement of wheeze severity documented by a healthcare provider

*Level 2b (2 health care providers)*

- Classified as wheeze by 2 health care providers without specific training i.e., neither a pulmonologist nor someone with formal auscultation training based on standard wheeze training tool, AND
- Immediate response to bronchodilator treatment i.e., absence of wheeze following treatment or improvement of wheeze severity documented by a healthcare provider, OR
- Infant diagnosed with acute bronchiolitis

*Level 3 (pre-existing diagnosis)*

- Classified as wheeze by 1 health care provider OR caretaker (e.g., parent / guardian / legally authorized representative) without specific training, AND
- Pre-existing physician diagnoses of a respiratory disease of which wheeze is a key symptom

The full Brighton Collaboration case definition is listed here but Level 3 of diagnostic certainty will not be required in this study and children with a pre-existing diagnosis of wheeze would not be enrolled in this study.

***Pneumonia:***

Rales and crackles sustained over 20 minutes, originating in the lower respiratory tract, usually accompanied by tachypnea, which do not clear with cough. This may be confirmed by x-ray showing areas of consolidation. Clinical assessment and diagnosis must be made by a medical professional with confirmation by a second medical professional, if possible.

***Laryngotracheobronchitis (croup):***

Barking cough, hoarseness, and inspiratory stridor and sustained over 20 minutes assessed and diagnosed by a medical professional with confirmation by a second medical professional, if possible.

Table 9-3 presents the DAIDS severity scale for AESIs, except wheeze, Grade 1 through 4.

**Table 9-3: DAIDS severity scale for AESIs, except wheeze**

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

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

Table 9-4 presents the Brighton Collaboration severity grading system for wheeze.

**Table 9-4: Brighton Collaboration severity grading system for wheeze**

| Grade 1 (mild) | Grade 2 (moderate) | Grade 3 (severe) |
|---|---|---|
| Wheeze only | Wheeze with respiratory distress | Wheeze with danger signs |
| Wheeze*† | Wheeze<br>AND<br>• Lower chest wall indrawing<br>OR<br>• prolonged expirium (i.e., I/E ratio > 1:3) | Wheeze‡<br>AND<br>• Oxygen saturation <92%<br>OR<br>• Central cyanosis<br>OR<br>• Confusion or drowsiness<br>OR<br>• Inability to speak or drink |

I/E, Inspiratory/Inspiratory

* There may even be tachypnea without other signs of respiratory distress

† There may be tachycardia without other signs of respiratory distress

‡ or silent chest on auscultation in a patient with history of wheeze

#### 9.1.1.3.6 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the product 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 an 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
- Related – There is a "reasonable possibility" that the AE was caused by the product administered, meaning that there is evidence or arguments to suggest a causal relationship

Note: By convention, all AEs reported at the administration site (whether solicited or unsolicited) and all solicited systemic AEs are considered to be related to the administered product and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

Adverse events likely to be related to the product, whether serious or not, 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.

### 9.1.2 Infectivity

There are no primary objectives for infectivity.

### 9.1.3 Immunogenicity

#### 9.1.3.1 Immunogenicity Definition

***RSV Serostatus***

For this Sanofi Phase I/II study, serum IgA detection was chosen as a biomarker for RSV encounter in infants and toddlers. IgA serostatus, ie RSV-naïve and RSV-experienced, will be defined as undetectable or detectable serum anti-RSV A IgA antibodies, respectively.

***RSV IgA Serostatus Assessment***

The RSV IgA [redacted] for serostatus determination will be performed at Sanofi HEXIM lab, Orlando, FL or at a qualified contract laboratory for Sanofi GCI, Swiftwater, Pennsylvania.

The IgA serostatus method to be used is summarized below.

***RSV IgA Method Description***

IgA antibodies to RSV F antigen will be measured using the anti RSV F IgA [redacted]. RSV F protein antigen is coated on the surface of microtiter plates. The plates are blocked, then unadsorbed coating antigen is washed from the wells and serially diluted human serum samples (test samples, reference, and quality controls) are incubated in the wells. Anti-RSV F protein specific antibodies in the serum samples bind to the immobilized RSV F protein antigen. Unbound antibodies are washed from the wells and horseradish peroxidase (HRP)-conjugated goat anti-human IgA enzyme conjugate is added. The conjugate binds to the antigen-antibody complexes. Excess conjugate is washed away, and a colorimetric substrate is added. Bound enzyme catalyzes a hydrolytic reaction which causes color development. The intensity of the color generated is proportional to the amount of antigen specific IgA antibody bound to the wells. The results are read on a spectrophotometer.

The concentration of IgA antibodies to RSV F antigen is calculated over 6 serial two-fold dilutions with an assigned value in [redacted] Units (EU)/mL.

#### 9.1.3.2 Immunogenicity Endpoints

The primary endpoint for the evaluation of immunogenicity is:

- RSV A serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4 in RSV-naïve participants.

RSV-experienced and RSV-naïve participants are defined in Section 9.1.3.1.

#### 9.1.3.3 Immunogenicity Assessment Methods

Immunogenicity of the vaccine candidate will be evaluated by determining RSV A serum neutralizing antibody titers (using the Microneutralization assay).

***RSV Neutralizing Antibody Assessment***

The RSV Microneutralization (MN) assay will be performed at Sanofi Pasteur GCI, Swiftwater, Pennsylvania or at a qualified contract laboratory for GCI.

The MN method to be used is summarized below. Development and qualification of this method is completed. The evaluation of an optimized MN assay (developed at Sanofi) and a micro plaque reduction neutralization test (being developed at CRO) are ongoing for Phase III studies (23) (28).

***RSV MN Method Description***

RSV neutralizing antibodies will be measured using a MN assay. Serial, two-fold dilutions of serum to be tested (previously heat-inactivated) are mixed with a constant concentration of the RSV-A2 strain (ATCC VR-1540). The mixtures are inoculated into wells of a 96-well microplate with permissive HEp-2 cells (ATCC CCL-23) and incubated for 2 days. A reduction in virus infectivity (viral antigen production) due to neutralization by antibody present in serum samples is detected by [redacted] After washing and fixation, RSV antigen production in cells is detected by successive incubations with an RSV-specific mAb, horse radish peroxidase anti-mouse IgG conjugate, and a chromogenic substrate. The resulting Optical Density is measured using a microplate reader. The reduction in RSV infectivity as compared to that in the virus control wells constitutes a positive neutralization reaction indicating the presence of neutralizing antibodies in the serum sample.

### 9.1.4 Efficacy

There are no primary objectives for efficacy.

## 9.2 Secondary Endpoints and Assessment Methods

### 9.2.1 Safety

#### 9.2.1.1 Safety Definitions

The safety definitions are presented in Section 9.1.1.1.

#### 9.2.1.2 Safety Endpoints

The secondary endpoints for the evaluation of safety are:

- Titer of vaccine virus shedding on D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4 measured by [redacted].

#### 9.2.1.3 Safety Assessment Methods

Shedding of the attenuated RSV vaccine strain in nasal swab samples will be evaluated by RSV quantitative Reverse Transcriptase Polymerase Chain Reaction [redacted], which can specifically detect and quantify RSVt ΔNS2 vaccine strain (RSV ΔNS2/Δ1313/I1314L) in human nasal swab samples. Based on the evaluation of precision (intra-assay and intermediate precision), dilutional accuracy, linearity, and specificity, RSVt [redacted] is suitable for clinical testing of human nasal swab samples in support of the development of RSV Vaccine candidates.

***RSVt NS2*** [redacted]

The RSVtNS2 [redacted] will be performed at Sanofi Pasteur GCI, Swiftwater, PA or at a qualified contract laboratory for GCI.

The RSVtNS2 [redacted] will be used to measure virus shedding from nasal swab samples from study participants. Development and qualification of this method is completed; this method will be validated prior to Phase III clinical testing.

***RSVt NS2*** [redacted] ***Description***

To quantify viral shedding in infants vaccinated with RSV ΔNS2/Δ1313/I1314L (RSVt) vaccine, a [redacted] was developed that would specifically detect and quantify RSV ΔNS2 candidate in nasal swab samples. Beyond the deletion of the NS2 gene, there are few sequence differences between RSV ΔNS2/Δ1313/I1314L vaccine and wt RSV A.

RSVt [redacted] was designed using the Light Cycler Probe system from Sigma. This system consists of two hybridization probes that are designed so that they bind the target 1-5 nucleotides apart. Probe 1 (donor) is labeled on the 3' end with a donor reporter. Probe 2 (acceptor) is labeled at the 5' end with an acceptor reporter. During the annealing step, the [redacted] primers and the LightCycler Probes hybridize to their specific target regions, bringing the probes in proximity. When this happens, the donor dye is excited by the LightCycler, and energy is transferred from the donor to the acceptor dye. The acceptor reporter's emission is detected by the Light Cycler at 640 nm.

If the probes bind, but are not in proximity, no signal is produced. The Light Cycler probes for the RSVt [redacted] target the deletion site of the NS2 gene in RSVt ΔNS2. Probe 1 binds before the deletion and Probe 2 binds across the deletion site. While the primers and probes may bind wild-type RSV A due to high sequence similarity, the two probes would not bind in close enough proximity to create signal as the NS2 gene is over 500 nucleotides long, making this method highly specific.

Collection of nasal swab samples from infants can be difficult and sample quality cannot be visually verified. Therefore, an RNase P assay, based on one developed by the CDC will be used in conjunction with the RSVt [redacted] to evaluate sample quality.

RNase P is a human housekeeping gene. Use of the RNase P assay will limit the impact of false negatives because of poor sample collection or handling. Amplification in the RNase P assay indicates the presence of human cells in a sample. An RNase P Cp of ≤ 37 indicates that the sample was appropriately collected, and that sample integrity was maintained. RNase P testing will be performed only when [redacted] (to detect and quantify RSVt ΔNS2 vaccine strain) yields negative results.

### 9.2.2 Infectivity

#### 9.2.2.1 Infectivity Endpoint

The secondary endpoint for the evaluation of infectivity is vaccinee infection with the vaccine virus. Infection is defined as detection of vaccine virus in nasal swab by [redacted] and / or a ≥ 4-fold rise in RSV A serum neutralizing antibody titers, or in RSV serum anti-F IgG antibody titers.

#### 9.2.2.2 Infectivity Assessment Methods

The infectivity assessment methods are presented in Section 9.2.1.3.

### 9.2.3 Immunogenicity

#### 9.2.3.1 Immunogenicity Endpoints

The secondary endpoints for the evaluation of immunogenicity are:

- RSV serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4 in RSV-experienced participants.
- RSV serum anti-F IgG antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.
- RSV A serum neutralizing and serum anti-RSV F IgG antibody titers after the RSV season or at least five months after last vaccine administration.

#### 9.2.3.2 Immunogenicity Assessment Methods

RSV-experienced and RSV-naïve participants are defined in Section 9.1.3.1.

Immunogenicity of the vaccine candidate will also be evaluated by determining RSV F protein binding antibody levels (by [redacted]).

***RSV Anti-F IgG*** [redacted]

The anti-RSV F IgG [redacted] will be performed at Sanofi Pasteur GCI, Swiftwater, Pennsylvania or at a qualified contract laboratory for GCI.

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

***RSV Anti-F IgG*** [redacted] ***Method Description***

Antibodies to RSV F antigen will be measured using the anti RSV F IgG [redacted]. Briefly, the RSV F antigen (from strain RSV A2) is coated onto a microtiter plate and serial 2-fold dilutions of human serum samples are added and incubated to allow binding to the RSV F antigen. Then an HRP-conjugated anti-human IgG detection antibody is added followed by colorimetric substrate. The concentration of IgG antibodies to RSV F antigen is calculated over 6-serial dilutions relative to qualified internal reference calibrated against WHO International standard (1st International

Standard for antiserum for Respiratory Syncytial Virus) with an assigned value (International Units /mL).

#### 9.2.4 Efficacy

There are no secondary objectives for efficacy.

### 9.3 Exploratory Endpoints and Assessment Methods

#### 9.3.1 Safety

##### 9.3.1.1 Safety Definitions

The safety definitions are presented in Section 9.1.1.1.

##### 9.3.1.2 Safety Endpoints

The exploratory endpoints for the evaluation of safety are:

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each and any vaccination.
- Occurrence of solicited (i.e., pre-listed in the participant's DC / eDC and in the CRB) administration site and systemic reactions within 28 days after each and any vaccination (i.e, Acute Phase).
- Occurrence of any unsolicited (spontaneously reported) AEs within 28 days after each and any vaccination.
- Occurrence of any AESIs within 28 days after each and any vaccination.
- Occurrence of any MAAE within 28 days after each and any vaccination.
- Occurrence of any SAEs throughout the study.

##### 9.3.1.3 Safety Assessment Methods

The safety assessment methods are presented in Section 9.1.1.3.

#### 9.3.2 Infectivity

There are no exploratory objectives for infectivity.

### 9.3.3 Immunogenicity

#### 9.3.3.1 Immunogenicity Endpoints

The exploratory endpoints for the evaluation of immunogenicity are:

- RSV A serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4 converted into international units (IU)/mL.
- RSV A serum neutralizing antibody titers converted into international units (IU)/mL, after the RSV season or at least 5 months after last vaccine administration.
- RSV◦B serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.
- RSV B serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4 converted into international units* (IU)/mL.
- RSV◦B serum neutralizing antibody titers after the RSV season or at least 5 months after the last vaccine administration.
- RSV B serum neutralizing antibody titers converted into international units (IU)/mL, after the RSV season or at least 5 months after last vaccine administration.
- RSV A and RSV B serum anti-Gcc IgG antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.
- RSV A and RSV B serum anti-Gcc IgG antibody titers after the RSV season or at least 5 months after last vaccine administration.
- RSV serum anti-F IgA antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.
- RSV serum anti-F IgA antibody titers after the RSV season or at least 5 months after last vaccine administration.

#### 9.3.3.2 Immunogenicity Assessment Methods

RSV-experienced and RSV-naïve participants are defined in Section 9.1.3.1.

The immunogenicity assessment methods by MN for the exploratory endpoints are the same as those presented in Section 9.1.3.3.

The RSV A and RSV B serum neutralizing antibody titer values obtained are further calibrated and converted into international units (IU)/mL against the World Health Organization (WHO) 1st international reference standard NIBSC 16/284 (with an assigned value of 2000 IU/mL) or converted with a qualified internal reference with an assigned IU/mL value. The calibrator (reference standard) is included in the same assay run.

***RSV Anti-F IgA [redacted] Method Description***

The method is described in Section 9.1.3.1.

### 9.3.4 Efficacy

#### 9.3.4.1 Efficacy Endpoints

The exploratory endpoints for the evaluation of efficacy assessed through the RSV season or post-vaccination surveillance period are:

- RSV medically attended acute respiratory illness (RSV MAARI)
- RSV medically attended acute lower respiratory illness (RSV MAALRI)
- A diagnosis of RSV MAARI requires a respiratory sample positive for RSV by [redacted] AND documented physical exam findings of respiratory tract illness including any of the following:
    - Fever
    - Acute otitis media
    - Upper respiratory tract illness:
        - Runny nose/rhinorrhea
        - Pharyngitis
        - Cough without LRI
    - Lower respiratory tract illness (see MAALRI below)
- A diagnosis of RSV MAALRI (a subset of MAARI) requires a respiratory sample positive for RSV by [redacted] AND documented physical exam findings of lower respiratory tract illness including any of the following:
    - Stridor
    - Rales
    - Tachypnea
    - Acute wheeze
    - Pneumonia
    - Laryngotracheobronchitis

#### 9.3.4.2 Efficacy Assessment Methods

The method for the exploratory efficacy endpoints is the [redacted], an automated qualitative nucleic acid multiplex *in vitro* diagnostic test designed to simultaneously detect and identify multiple respiratory viral and bacterial nucleic acids in NS samples.

[redacted] **Method**:

The ePlex system which is used to run the [redacted] is a closed system that automates all aspects of nucleic acid testing including extraction, amplification, and detection. Electrowetting or digital microfluidics use electrical fields to manipulate droplets on the surface of a

hydrophobically coated printed circuit board (PCB). Samples and reagents are moved in a programmable fashion in the ePlex cartridge to complete all portions of the sample processing. Nucleic acid extraction from biological samples occurs within the cartridge via cell lysis, followed by nucleic acid capture onto magnetic beads and release for [redacted] amplification. Thereafter, exonuclease digestion creates single-stranded DNA in preparation for eSensor detection. eSensor technology is based on the principles of competitive DNA hybridization and electrochemical detection, which is highly specific and is not based on fluorescent or optical detection. Competitive DNA hybridization: the single-stranded target DNA binds to a complementary, single-stranded capture probe, immobilized on the working gold electrode surface. The single-stranded signal probes (labeled with electrochemically active ferrocenes) bind to a specific target sequence/region adjacent to the capture probe. Simultaneous hybridization of the target to signal probes and capture probe is detected by alternating current voltammetry (ACV). Each working electrode on the array contains specific capture probes, and the sequential analysis of each electrode allows for the detection of multiple analyte targets.

The [redacted] is a qualitative assay. It will only indicate the presence or absence of a viral or bacterial target in a nasal swab sample collected in viral transport medium (VTM) and will not be used to calculate a viral titer. The [redacted] can detect and distinguish between sixteen respiratory viral targets and two respiratory bacterial targets as shown in Table below.

Each clinical sample (NS sample in VTM) will be tested in singleton in an individual cartridge. One Negative Control (NC) must be included within each batch of clinical samples being tested. When possible, the NC should be the last sample of the batch to be loaded in cartridge. One set of Positive Control (comprising of six PC(s) designated PC1-PC6)) must be run simultaneously as the first Batch on the day clinical samples are tested.

# 10 Reporting of Serious Adverse Events

To comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational product(s). It is the responsibility of the Investigator to request all necessary documentation (e.g., medical records, discharge summary, and verbal autopsy in order to provide comprehensive safety

information). All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

## 10.1 Initial Reporting by the Investigator

Serious adverse events occurring during a participant's participation in the study or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The investigator (licensed physician [M.D. or D.O.]) must validate the information entered on the AE CRF by completing the investigator validation form.

The Investigator must indicate on the AE CRF that the event was serious and must complete the relevant SAE section of this form as well as the appropriate Safety Complementary Information CRFs. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the Clinical Team Leader with relevant SAE information details.

If the EDC system is unavailable, the site must notify the Sponsor, using the paper version of the CRB, as described in the operating guidelines.

The Investigator must complete the paper copies of the AE CRF and of the appropriate Safety Complementary Information CRFs and send them to the Sponsor by one of the following means:

- By fax, to the following number: 570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: SanofiPasteurPharmaco@sanofi.com

  By express mail, to the following address:

  Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global Pharmacovigilance
  Mail Drop: 45D38
  Discovery Drive
  Swiftwater, PA 18370

When the EDC system becomes available, the Investigator must transcribe the information from the paper forms into the EDC system.

If there is need for urgent consultation, the Investigator is to contact the RMO. If the RMO cannot be reached, the Investigator may contact the Call Center as described in Section 5.3.

## 10.2 Follow-up Reporting by the Investigator

The AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (e.g., outcome, precise description of medical history, results of the investigation). All relevant information must be included directly in the AE CRF and the appropriate Safety Complementary Information CRFs. An e-mail alert will be sent automatically to the GPV Department and to the CRA. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by the GPV Department.

The anonymity of the participant must always be respected when forwarding this information.

## 10.3 Reporting of SAEs Occurring After a Participant Has Completed the Study

Any SAE that occurs after a participant has completed the study but that is likely to be related to the investigational product(s), other products (e.g., a benefit vaccine), or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

## 10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.1.1.3.6.

Following this, the Sponsor's Global Safety Officer will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The causal relationship to study procedures will be also assessed in the CRB.

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Investigators.

## 10.5 Reporting SAEs to Health Authorities and IECs / IRBs

The Sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory requirements. Reporting to the health authorities will be according to the Sponsor's standard operating procedures.

The Sponsor's RMO will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the study protocol.

## 10.6 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 participant participating in the study, 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, are provided in the Operating Guidelines.

# 11 Data Collection and Management

## 11.1 Data Collection and CRB Completion

Individual diary cards / electronic diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.1.1.3. These diary cards / electronic diary cards will include pre-listed terms and intensity scales (see Table 9-1 and Table 9-2) as well as areas for free text to capture additional safety information or other relevant details. Parents / guardians / legally authorized representatives will also be provided with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct parents / guardians / legally authorized representatives on how to correctly use these tools.

During the period between the final vaccination and the final visit, follow-up will be done by interviewing participants either during a visit or over the telephone using a questionnaire to capture SAEs, MAAEs and AESIs, if applicable. A memory aid may be provided to the participants at the preceding study visit to help them record information on events occurring between this visit and the 6-month follow-up.

Relevant information will be transcribed into the AE CRF. Any SAEs captured during this 6-month follow-up period will be reported and followed-up as per the normal process for reporting SAEs.

At specified intervals, the Investigator or an authorized designee will interview the parents / guardians / legally authorized representatives to collect the information recorded in the diary card / electronic diary card and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the diary card / electronic diary card will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study under the responsibility of the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the CRBs, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to all site staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion instructions will be provided to assist with data entry during the course of the study.

Upon completion of training, each user requiring access to the EDC system will be issued a unique username and password. In the event of a change in study personnel, each newly assigned individual will receive a unique username and password; the username and password of a previous user may not be reissued. If any study personnel leave the study, the Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be initiated in the EDC system at the time of the first data entry to track all modifications and ensure database integrity.

The Investigator is responsible for the timeliness, completeness, and accuracy of the information in the CRBs; must provide explanations for all missing information; and must sign the CRB using an e-signature.

## 11.2 Data Management

***Management of SAE***

During the study, SAE data (reported on the AE, Death, and Safety Complementary Information CRFs) will be integrated into the Sponsor's centralized GPV database upon receipt of these forms and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the Global Safety Officer and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new of the case will be created.

The information from the GPV database cases will be reconciled with that in the clinical database.

***Management of Clinical and Laboratory Data***

Clinical data, defined as all data reported in the CRB, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.

During the study, clinical data reported in the CRBs will be integrated into the clinical database under the responsibility of the Sanofi Pasteur CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and / or consistency checks will be systematically applied to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. Any questions pertaining to the reported clinical data will be submitted to the investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

The validation of the immunogenicity data will be performed at the laboratory level following the laboratory's procedures. Information from the laboratory will be checked for consistency before integration into the clinical Datawarehouse.

After integration of all corrections in the complete set of data, and after the SAE information available from CDM and the GPV Department has been reconciled, the database will be released for statistical analysis.

## 11.3 Data Review

A blind review of the data is anticipated through the data review process led by Data Management before database lock.

# 12 Statistical Methods and Determination of Sample Size

## 12.1 Statistical Methods

### 12.1.1 Hypotheses and Statistical Methods for Primary Objectives

#### 12.1.1.1 Hypotheses

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

#### 12.1.1.2 Statistical Methods

The statistical methodology will be based on the use of two-sided 95% confidence intervals (CI).

The 95% CIs of point estimates will be calculated using the exact binomial distribution (Clopper-Pearson method (37) for proportions.

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

***Safety***

Solicited adverse reactions (ARs), unsolicited AEs (including SAEs), MAAEs and AESIs will be summarized. The main parameters will be described with 95% CI. At least the following parameters will be presented by vaccine group after each and any vaccination, in all participants regardless of baseline serostatus:

- Unsolicited systemic AEs occurring within 30 minutes of administration (immediate unsolicited AEs)
- Solicited administration site reactions and solicited systemic reactions within 28 days after each and 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. When more than 1 intensity level is reported within a time period, the highest intensity will be used.
- Unsolicited AEs occurring within 28 days after each and 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 throughout the study by SOC and PT, seriousness criteria, time to onset, outcome, relationship, and whether the SAE led to early termination throughout the study
- All MAAEs and AESIs reported within 28 days after each and any vaccination by SOC and PT and relationship

A Bayesian approach based on Posterior Distribution may be used to assess the difference between each RSV formulation and placebo on the following safety endpoints:

- Any Grade 3 lower respiratory tract illness e.g., wheezing, pneumonia, sustained tachypnea, laryngotracheobronchitis
- Grade 3 fever

See Section 15 for further details.

***Immunogenicity***

The point estimates and their 95% CI of the following parameters will be presented for RSV A neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4, for each vaccine group in RSV-naïve participants:

- GMT
- GMTR based on the baseline antibody titer
- Seroresponse rates defined as percentage of participants with a ≥ 4-fold rise in RSV A serum neutralizing antibody titers based on the baseline value.
- Reverse cumulative distribution curves (RCDCs) will be presented
- Pairwise comparisons between vaccine groups may be conducted as exploratory analyses to compare seroresponse rates or GMTs for descriptive purpose.

The 95% CIs of the difference of proportions between 2 groups would be computed using the Wilson Score method without continuity correction. CIs of ratio of GMTs between 2 groups will be computed from the difference in means of log10 transformed titers between 2 groups with normal approximation.

### 12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

#### 12.1.2.1 Hypotheses

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

#### 12.1.2.2 Statistical Methods

***Safety***

The point estimates and their 95% CI of the following parameter will be presented 7 days after each vaccination (D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4) for each vaccine group by baseline serostatus:

- GMT of vaccine virus shedding measured by [redacted]

***Infectivity***

The point estimate and its 95% CI of the following parameters will be presented after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 for each vaccine group by baseline serostatus:

- Proportion of vaccinees infected with the vaccine virus. Infection defined as detection of vaccine in nasal swab by [redacted] and / or a ≥ 4-fold rise in RSV A serum neutralizing antibody titers or RSV serum anti-F IgG antibody titers.

***Immunogenicity***

The point estimates of GMT and GMTR and their 95% CI will be presented by vaccine group for the following endpoints:

- RSV A serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4, in RSV-experienced participants
- RSV serum anti-F IgG antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4 by baseline serostatus.
- RSV A serum neutralizing and anti-RSV F IgG antibody titers after RSV season or at least 5 months after last vaccine administration by baseline serostatus.

Seroresponse may also be presented, as applicable.

### 12.1.3 Statistical Methods for Exploratory Objectives

***Safety***

Solicited ARs, unsolicited AEs (including SAEs), MAAEs and AESIs will be summarized. The main parameters will be described with 95% CI. Main parameters, as described in Section 12.1.1.2, will be presented by vaccine group after each and any vaccination by baseline serostatus.

***Immunogenicity***

The point estimates of GMT and GMTR and their 95% CI will be presented by vaccine group and by baseline serostatus for the following endpoints:

- RSV A serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4, converted into international units (IU)/mL.
- RSV A serum neutralizing antibody titers converted into IU/mL, after the RSV season or at least 5 months after last vaccine administration.
- RSV B serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.
- RSV B serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4, converted into IU/mL.
- RSV B serum neutralizing antibody titers after the RSV season or at least 5 months after last vaccine administration.
- RSV B serum neutralizing antibody titers converted into IU/mL, after the RSV season or at least 5 months after last vaccine administration.
- RSV A and RSV B serum anti-Gcc IgG antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.

- RSV A and RSV B serum anti-Gcc IgG antibody titers after the RSV season or at least 5 months after last vaccine administration.
- RSV serum anti-F IgA antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4.
- RSV serum anti-F IgA antibody titers after the RSV season or at least 5 months after last vaccine administration.

Seroresponse may also be presented, as applicable.

***Efficacy***

RSV Medically attended respiratory illness collected during the RSV season or at least 5 months after last vaccine administration will be summarized. The main parameters will be described with 95% CI. At least the following parameters will be presented by vaccine group:

- RSV medically attended acute respiratory illness (RSV MAARI) by SOC and PT, intensity, time to onset, and duration
- RSV medically attended lower respiratory illness (RSV MAALRI) by SOC and PT, intensity, time to onset, and duration

## 12.2 Analysis Sets

### 12.2.1 Full Analysis Set

The full analysis set (FAS) is defined as the subset of randomized participants who received at least 1 administration of the study vaccine. The data for any participant infected by laboratory confirmed wt RSV will be excluded from immunogenicity and viral shedding analyses from the date of wt RSV infection.

### 12.2.2 Safety Analysis Set

The safety analysis set (SafAS) is defined as those participants who have received at least 1 administration of the study vaccine. All participants will have their safety analyzed after each administration according to the vaccine they actually received and after any vaccination according to the vaccine received at the first administration.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

### 12.2.3 Per-Protocol Analysis Set

The per-protocol analysis set (PPAS) is a subset of the FAS. Two specific PPAS will be defined: PPAS1 after 1 administration (for participants in Cohorts 1, 2, 3 and 4) and PPAS2 after 2 administrations (for participants in Cohorts 2 and 4).

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:

- Baseline serology blood sample was not collected at visit 01 (D0).

- Participant with temporary contraindication did not receive vaccination 1 in the proper time window from randomization.
- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Participant did not receive vaccine / did not complete the vaccination schedule
- Participant received a vaccine other than the one that he / she was randomized
- Preparation and / or administration of vaccine not done as per-protocol
- Participant received a protocol-prohibited therapy before the post-vaccination serology blood sample (see Section 6.7.1)
- Participant with confirmed diagnosis of wt RSV before the post-vaccination serology blood sample
- Participant with an emergency unblinding performed by the Investigator

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS1 only:

- Post-vaccination 1 serology blood sample not collected at visit 03
- Post-vaccination 1 serology blood sample not collected at visit 03 in the proper time window

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS2 only (for participants in Cohorts 2 and 4):

- Participant did not receive vaccination 2 at visit 03 in the proper time window
- Post-vaccination 2 serology blood sample not collected at visit 05
- Post-vaccination 2 serology blood sample not collected at visit 05 in the proper time window

In addition to the reasons listed above, participants will also be excluded from the PPAS if their baseline serology sample or their post-vaccination serology sample did not produce a valid test result (i.e., result for RSV A serum neutralizing antibody titers is missing).

Note: For PPAS1 (after 1 administration), timepoints to be considered are: D0 (visit 01) for vaccination and D56 (visit 03) for the post-vaccination serology sample. For PPAS2 (after 2 administrations), timepoints to be considered are: both D0 (visit 01) and D56 (visit 03) for vaccinations and D84 (visit 05) for the post-vaccination serology sample.

### 12.2.4 Other Analysis Set(s)

***Randomized participants***

A randomized participant is a participant for whom a vaccine group has been allocated.

### 12.2.5 Populations Used in Analyses

The safety analysis will be performed on the SafAS. Participants will be analyzed after each vaccination according to the vaccine they actually received, and after any vaccination according to the vaccine received at the first administration.

Immunogenicity analyses will be performed on the Full Analysis Set, and on the Per-Protocol Analysis Set for main immunogenicity parameters. In the FAS, participants will be analyzed by the vaccine group to which they were randomized. In the PPAS, participants will be analyzed according to the vaccine they actually received.

## 12.3 Handling of Missing Data and Outliers

### 12.3.1 Safety

No replacement will be done. Nevertheless, missing relationship will be considered as related at the time of the statistical analysis. No search for outliers will be performed. In all participant listings, partial and missing data will be clearly indicated as missing.

### 12.3.2 Immunogenicity

Missing data will not be imputed. No test or search for outliers will be performed.

For the calculation of GMT and proportion of participants with nAb titers above thresholds, any pre-vaccination or post-vaccination value reported as < lower limit of quantification (LLOQ) will be converted to a value of ½ LLOQ.

For the calculation of GMTR, any pre-vaccination value reported as < LLOQ will be converted to LLOQ, and any post-vaccination value reported as < LLOQ will be converted to a value of ½ LLOQ when only either the numerator or the denominator is < LLOQ. If both numerator and denominator are < LLOQ, then both will be converted in the same way so that individual titer ratio = 1.

Any value reported as > upper limit of quantification (ULOQ) will be converted to ULOQ.

### 12.3.3 Efficacy

Missing data will not be imputed. No test or search for outliers will be performed.

## 12.4 Interim / Preliminary Analysis

The analysis will be performed with a stepwise approach.

Several blinded early safety data reviews will be performed on safety data collected in participants from each cohort at specific timepoints (see Section 5.1.6).

An unblinded interim analysis is planned on participants from Cohorts 1, 2 and 3, and at least 90 participants enrolled in Cohort 4. The interim analysis will take place when participants have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. This unblinded interim analysis requires the unblinding of data; a specific process will be implemented to maintain the blind at the participant and Investigator levels.

An unblinded early analysis is planned on participants from all Cohorts (Cohorts 1, 2, 3, and 4). The early analysis will take place when all participants have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. This early analysis requires unblinding

of data; a specific process will be implemented to maintain the blind at the participants and Investigator levels. Based on the results of this analysis, a dose will be confirmed for future studies.

The final unblinded statistical analysis will address the objectives on all participants including post season data.

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

## 12.5 Determination of Sample Size and Power Calculation

No sample size calculation was done as there are no statistical hypotheses in this study.

A total of 300 participants are planned to be enrolled into 1 of the 4 cohorts sequentially:

- Cohort 1 (1 administration): 40 participants, i.e., 20 per vaccine group (RSV low-dose or placebo)
- Cohort 2 (2 administrations): 40 participants, i.e., 20 per vaccine group (RSV low-dose or placebo)
- Cohort 3 (1 administration): 40 participants, i.e., 20 per vaccine group (RSV high-dose or placebo)
- Cohort 4 (2 administrations): 180 participants, i.e., 60 per vaccine group (RSV high-dose or RSV low-dose or placebo).

Although there are no statistically powered hypotheses and no sample size computation in this study, the sample size of 100 participants in the RSV low-dose group (20 from Cohort 1, 20 from Cohort 2 and 60 from Cohort 4) will provide a probability of 95% to observe an event that has a true incidence of 3%. The sample size of 80 participants in the RSV high-dose group (20 from Cohort 3 and 60 from Cohort 4) will provide a probability of 95% to observe an event that has a true incidence of 3.75%.

A total of 300 participants are planned to be enrolled in the study. This corresponds to 120 participants in Placebo group, 100 participants in RSV low-dose group and 80 participants in RSV high-dose group. Table 12-1 below presents the number of participants by serostatus, in total and by RSV group, according to varying possible RSV-experienced rates ranging from 5% to 35% (derived from LID/NIH screening data) and provides a global overview of the proportion of RSV-naïve/RSV-experienced participants that will be enrolled in the study.

**Table 12-1: Number of Participants by Serostatus, in Total and by RSV Group, According to Varying Possible RSV-experienced Rates Ranging from 5% to 35%**

| % RSV experienced | Total (N=300) | | RSV low-dose group (N=100) | | RSV high-dose group (N=80) | |
|---|---|---|---|---|---|---|
| | #RSV experienced | #RSV-naïve | #RSV experienced | #RSV-naïve | #RSV experienced | #RSV -naïve |
| 5% | 15 | 285 | 5 | 95 | 4 | 76 |
| 10% | 30 | 270 | 10 | 90 | 8 | 72 |
| 15% | 45 | 255 | 15 | 85 | 12 | 68 |
| 20% | 60 | 240 | 20 | 80 | 16 | 64 |
| 25% | 75 | 225 | 25 | 75 | 20 | 60 |
| 30% | 90 | 210 | 30 | 70 | 24 | 56 |
| 35% | 105 | 195 | 35 | 65 | 28 | 52 |

# 13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

## 13.1 Ethical Conduct of the Study / Good Clinical Practice

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and / or national regulations and directives.

## 13.2 Source Data and Source Documents

“Source data” are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards / electronic diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets. The purpose of study source documents is to document the existence of participants and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

For missing or discrepant data on a diary card / electronic diary card, the study coordinator will obtain verbal clarification from the participant, enter the response into the “investigator’s comment” page of the diary card / electronic diary card, and transfer the information to the CRB.

The participant pre-screening log should list all individuals contacted by the Investigators to participate in the study, regardless of the outcome.
The Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any subsequent changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

[a] Unless the electronic medical records are managed by validated computerized systems that are compliant with US 21 CFR Part 11, in which case they are acceptable on their own.

Good Documentation Practice should be followed by the Investigator and the site staff managing source documents.

## 13.3 Confidentiality of Data, Data Protection, and Access to Participant Records

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur. In the event a participant's medical records are not at the investigational site, it is the responsibility of the investigator, to obtain those records if needed.

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations, including the GDPR (Global Data Protection Regulation). 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.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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.

## 13.4 Monitoring, Auditing, and Archiving

### 13.4.1 Monitoring

Before the start of the study (i.e., before the inclusion of the first participant in the first center), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB completion, and the handling of samples and products. The Sponsor's staff or a representative will ensure and document that all material to be used during the study has been received at the site; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the study, GCP and regulatory requirements, and the Sponsor's procedures. Specific training sessions for the study investigator team and the CRAs on these topics may be performed as necessary and should be documented.

The following instruction manuals will be provided: the CRF Completion Instructions for entering data into the CRB, and the Operating Guidelines for detailed study procedures such as the product management and sample-handling procedures.

After the start of the study, the Sponsor's staff or a representative will be in regular contact with the investigational team through telephone calls and regular follow-up visits. The Investigator or delegate must be available for these visits and must allow the Sponsor/delegate staff direct access to participant medical files and CRBs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the study, a close-out visit will be performed to ensure that:

- The center has all the documents necessary for archiving
- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

### 13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's Clinical Quality Assessment department (CQA) or by independent auditors to verify that the study has been conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. The Investigator must allow direct access to study documents during these inspections and audits.

### 13.4.3 Archiving

The Investigator and the study site shall retain and preserve 1 copy of the study file containing the essential documents related to the study and records generated during the study ("Study File") for the longer of the 2 following periods ("Retention Period"):

- 25 years after the signature of the final study report or
- such longer period as required by applicable regulatory requirements

If during the Retention Period, the study site is no longer able to retain the Study File due to exceptional circumstances (such as bankruptcy), the study site shall contact the Sponsor to

organize the transfer of the Study File to the Sponsor's designee at the Sponsor's expense. Following the Retention Period, the Investigator and/or the study site are responsible to dispose of the Study File according to the applicable regulations. Patient medical records shall be retained in compliance with local regulations.

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the study will be kept by the Sponsor in the Trial Master File (TMF). Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

## 13.5 Financial Contract and Insurance Coverage

A Clinical Trial Agreement will be signed by all the parties involved in the study's performance, if relevant. The Sponsor has an insurance policy to cover any liabilities that may arise from use of the product and / or the study protocol.

## 13.6 Stipends for Participation

Participants' parent / guardian / legally authorized representative may be provided with a stipend, according to local practice, to compensate for the time and travel required for study visits and procedures.

## 13.7 Publication Policy

Data derived from this study are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the study must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives recognition to the study group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

Sanofi Pasteur must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study at least 90 days prior to submission for publication / presentation. Any information identified by Sanofi Pasteur as confidential must be deleted prior to submission, it being understood that the results of this study are not to be considered confidential.

Sanofi Pasteur's review can be expedited to meet publication guidelines.

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# 15 Appendix

## Bayesian approach for safety signal detection

At each safety evaluation, a Bayesian approach based on Posterior Distribution may be used to assess the difference between each RSV formulation and Placebo on the following safety endpoint:

- Any Grade 3 lower respiratory tract illness e.g., wheezing, pneumonia, sustained tachypnea, laryngotracheobronchitis
- Grade 3 fever

The probability that the difference of percentages of events between one RSV formulation and Placebo is greater than a pre-specified margin (δ) can be calculated based on posterior distribution, using non-informative prior Beta (1,1) (33) and observed binomial data:

**Proba (%RSV - %Placebo > δ)**

If this probability is high (e.g., >=80%) then it may be recommended to drop the formulation. Thus, it can help decision making for safety evaluation by SMT and/or IDMC (if applicable) and can also be applied at the end of the study.

Example of application: SMT
Consider δ = 5% the maximum difference of percentages of events tolerated between groups.
Number of participants is planned to be 20 per group in Cohort 1, Cohort 2 and Cohort 3 for early safety data review.

Probabilities P(%RSV - %Placebo > δ) are calculated according to each possible distribution of up to 6 observed events between the 2 groups, as shown in the table below.

**Probabilities P (%RSV - %Placebo > δ) according to the distribution of observed events between RSV and Placebo groups**

| #events (RSV) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| 6 | N=6 / P=98,5% (97,3% - 99,3%) | | | | | | |
| 5 | N=5 / P=96,6% (94,3% - 98,1%) | N=6 / P=88,9% (82,8% - 93,4%) | | | | | |
| 4 | N=4 / P=92,5% (88,8% - 95,2%) | N=5 / P=79,9% (72,0% - 86,3%) | N=6 / P=64,2% (53,5% - 74,2%) | | | | |
| 3 | N=3 / P=84,0% (78,6% - 88,5%) | N=4 / P=65,9% (57,1% - 74,0%) | N=5 / P=47,9% (37,8% - 58,3%) | N=6 / P=32,6% (23,0% - 43,3%) | | | |
| 2 | N=2 / P=68,4% (61,7% - 74,6%) | N=3 / P=46,9% (38,6% - 55,4%) | N=4 / P=30,0% (22,3% - 38,8%) | N=5 / P=18,0% (12,0% - 25,7%) | N=6 / P=10,2% (5,9% - 16,2%) | | |
| 1 | N=1 / P=44,0% (37,9% - 50,5%) | N=2 / P=25,5% (19,8% - 32,0%) | N=3 / P=14,0% (9,7% - 19,4%) | N=4 / P=7,3% (4,5% - 11,2%) | N=5 / P=3,6% (2,0% - 6,2%) | N=6 / P=1,7% (0,8% - 3,3%) | |
| 0 | N=0 / P=16,6% (13,5% - 20,2%) | N=1 / P=7,9% (5,7% - 10,6%) | N=2 / P=3,6% (2,3% - 5,4%) | N=3 / P=1,6% (0,9% -2,7%) | N=4 / P=0,7% (0,4% - 1,3%) | N=5 / P=0,3% (0,1% - 0,6%) | N=6 / P=0,1% (0,0% - 0,3%) |
| | | | | | | | #events (Placebo) |

N = Total number of events observed in the 2 arms considered in the analysis (one RSV formulation and Placebo)
P = Bayesian probability calculated in the context of balanced design (20RSV/20PL)
Range = (Pmin - Pmax) where Pmin and Pmax are bayesian probabilities calculated in the context of unbalanced design (22RSV/18PL and 18RSV/22PL respectively)

Given a total number of events observed in blind, these results may help safety signal management by assessing the underlying potential safety issues. For instance, cases may be unblinded once a total of 3 events occur.

# 16 Signature Page