IMPAACT 2021

Primary Statistical Analysis Plan

Version 5.0

Randomized Phase I/II Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccines RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s, RSV 276 or Placebo, Delivered as Nose Drops to RSV-Seronegative Children 6 to 24 Months of Age

Protocol Version 3.0

Clarification Memo #1, Letter of Amendment #1

ClinicalTrials.gov Identifier: NCT03916185

November 7, 2023

This is IMPAACT 2021 SAP Version 5.0 with names of authors, names of publication writing team members and analysis timeline redacted.

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Version History

Version	Changes Made	Date Finalized
1.0	Original Version	08MAY2019
1.1	Updated with protocol LoA #1 • Revised footnote for Appendix 1 Clarify that we will use Wilcoxon signed-rank tests for pair-wise comparisons rather than Wilcoxon rank sum tests (Section 4.3.1) Update Attachment 1: Writing team roster	10MAR2020
2.0	Updated with protocol version 2.0 • Clarified that the window for Post-RSV season visits may be extended to September 30 due to operational interruptions related to COVID-19. • Updated text to indicate that Illness Visit specimens may be collected by either nasal wash (if Illness Visit prior to COVID-19 pandemic) or nasal swab (if Illness Visit after COVID-19 pandemic). • Updated text regarding sample size and study design indicating RSV 276 arm was closed. • Removed the specification that viral vaccine will be isolated by culture for Go/No-Go Criteria #3. Quantitation will now be based primarily on PCR, as viral culture will not be reliable on samples collected by parents/guardians. • Further clarified that we will use Wilcoxon signed-rank tests for paired comparisons between time points and pair-wise Wilcoxon rank sum tests for comparisons between arms. (Section 4.3.1). • Added additional analyses for primary and secondary objectives to examine seasonal effects and account for potential ascertainment differences related to COVID-19. • Updated Attachment 1: Writing team roster.	02SEP2021

3.0	Updated with protocol version 3.0 • Clarified that the RSV season surveillance period starts in the calendar year of the participant's study product administration. • Clarified that the Post-RSV visit is to occur between April 1 - April 30 in the calendar year following study product administration. • Updated language to further clarify when the go/no-go assessment would be assessed. • Clarified language regarding children from the same household. For immunogenicity analyses, one participant will be randomly selected to be included in the primary analysis if two or more participants are enrolled from the same household on the same date. Also updated conditions for enrollment of multiple children from same household. • Updated Attachment 1: Writing team roster.	14JUN2022
4.0	Updated with clarification memo #1 to protocol version 3.0 • Updated go/no-go criteria from *RSV neutralizing antibody* to *IgG antibody to RSV F protein* • Added bronchiolitis to the list of solicited adverse events • Removed language specifying RSV virus (wt or vaccine virus) corresponding to Illness Visits would only be detected by "immunoplaque assay". • Revised text to indicate that tests for homogeneity will be based on Breslow-Day test.	10MAR2023
5.0	Updated with letter of amendment #1 to protocol version 3.0 • Clarified that participants who receive concomitant medications that may confound results will be excluded from the immunogenicity analysis population and virology-based analyses. • Updated Attachment 1: Writing team roster.	07NOV2023

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes analyses of the primary and secondary outcome measures of IMPAACT 2021 which address the primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov.

Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Analysis Report are included in the Analysis Implementation Plan (AIP). Analyses for the Primary Statistical Analysis Report will be initiated once the last participant has completed their Day 56 follow-up visit and associated immunologic and virologic data are in the study database, all queries have been resolved, and the database frozen for analysis. As this study has extended follow-up beyond the primary completion date, an additional statistical analysis report addressing the remaining objectives will be initiated once the last participant has completed their Post-RSV Season Visit and all virology data are in the study database, all queries have been resolved, and the database frozen for analysis. Outlines of analyses for exploratory objectives and outcome measures not included in the Primary SAP will be provided in a separate SAP for Other Objectives.

2 Study Overview

2.1 Study Design

IMPAACT 2021 is a multi-center, Phase I/II, double-blind, randomized, placebo-controlled study to assess the safety and immunogenicity of three Respiratory Syncytial Virus (RSV) vaccine candidates (RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s and RSV 276) in RSV-seronegative children, and to determine whether any vaccines are good candidates to move forward into larger efficacy studies. Under protocol V2.0, participants will be randomized equally to receive RSV ΔNS2/Δ1313/I1314L vaccine, RSV 6120/ΔNS2/1030s vaccine, or placebo (a third vaccine, RSV 276, was previously included under protocol V1.0; no participants will receive this vaccine under protocol V2.0). Approximately 130 healthy RSV-seronegative children 6 to <25 months of age will be randomized, including approximately 40 each in the placebo and two candidate vaccine arms that remain open under protocol V2.0, as well as all participants previously randomized to receive RSV 276 under protocol V1.0 prior to closure of this arm.

Eligible children from the same household are allowed to enroll: they must either be enrolled on the same date and to the same study arm or additional children in the household can be enrolled and randomized independently after other children in the household complete the Day 56 Visit. Enrollment will take place outside the time during which wt RSV circulates in the community at each site. RSV circulation will be determined by the Protocol Team through local and national surveillance and communication with the study sites, with additional guidance provided in the Manual of Procedures (MOP)). Children will remain on study until they complete the Post-RSV Season Visit between April 1 – April 30 in the calendar year following study product administration; however, this window may be extended to September 30 if sites experience operational disruptions due to COVID-19). Expected length of follow-up for a given participant is between 4 and 15 months depending on time of enrollment.

2.2 Hypotheses

The live-attenuated RSV vaccine candidates RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s, and RSV 276 will each be safe and immunogenic in RSV-seronegative recipients. However, these vaccine candidates may have safety signals that become apparent only when analyzed in a larger number of participants, and the candidates may differ in the magnitude and longevity of antibody responses, and in responses observed following naturally occurring RSV infection. To move forward, the vaccines should:

- *be safe, and*
- *result in at least 70% of the population of vaccine recipients having a ≥4-fold rise in serum RSV-neutralizing antibody titers from pre-study product administration to the Day 56 Visit after study product administration*

2.3 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. Other study objectives in the protocol will be addressed in subsequent analysis plans.

2.3.1 Primary Objectives

- Safety: To estimate and compare (each vaccine group to placebo) the frequency and severity of adverse events (AEs) following study product administration (Day 0) through Day 56
- Immunogenicity: To estimate and compare (between the vaccine groups and to the benchmark of 70%) the percentage of vaccinees having a ≥4-fold rise in serum RSV-neutralizing antibodies at the Day 56 Visit

2.3.2 Secondary Objectives

- Immunogenicity: To estimate and compare (between the vaccine groups) the percentage of vaccinees with a ≥4-fold rise in serum IgG antibody to RSV F protein (RSV F IgG) at the Day 56 Visit
- Immunogenicity: To estimate and compare (between the vaccine groups) the titers of serum RSV F IgG and serum RSV-neutralizing antibodies at the Day 56 Visit
- Safety: To describe and compare 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 the placebo and vaccine arms during RSV season

2.4 Overview of Sample Size Considerations

The target sample size of approximately 40 per arm was chosen to gather more data on safety and to yield sufficiently precise confidence intervals around Day 56 immunogenicity to help inform which candidate vaccines should go forward into larger studies. The total expected sample size is approximately 130, including approximately 40 each in the placebo and two candidate vaccine arms that remain open under protocol V2.0 (RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s), as well as all participants previously randomized to receive RSV 276 under protocol V1.0 prior to closure of this arm.

To fully assess safety, much larger sample sizes will be required, and additional studies will need to be conducted on the candidate vaccines identified as promising in this trial. Declaring superiority in immunogenicity of one vaccine candidate over another will only be possible if one candidate has very poor immunogenicity. Additional details regarding sample size considerations are included in Section 9.3 of the protocol.

2.5 Overview of Formal Interim Monitoring

The NIAID Intramural Data and Safety Monitoring Board (DSMB) will provide independent oversight to safeguard the well-being of study participants and to monitor study integrity. The DSMB will meet bi-annually to monitor participant safety with regard to adverse events and efficacy; to review analyses outlined in the statistical section of the protocol; and to discuss problems regarding accrual, study compliance, data quality and completeness.

If IMPAACT 2021 is not fully accrued at the end of an enrollment season and an additional enrollment season is considered, the DSMB will review unblinded data to determine if all candidate vaccines should remain in the study. The DSMB will use the following Go / No-Go criteria as specified in the protocol as guidance in making that decision.

	Yes	No
1. Is there a statistically significant ($p<0.05$) difference in the percentage with immune response (e.g., ≥4-fold rise in serum IgG antibody to RSV F protein) to the candidate vaccines such that one or two products can be identified to be immunologically superior to the remaining product or products, with the absence of a safety signal among the higher performing product(s)?		
If yes, the DSMB may recommend that the study close to accrual		
If no, the DSMB will consider the following questions for each specific product:		
2. Is the upper limit of the 95% confidence interval for the percentage of participants exhibiting immune response (e.g., ≥4-fold rise in serum IgG antibody to RSV F protein) at the Day 56 Visit less than 70%?		
3. Have more than two participants receiving the specific product experienced lower respiratory illness (LRI) of ≥ Grade 2 in the 28 days following study product administration for which vaccine virus was isolated without other potential explanation?		

4. Were there two or more participants who experienced vaccine-associated Grade 4 events of similar type (as listed below) after study product administration with presence of vaccine virus without other potential explanation? Otitis media within 28 days of study product administration Pharyngitis within 28 days of study product administration		

3 Outcome Measures

3.1 Primary Outcome Measures

Safety Outcome measures:

- Grade 1 or higher solicited AEs as defined in Appendix 1 from Day 0 through Day 28
- Grade 2 or higher LRIs as defined in Appendix 1 from Day 0 through Day 28
- Serious AEs as defined in Appendix 4 from Day 0 through Day 56

Additional grading criteria are included in Appendix 2 and 3.

Immunogenicity Outcome measure:

- ≥4-fold rise in serum RSV-neutralizing antibody titer from pre-study product administration (screening) to the Day 56 Visit

3.2 Secondary Outcome Measures

Immunogenicity Outcome measure [Secondary Objective 1]:

- ≥4-fold rise in serum RSV F IgG from pre-study product administration (screening) to the Day 56 Visit

Immunogenicity Outcome measures [Secondary Objective 2]:

- Titer of serum RSV F IgG at the Day 56 Visit
- Titer of serum RSV-neutralizing antibodies at the Day 56 Visit

Safety Outcome measures [Secondary Objective 3]:

- RSV-MAARI and maximum grade (if more than one illness within a participant)
- RSV-MAALRI and maximum grade (if more than one illness within a participant)

4 Statistical Principles

4.1 General Considerations

4.1.1 Analysis populations

- Any participants found to be ineligible will be included in screening, accrual and eligibility summaries only.
- *Safety population:* All children (regardless of the number of children enrolled in a given household on the same date) who receive study product will be included in safety analyses. Safety outcome measures will be included if they occur after study product administration.
- *Immunogenicity population:* Children who received study vaccine and who have available data regarding outcome measures at screening and Day 56. If more than one child from a household is enrolled on the same date, one participant will be randomly selected to be included in the primary analysis.
    - Participants who have received the following treatments prior to the Day 56 visit will be excluded from the immunogenicity population (See Section 5.11.2 of the protocol for additional details):
        - 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;
        - anti-RSV products (such as ribavirin or RSV IG or RSV mAb).

4.1.2 Key Definitions

- “Pre-study product administration”
    - At screening, a blood draw is performed for RSV serum antibody testing. The measurement corresponding to this blood draw is referred to as the “pre-study product administration” measurement.
- “Day 0”
    - The date of study product administration. Study product administration must occur within 42 days of collection of the screening sampling and ideally on the same day as randomization, or, if needed, up to 5 days after randomization.
- “Baseline”

  Baseline summaries will use the last evaluation on or before the date of study product administration (Day 0).
- Lower (LRI) and Upper (URI) respiratory illness
    - Solicited adverse events include fever, acute otitis media, LRIs (identified by wheezing, pneumonia, croup, rhonchi or rales), and URIs (identified by rhinorrhea, pharyngitis, cough without LRI and hoarseness), each defined in Appendix 1 of this document. URIs and LRIs are counted as having occurred if any of their associated signs, symptoms or diagnoses are reported.

4.1.3 Analysis windows

- There are three time periods of interest (Acute, Post-Acute, and RSV Season Surveillance). For the purposes of analysis, data included are from:

- Acute Phase: Day 0 – 28
  - The Acute Phase begins with study product administration (Day 0) and ends at midnight on the 28th day after study product administration.
- Post-Acute Phase: Day 29 – 56
  - The Post-Acute Phase begins at 12:01 am on the 29th day after study product administration and ends at midnight on the 56th day after study product administration.
- RSV Season Surveillance: Nov 1 to March 31 or as specified in MOP
  - This period starts in the calendar year of the participant's study product administration.
- Post-RSV Season Visits: April 1-30
  - Visits are to occur in the calendar year following study product administration.
  - The allowable window for Post-RSV Season Visits may be extended to September 30 if sites experience operational disruptions due to COVID-19.
- Other: after Day 56 and before November 1

- It is possible for the Acute or Post-Acute Phase and the RSV Season Surveillance period to overlap. If participants are enrolled fewer than 56 days before the start of the RSV Season Surveillance period, reportable events occurring before Day 56 (possibly during the RSV Season Surveillance period) will be included in Acute/Post-Acute summaries rather than the RSV Season Surveillance period (unless otherwise specified, see 4.3.2).

4.1.4 Variable summaries

- Baseline characteristics will be summarized by arm, but with no statistical comparisons comparing arms because of the randomized study design.
- Significance levels $p < 0.05$ will be highlighted in the text, but must be interpreted with caution since there will be many statistical tests and no adjustments for interim monitoring.
- Categorical data will be summarized using N (%), and continuous data using N, min, Q1, median, Q3, max, and mean/geometric mean (standard deviation (SD) or 95% confidence intervals) (when appropriate).
- Any modifications to this statistical analysis plan after the team has seen data that were collected after randomization will be identified as such in the analysis report.

4.2 Analysis Approaches (Primary Objectives)

4.2.1 Analysis of the primary safety objective

There are three primary safety outcome measures (Section 3.1). For each, the number and proportion of participants experiencing at least one primary safety outcome measure in the identified time frames will be summarized by arm with 95% exact confidence intervals (CIs) using the Clopper-Pearson method. Proportions in each vaccine group will be compared to the placebo group using two-tailed Fisher's exact tests with a nominal significance level of 0.05. Differences in proportions between each vaccine arm and the placebo arm will be summarized with 95% CIs.

To account for potential ascertainment differences related to COVID-19, differences in proportions between each vaccine arm and the placebo will be summarized by calendar year of enrollment. A Breslow-Day test with a nominal significance level of 0.05 will be used to test for homogeneity in the vaccine effect by calendar year for each comparison between arms. Unless the Breslow-Day test indicates there is not homogeneity in vaccine effect by calendar year, a strata-adjusted difference in proportions will be summarized using a Cochran-Mantel-Haenszel method with 95% Klingenberg (2014) confidence limits.

In addition, for each primary safety outcome measure, the worst (highest) grade experienced by each participant will be summarized. The severity of solicited AEs from Days 0-28, unsolicited AEs from Days 0-28, and serious AEs from Days 0-56 will be summarized by category and by MedDRA Preferred Term (PT). The worst (highest) adverse event grade within each PT is counted for each participant. Rare events (LRIs and serious AEs) will be listed with details including site-assessed relationship with the study product.

4.2.2 Analysis of the primary immunogenicity objectives

Children will be classified as a responder to the vaccine if they achieve a ≥4-fold increase in serum RSV-neutralizing antibody titers from pre-study product administration to the Day 56 Visit. Proportions (95% CIs) of responders will be summarized by arm. Each confidence interval will be assessed to determine if the upper limit is less than 70%. Differences between each vaccine arm and the placebo arm (which take into account background rates which could vary by season), as well as differences between each combination of vaccine arms, will be summarized with 95% CIs. Pair-wise differences in response rates between the vaccine arms (and differences between vaccine and placebo arms) will be assessed using two-tailed Fisher's exact tests with a nominal significance level of 0.05.

Sensitivity and secondary analyses of the primary immunogenicity objective

Sensitivity analysis will include:

(i) Repeat above-described analyses after replacing the selected child with other siblings or other children from the same household who enrolled on the same date.

Secondary analyses will include:

(i) Repeat above-described analyses with participants missing their Day 56 antibody titer re-classified as failures.

(ii) Repeat above-described analyses using an intent-to-treat population that includes all participants as-randomized regardless of vaccine receipt.

(iii) Repeat above-described analyses using an outcome measure defined as a ≥4-fold increase in serum RSV-neutralizing antibody titers from pre-study product administration to the Day 56 Visit and no wild-type RSV infection detected before Day 56.

(iv) To examine seasonal effects and account for potential ascertainment differences related to COVID-19, response rates for each arm and differences in proportions between each arm will be summarized by calendar year of enrollment. A Breslow-Day test with a nominal significance level of 0.05 will be used to test for homogeneity in the vaccine effect by calendar year for each comparison between arms. Unless the Breslow-Day test indicates there is not homogeneity in vaccine effect by calendar year, a strata-adjusted difference in proportions will be summarized using a Cochran-Mantel-Haenszel method with 95% Klingenberg (2014) confidence limits.

4.3 Analysis Approaches (Secondary Objectives)

4.3.1 Secondary immunogenicity up to Day 56

The proportion of participants achieving ≥4-fold increases in serum RSV F IgG titers from pre-study product administration to Day 56 will be summarized using the same methods as for the primary initial response to vaccine immunogenicity outcome measured by serum RSV-neutralizing antibodies.

Titers of serum RSV-neutralizing antibodies and RSV F IgG will be summarized at pre-study product administration and the Day 56 visit. Changes from the pre-study product administration to Day 56 will also be summarized. Levels and changes will be compared between time points using Wilcoxon signed-rank tests and between arms using pair-wise Wilcoxon rank sum tests. Titers will be analyzed on the reciprocal $\log_2$ scale. Sensitivity analyses will be performed by replacing the selected child with other siblings or other children from the same household who enrolled on the same date. If enrollment extends over more than one season, response rates will be summarized by calendar year of enrollment to examine seasonal effects.

Titers below the lower limit of detection or above the upper limit of detection will be assigned a value equal to the corresponding limit of detection.

4.3.2 RSV medically-attended illness during RSV surveillance

Numbers and proportions (with 95% CIs) of participants experiencing RSV-associated medically attended acute respiratory illness (RSV-MAARI) and RSV-associated acute lower respiratory illness (RSV-MAALRI) will be summarized by arm. In addition, the worst graded event experienced by a participant (if a participant experiences more than one illness during the season) will be summarized. Since the number of these events is expected to be small, no formal statistical comparison tests are planned.

If RSV-MAARI or RSV-MAALRI events occur during the RSV surveillance period but prior to Day 56, they will be included in analyses corresponding to this objective.

Participants who receive the following treatments will be excluded from analyses, unless they experienced an RSV-associated medically attended illness prior to receiving treatment:

- 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;

- anti-RSV products (such as ribavirin or RSV IG or RSV mAb).

4.4 Analysis Approaches (Go / No-Go criteria)

There are four Go / No-Go criteria (Section 2.5) that will be reviewed by the DSMB when making decisions regarding the removal of candidate vaccine arms from the study. For each candidate vaccine arm, all four criteria will be evaluated (yes/no).

4.5 Analysis Approaches (Virology)

At each Illness Visit, a respiratory viral sample will be collected (i.e., nasal wash or nasal swab) to evaluate for the presence of RSV and other respiratory pathogens (adventitious agents). Note: Under protocol version 1.0, nasal wash samples were collected from participants. Under protocol version 2.0, the collection has been changed to nasal swab samples to decrease potential exposure of study staff to SARS-CoV-2 and allow parents/guardians to collect samples, if possible and feasible for parents/guardians. During each study period (Acute Phase, Post-Acute Phase, and RSV Season Surveillance), more than one nasal wash/swab might be performed. The overall number and proportion of children with at least one Illness Visit nasal wash/swab will be calculated for each vaccine arm by study period. Frequencies will also be calculated for each calendar year and collection method (caretaker versus medical personnel).

Among those with respiratory viral sample test results, the number and proportion with each observed combination of vaccine virus RSV, wt-RSV, and other adventitious agents will be calculated by study period and by arm. Among all children, the number and proportion with an Illness Visit where RSV virus (wt or vaccine virus) was detected (with or without other adventitious agents detected) will also be calculated for each vaccine arm by study period. Frequencies will also be calculated for each calendar year and collection method (caretaker versus medical personnel).

Participants who receive the following treatments will be excluded from analyses, unless they experienced an illness visit prior to receiving treatment:

- 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;
- anti-RSV products (such as ribavirin or RSV IG or RSV mAb).

5 Report Contents

Detailed descriptions of the content of each of the following sections are given in the AIP.

1. Accrual
    a. Screening
        i. Number screened
        ii. Screening failure reasons
    b. Enrollment
        i. Number enrolled
2. Baseline characteristics
    a. Summary table for key characteristics, including site, sex, age, race, ethnicity, HIV exposure
3. Protocol deviations
    a. Summary of serious protocol deviations reportable per standard IMPAACT policies
4. Study and vaccine status
    a. Number receiving vaccine
    b. Number off study prematurely, by reason and arm
    c. Consort diagram
5. Visit completeness
    a. Number of expected and observed clinic visits
6. Primary safety outcome measures as described in Section 4.2.1
    a. Solicited AEs (Day 0 – 28)
    b. LRIs ≥ Grade 2 (Day 0 – 28)
    c. Serious AEs (Day 0 – 56)
7. Primary immunogenicity outcome measures as described in Section 4.2.2
    a. Initial response to vaccine measured by serum RSV-neutralizing antibody
8. Secondary immunology outcome measures as described in Section 4.3.1
    a. Initial response to vaccine measured by RSV F IgG
    b. Titers achieved by Day 56
9. Secondary RSV medically-attended illness during RSV surveillance as described in Section 4.3.2
10. Go / No-Go criteria evaluation as described in Section 4.4
11. Virology as described in Section 4.5

6 Appendix 1: Definitions of Solicited Adverse Events

Event	Defined
Fever	Temporal temperatures ≥100.0ºF unconfirmed by rectal temp -or- Rectal temperature of ≥100.4ºF.
Acute Otitis Media[1]	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.
Upper Respiratory Tract Illness (URI)	
Rhinorrhea	Two or more consecutive days of clear or purulent discharge from the nares. Note: Not associated with crying, change of room temperature, or eating and drinking.
Pharyngitis[1]	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.
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. Note: Not associated with eating, drinking or choking.
Hoarseness	An unnaturally deep or rough quality of voice.
Lower Respiratory Tract Illness (LRI)	
Wheezing[2,3] (may include bronchiolitis[5])	Sustained, high pitched, musical breath sounds, especially during the expiratory phase, which do not clear with cough.
Pneumonia[1,2,3]	Rales and crackles, originating in the lower respiratory tract, usually accompanied by tachypnea, which do not clear with cough. May be confirmed by x-ray showing areas of consolidation.

Laryngotracheobronchitis (croup) [1,2,4]	Barking cough, hoarseness, and inspiratory stridor
Rhonchi[2,3]	Coarse breath sounds which are not transmitted noises from the upper airway and do not clear with cough.
Rales[2,3]	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.

1 Diagnosis must be made by a medical professional

2 Must be sustained over 20 minutes.

3 Clinical assessment must be made by a medical professional and confirmed by a second medical professional, if possible.

4 It is not necessary for medical professional(s) to witness inspiratory stridor as long as parent or guardian report is consistent with stridor and a medical professional judges the symptoms in total to be consistent with croup.

5 Bronchiolitis should be recorded as a solicited AE whether wheezing is detected or not.

7 Appendix 2: Grading Table for Solicited AEs

Severity	Defined
Grade (1) Mild	No medical intervention required; may include use of over-the-counter medications managed by the caregiver for treatment of symptoms; does not interfere with usual activities (e.g., eating, sleeping, playing)
Grade (2) Moderate	Moderate symptoms, i.e., symptoms interfering to some degree with usual activities. In most cases, symptoms severe enough to necessitate a medical care visit would likely meet this criterion; however, if medical care is sought and symptoms are assessed as only mild, the event may remain Grade 1. If prescription medication is used or recommended for symptoms, the event automatically moves to at least Grade 2.
Grade (3) Severe	Prolonged medical intervention and/or hospitalization required
Grade (4) Life threatening	Illness requiring hospitalization with intensive care
Grade (5) Death	Event resulting in fatal outcome to the participant

8 Appendix 3: Fever Grading*

Severity	Defined
Grade (0)**	≥100.0ºF but <100.4ºF (≥37.8ºC but <38ºC)
Grade (1)	≥100.4ºF but <101.5ºF (≥38ºC but <38.6ºC)
Grade (2)	≥101.5ºF but <102.5ºF (≥38.6ºC but <39.2ºC)
Grade (3)	≥102.5ºF but <104.9ºF (≥39.2ºC but <40.5)
Grade (4)	≥104.9ºF (≥40.5ºC)

* Applies to any modality of temperature measurement

** Grade 0 is to be used only when temporal temperature is ≥100.0 but <100.4 and no rectal temperature is measured.

9 Appendix 4: Definition of Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is an AE, whether considered related to the study product or not, that:

1. Results in death during the period of protocol-defined surveillance
2. Is life threatening: defined as an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death were it more severe
3. Requires inpatient hospitalization (or prolongation of existing hospitalization): defined as at least an overnight stay in the hospital or emergency ward for treatment that would have been inappropriate if administered in the outpatient setting
4. Results in a persistent or significant disability/incapacity
5. Is a congenital anomaly or birth defect
6. Is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.